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# Cortisol, Cognition and the Ageing Prefrontal Cortex

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## **Declaration**

The research presented in this thesis is the unaided work of the author, unless where explicitly acknowledged. Where work is the product of collaboration, co-authors are acknowledged, and have agreed to its submission herein. This work has not been previously submitted, nor is under consideration for any other degree or professional qualification.

Simon Riddington Cox

August 2012



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## **Abstract**

The structural and functional decline of the ageing human brain varies by brain region, cognitive function and individual. The underlying biological mechanisms are poorly understood. One potentially important mechanism is exposure to glucocorticoids (GCs; cortisol in humans); GC production is increasingly varied with age in humans, and chronic exposure to high levels is hypothesised to result in cognitive decline via cerebral remodelling. However, studies of GC exposure in humans are scarce and methodological differences confound cross-study comparison. Furthermore, there has been little focus on the effects of GCs on the frontal lobes and key white matter tracts in the ageing brain. This thesis therefore examines relationships among cortisol levels, structural brain measures and cognitive performance in 90 healthy, elderly community-dwelling males from the Lothian Birth Cohort 1936. Salivary cortisol samples characterised diurnal (morning and evening) and reactive profiles (before and after a cognitive test battery). Structural variables comprised Diffusion Tensor Imaging measures of major brain tracts and a novel manual parcellation method for the frontal lobes. The latter was based on a systematic review of current manual methods in the context of putative function and cytoarchitecture. Manual frontal lobe brain parcellation conferred greater spatial and volumetric accuracy when compared to both single- and multi-atlas parcellation at the lobar level. Cognitive ability was assessed via tests of general cognitive ability, and neuropsychological tests thought to show differential sensitivity to the integrity of frontal lobe sub-regions. The majority of, but not all frontal lobe test scores shared considerable overlap with general cognitive ability, and cognitive scores correlated most consistently with the volumes of the anterior cingulate. This is discussed in

light of the diverse connective profile of the cingulate and a need to integrate information over more diffuse cognitive networks according to proposed de-differentiation or compensation in ageing. Individuals with higher morning, evening or pre-test cortisol levels showed consistently negative relationships with specific regional volumes and tract integrity. Participants whose cortisol levels increased between the start and end of cognitive testing showed selectively larger regional volumes and lower tract diffusivity (correlation magnitudes  $<.44$ ). The significant relationships between cortisol levels and cognition indicated that flatter diurnal slopes or higher pre-test levels related to poorer test performance. In contrast, higher levels in the morning generally correlated with better scores (correlation magnitudes  $<.25$ ). Interpretation of all findings was moderated by sensitivity to type I error, given the large number of comparisons conducted. Though there were limited candidates for mediation analysis, cortisol-function relationships were partially mediated by tract integrity (but not sub-regional frontal volumes) for memory and post-error slowing. This thesis offers a novel perspective on the complex interplay among glucocorticoids, cognition and the structure of the ageing brain. The findings suggest some role for cortisol exposure in determining age-related decline in complex cognition, mediated via brain structure.

## Glossary

ACC	Anterior Cingulate Cortex
ATOS	Anterior termination of the olfactory sulcus
ATR	Anterior thalamic radiation
dACC	Dorsal ACC
D-KEFS	Delis-Kaplan Executive Function System
DLPFC	Dorsolateral prefrontal cortex
END	Salivary cortisol sampled at the end of neuropsychological testing
EVENING	Salivary cortisol levels provided at 10pm at home on a weekday
FP	Frontal pole
<i>g</i>	General cognitive ability / fluid intelligence
IFG	Inferior frontal gyrus
IFS	Inferior frontal sulcus
ILF	Inferior longitudinal fasciculus
IntFS	Intermediate frontal sulcus
LOS	Lateral orbital sulcus
MFG	Middle frontal gyrus
mPFC	Medial prefrontal cortex
mSFG	Medial superior frontal gyrus
OFC	Orbitofrontal cortex
PC	Principal Component
PCS	Paracingulate sulcus
PES	Post-error slowing
PrCS	Precentral Sulcus
PVN	Paraventricular nucleus of the thalamus
SFG	Superior frontal gyrus
SFS	Superior frontal sulcus
SOPT	Self-ordered pointing task
SRS	Superior rostral sulcus
START	Salivary cortisol sampled at the start of neuropsychological testing
vACC	Ventral ACC
VMPFC	Ventromedial prefrontal cortex
WAKING	Salivary cortisol levels provided on waking at home on a weekday
WMH	White matter hyperintensities

## Chapter 1: General Introduction

Increasing age is accompanied by a decline in cognitive abilities which has an impact on independent living and quality of life (Korten et al., 1999; Tomaszewski Farias et al., 2009). Age appears to affect some cognitive abilities more than others, and the degree of cognitive impairment experienced varies from one individual to the next (Kemp, Després, Sellal, & Dufour, 2012; Salthouse, 2004). The brain undergoes changes to its structure (both cortex and interconnective white matter; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003) and organisation (Goh, 2011; Park & Reuter-Lorenz, 2009) with age, and it is these changes that are thought to underlie age-related cognitive decline. Many countries face an increasingly ageing demographic, with the potential for larger populations than ever facing a loss of cognitive functioning that may require long-term care; thus the determinants of these brain changes and their functional sequelae are of increasing interest (Kirkwood, 2008). The following section outlines the focus of this thesis on three types of variable (brain structure, cognitive function and cortisol levels), and the utility of examining their covariances in old age, though the ensuing three chapters will focus on each in more detail.

The frontal lobes of the brain are intimately involved in cognitive processes such as attention, reasoning, planning, social and emotional functioning. This region of the brain is also particularly susceptible to the effects of age; its gross volume, cortex (volume and thickness) and white matter (volume and tract-based measure of integrity) show disproportionate age-related decreases compared to other parts of the brain (Burzynska et al., 2012; Driscoll et al., 2009; Fjell et al., 2009; Sullivan &

Pfefferbaum, 2007). This predominant deterioration of the frontal lobes and their connectivity is thought by some to be responsible for many age-related cognitive changes (MacPherson, Phillips, & Della Sala, 2002; Moscovitch & Winocur, 1995; O’Sullivan et al., 2001). The frontal lobe is a complex multi-component brain area, rather than a single entity with a single unitary function. Different frontal lobe regions possess different cellular organisations and have distinct patterns of connectivity with other brain structures, which constrain the types of information they can process (Yeterian, Pandya, Tomaiuolo, & Petrides, 2012; Zald, 2007). Functional neuroimaging and patient studies also suggest that different parts of the frontal lobe make distinct contributions to cognitive processes (Stuss & Levine, 2002). Age has been reported to affect the structure of different frontal sub-regions differentially, though studies do not necessarily agree on which are most and least affected (Grieve, Clark, Williams, Peduto, & Gordon, 2005; Raz et al., 2010; Resnick et al., 2003). Age appears to exert partially independent effects on abilities that are thought to rely on different frontal regions (Kemp et al., 2012). As a consequence, factors that might determine the pattern and extent of age-related decline in frontal lobe structure and function could be of central relevance to developing therapeutic interventions.

One such determinant may be individual differences in exposure to glucocorticoids (GCs; cortisol in humans, corticosterone in rodents). Evidence from animal models and from humans with Cushing’s disease (which is characterised by hypercortisolaemia) suggests that chronic exposure to elevated GCs is deleterious to both brain structure and cognitive function (McEwen & Gianaros, 2010; Patil, Lad, Katznelson & Laws, 2007). In old age, there is increased variance in resting cortisol

levels that form part of the circadian rhythm, and in cortisol levels in response to stress (Heaney, Phillips, & Carroll, 2010; Otte et al., 2005), leading researchers to propose that elevated GCs facilitate structural and functional brain deterioration with ageing (Landfield, Blalock, Chen, & Porter, 2007; Sapolsky, Krey, & McEwen, 1986). Markers of chronic exposure to elevated cortisol have been linked to impaired cognitive abilities in old age in several studies (e.g. Lee et al., 2007; Lupien et al., 1994; MacLulich et al., 2005; O'Brien, Schweitzer, Ames, Tuckwell, & Mastwyk, 1994). Studies have focussed primarily on the negative relationship between GC levels, hippocampal structure and memory function, but more recently there has been interest in how GC levels in old age relate to the structure of the brain's frontal lobes (Kremen, Panizzon, Lyons, & Franz, 2010). Evidence, predominantly from rodent research, indicates that some frontal lobe sub-regions may be more susceptible to the damaging effects of elevated cortisol than others (Cerqueira, Mailliet, Almeida, Jay, & Sousa, 2007; Patel, Katz, Karssen, & Lyons, 2008), and elevated GC levels may also impair axonal repair (DeKosky, Scheff & Cotman, 1984; Scheff, Benardo, & Cotman, 1980). It is therefore possible that age-related decline in some cognitive abilities may be determined by the selective negative effects of elevated GCs on the integrity of frontal sub-regions and their connections to other brain areas.

However, in the human ageing literature there have been relatively few studies that have combined measures of cortisol levels with both estimates of frontal lobe sub-regional structure and cognitive measures. Of these, none have included manual volumetric measures of all frontal lobe sub-regions, measures of the integrity of major white-matter tracts, cognitive tests of social and emotional processing, nor



mediation analysis to formally test the hypothesis that brain structure mediates the relationship between cortisol and cognitive functioning in old age.

To address this gap in the brain and cognitive ageing literature, this thesis aims to examine relationships between cortisol levels and frontal lobe structure and function in a sample of 90 healthy, community-dwelling elderly men. The introductory chapters address methodological questions of measuring the functioning and volume of frontal sub-regions, and review previous findings relating to cortisol, brain structure and function in old age. Comparisons of a) automated versus manual frontal lobe parcellation techniques and b) cognitive measures from differential psychology versus neuropsychology address other relevant methodological issues. Next, covariance amongst cortisol levels, estimates of brain structure (frontal sub-regional volumes and DTI-derived tract integrity) and cognitive functioning are analysed. Finally, the hypothesis that measures of brain structure mediate the relationship between cortisol and cognition is tested formally. Given the study's cross-sectional nature and the homogeneity of participants' age, it is not possible to directly examine cortisol, cognition and brain structure in *ageing*; rather the interactions of these key variables *in old age* are characterised herein. Such correlational data are nevertheless useful in investigating the implications of causal hypotheses, and the novel scrutiny of covariances between white matter tracts, manually-parcellated frontal lobe sub-regions, detailed cognitive test scores and both reactive and diurnal cortisol measures offer unique insights into cortisol as a potential determinant of cognitive ageing.

## Chapter 2: Frontal Lobe Functions

Some of the work presented in this chapter is based on the forthcoming volume, which aims to review the evidence for sub-regional specificity of numerous neuropsychological tasks:

Della Sala, S., MacPherson, S.E., Cox, S.R., Girardi, A. & Iveson M. (forthcoming). *Handbook of Frontal Lobe Assessment*, Oxford University Press, UK.

The frontal lobes are a structurally and functionally complex region of the brain. The complex cognitive abilities this brain region affords are thought to be the seat of that which truly differentiates humans from other members of the animal kingdom (Stuss & Levine, 2002). Thanks to the wide range of cognitive abilities this brain region facilitates, humans are able to function within complicated social environments, organise and monitor thoughts and actions against a backdrop of competing demands, and integrate sensory input from multiple modalities in order to guide decision-making. Increasing age is associated with reductions in overall brain volume, (Resnick et al., 2000; Scahill et al., 2003) and poorer white matter integrity (Charlton et al., 2006; Pfefferbaum & Sullivan, 2003), and it appears that the frontal lobes and their putative cognitive functioning seem to exhibit greater decline than most regions with ageing (Haug et al., 1983; Tumeh et al., 2007). Though the onset and speed with which this occurs seem to vary between individuals, determinants of cognitive ageing remain elusive for the most part. A decrement in complex cognitive abilities has an undeniable impact on quality of life and independent living. Thus, identifying potential determinants of such decline is of undoubted benefit in the search for therapeutic and clinical interventions which might forestall cognitive ageing, increase quality of life and prolong independent living.

However, conceiving of the frontal lobes as a single entity subserving a unitary function is untenable in the face of the large body of evidence discussed herein, which has clear implications for the study of influential or explanatory factors in cognitive ageing research. Rather, our anterior cortex can be parsed into several sub-regions based on neuronal density, presence of granule cells, glia content and different afferent and efferent connectivity (Zald, 2007), phylogenetic development

(Sanides, 1969) and function (Phillips, MacPherson, & Della Sala, 2002; Stuss & Levine, 2002). Furthermore, studies examining change to brain structure repeatedly report that in pathology or normal ageing, frontal lobe decline does not appear unitary. For example, atrophy in the frontal variant of frontotemporal dementia (fvFTD) is thought to progress to dorsal and lateral frontal regions (Diehl et al., 2004; Ibach et al., 2004; Salmon et al., 2003), and anterior temporal and ventral frontal regions are thought to be more susceptible to decline in semantic dementia (Brambati et al., 2009).

During the normal ageing process, several reports observe divergent patterns of volumetric change over time for different frontal regions, though the findings are not always consistent. For example, several reports suggest that the lateral frontal lobe exhibits greater volumetric decrease with age than other frontal regions (Burzynska et al., 2012; Driscoll et al., 2009; Fjell et al., 2009; Grieve et al., 2005; Raz et al., 2005) whilst others identify predominantly orbital and medial frontal decline (Resnick et al., 2003). A recent semi-longitudinal study examined the change in sub-regional brain volumes at three time periods over 30 months across a broad age-range (49-85 years). They reported significant and widespread individual differences in the change of frontal sub-regions over the lifecourse, and this heterogeneity appears to intensify with age (Raz et al., 2010), which raises a number of questions regarding the determinants and functional sequelae of such change<sup>1</sup>.

It is logical to assume that age-related decrements in frontal sub-regions will also have a functional impact. While frontal lobe regions are by no means the only

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<sup>1</sup> It is likely that differences in brain imaging analysis techniques partially contribute to the inconsistencies in this literature - these are discussed in the following chapter in more detail.

brain areas to exhibit decline (which then contributes to cognitive performance)<sup>2</sup>, there have been several reports that functions thought to be subserved by the dorsolateral prefrontal cortex (DLPFC) exhibit decline more rapidly than those that rely on the orbitofrontal cortex (OFC) which remain relatively unchanged, or even improve (Happé, Winner, & Brownell, 1998; Keightley, Winocur, Burianova, Hongwanishkul, & Grady, 2006; MacPherson et al., 2002; Maylor, Moulson, Muncer, & Taylor, 2002). However, others have identified age-related cognitive decline in both tasks tapping the OFC and DLPFC (Lamar & Resnick, 2004; Resnick, Lamar, & Driscoll, 2007). A recent review suggests that there is at least some age-related decline in social cognition (an ability generally associated with the OFC), but that this decline appears to be at least partially independent of a decline in general cognitive function and executive abilities (primarily thought to tap the DLPFC; Kemp, Després, Sellal, & Dufour, 2012). Thus, it does not appear that the frontal lobes unitarily decline with age. Was this the case, one would expect general and concomitant decline in all frontal sub-regions and all relevant cognitive abilities. Rather, the current evidence suggests partially unrelated decline in frontal sub-regional structure and function with increasing age. Such variability in both structural and functional decline could well be driven by individual differences in exposure to a multitude of environmental and genetic risk - or protective - factors that could exert region-specific influences in deterioration over the lifecourse. The remainder of this chapter will focus on the fractionation of the frontal lobes and the evidence that some cognitive tests are sensitive to frontal sub-regional function.

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<sup>2</sup> Declines in white matter integrity are greater in anterior than posterior regions with age (Head et al., 2004).

## 2.1 Differentiation of the Frontal Lobe Regions

Cellular, evolutionary and connective characteristics consistently differentiate the same broadly-circumscribed frontal lobe sub-regions. A brief overview of such differences sheds light on the biological plausibility of theorised functional divisions (as physical properties must have implications for processing capabilities) and susceptibility to factors of epidemiological significance. Frontal lobe sub-regions are most commonly differentiated using the nomenclature of Brodmann (1909)<sup>3</sup> who identified numerous cortical sub-fields based on cytoarchitectural differences.

Frontal lobe sub-regions are often referred to as sub-groupings of these fields, such as the dorsolateral prefrontal cortex (DLPFC) which comprises Brodmann's Areas (BAs) 9 and 46, the anterior cingulate cortex (ACC; BAs 24, 25, 32 and 33), the inferior frontal gyrus (IFG; BAs 44,45 and dorsal parts of 47), the orbitofrontal cortex (OFC; BAs 11,12,13,14 and ventral parts of 47) and the frontal pole (BA10; Devinsky, Morrell & Vogt, 1995; Pandya & Yeterian, 1996; Rajowska & Goldman-Rakic, 1995; Uylings et al., 2010). Primary motor (BA4), supplementary motor regions (BA6) and the frontal eye fields (BA8) are also part of the frontal lobe as they are all situated anterior to the central sulcus, but tend to be excluded from the more anterior 'prefrontal' definition (Semendeferi et al., 2001)<sup>4</sup> as they are not

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<sup>3</sup> This is in spite of the advantages that more recent systems may confer, such as that of von Economo and Kosinas (Triarhou 2007a, 2007b) or Campbell (who combined neuro and myeloarchitecture; ffytche & Catani, 2005), flaws in the objectivity and reproducibility of Brodmann's map (Baliey & von Bonin, 1951 cited in Zilles & Amunts 2010) and the absence of information on intersubject variability or how cellular fields relate to intrasulcal cortex. Nevertheless, it has been adopted as the default framework when attempting to link functionally relevant information (such as lesion location, functional activation or target of stimulation) to cortical loci for cross-study comparison, and so will be adopted in this thesis.

<sup>4</sup> However, it is important to note that the term prefrontal has also been taken to additionally exclude BAs 44 & 45 (Malloy et al., 1993) or include BA 8 (Rolls, 2004), and various other criteria for defining 'prefrontal' can be used (as discussed in Uylings, Groenewegen & Kolb, 2003).

thought to play a role in complex cognitive behaviour, decision-making, or moderating social behaviour.

Influential proposals of frontal lobe sub-divisions have been influenced by cellular structure, anatomical connectivity and functionality (DLPFC, OFC, ACC from Stuss & Benson, 1986; DLPFC, OFC and ACC from Fuster, 1997, 2001; supplementary motor, frontal eye fields, DLPFC, OFC, ACC from Tekin & Cummings, 2002). It is notable that the frontal pole and IFG are not considered distinct in each of these schemas, and the central focus on DLPFC, OFC and ACC is relatively dominant in the brain sciences. Perhaps as a result, comparatively little work has centred on the development of tasks sensitive to frontal pole functioning; this can be partially ascribed to the fact that functional imaging studies implicate this part of the brain in a wide range of cognitive abilities, confounding assessment of its specific functional contribution (reviewed in Burgess, Simons, Dumontheil, & Gilbert, 2006; and in Gilbert et al., 2006). In fact, very little work on fronto-polar function has been conducted outside the research group of Burgess and colleagues, and tasks that produce activations in the scanner do not always relate to tasks that can be easily administered in patient assessment. Lesions to the IFG have been linked with language deficits such as speech articulation, but it may be difficult to gauge fine-grained individual differences in articulation that could exist in healthy ageing individuals (with whom the current thesis is concerned). Functional imaging studies implicate the IFG as part of a mirror-neuron system (Gallese, 2007), reporting activity during the imitation and viewing of emotional faces (Dapretto et al., 2006), but cognitive tests that allow such abilities to be directly quantified and related to brain integrity are scarce. For example, it was recently reported that only one

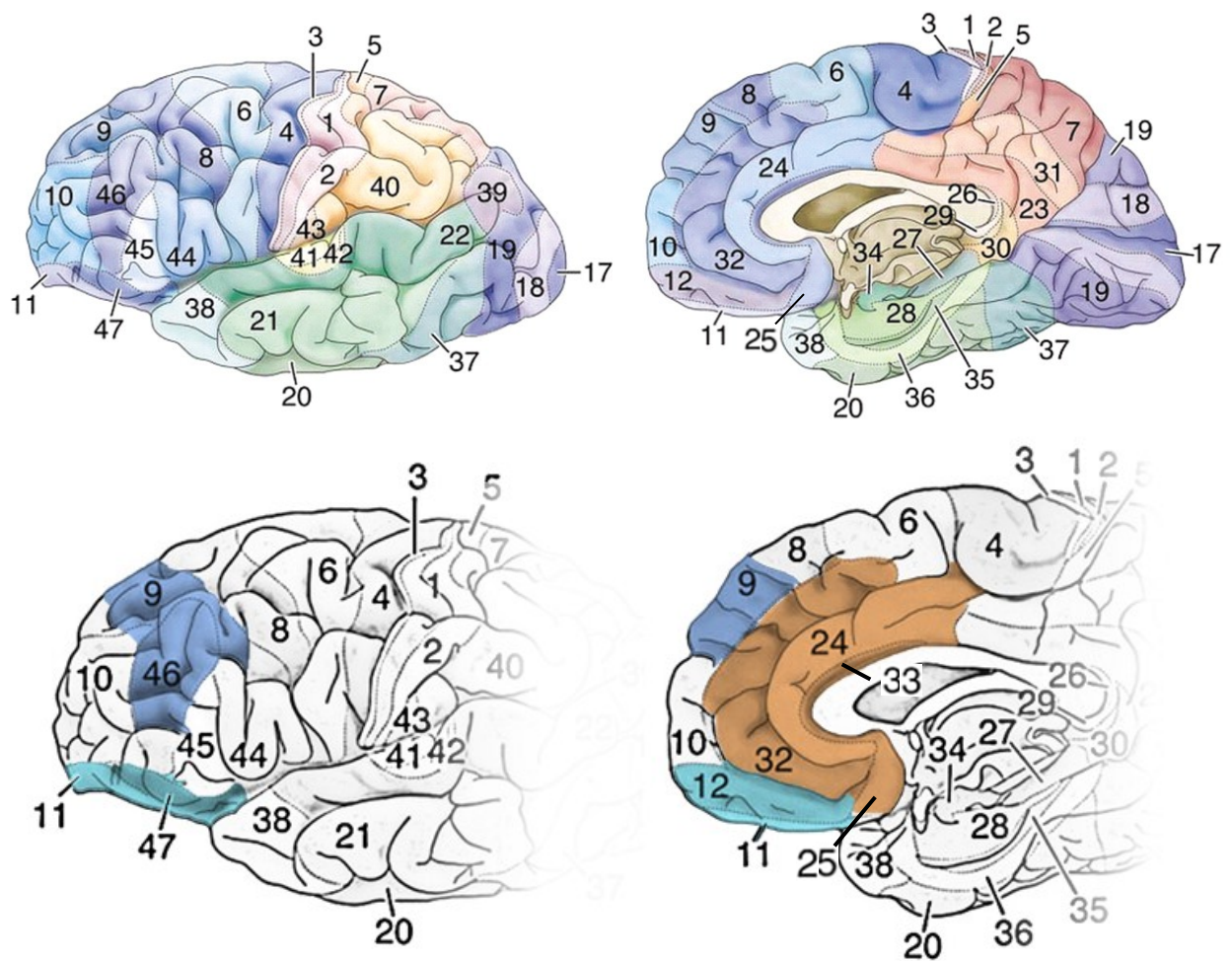
measure has demonstrated a double-dissociation between IFG and ventro-medial<sup>5</sup> lesions for different aspects of empathy (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). The absence of relatively pure fronto-polar or IFG lesions<sup>6</sup> may also have hindered the testing of well-established neuropsychological tests on FP and IFG patients. This also considerably limits our ability to a) rule out possible functional contributions of these regions to task performance and b) identify tasks sensitive to the FP or IFG to the exclusion of the DLPFC, OFC and ACC. Consequently, the following chapter will concentrate predominantly on the differentiation between the DLPFC, OFC and ACC.

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<sup>5</sup> The ventromedial prefrontal cortex (VMPFC) is a term often used in the neuropsychology literature to refer to both orbital and medial frontal regions, though it is often not explicitly defined in terms of BAs. In this thesis, VMPFC refers to the OFC and ventral portions of the anterior cingulate and frontal pole.

<sup>6</sup> And an ability to accurately identify the frontal pole in MRIs as this region has no clear topographical boundary (John et al., 2006; 2007 – discussed in the next chapter).

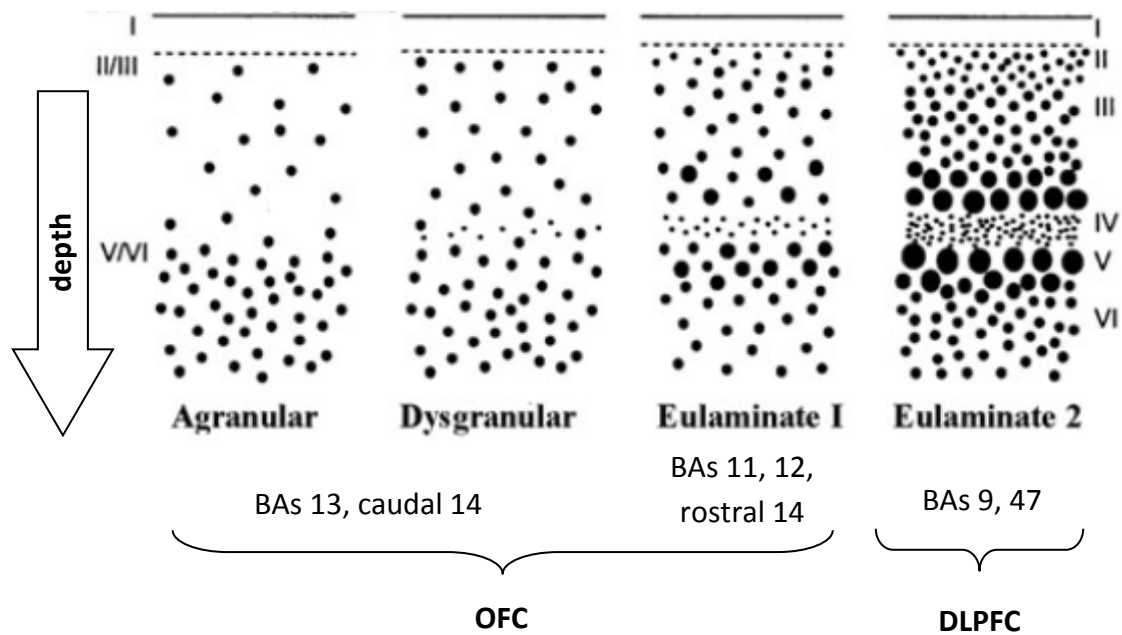




*Figure 2.1.* Top row: Brodmann's areas mapped onto lateral (left) and medial (right) views of the cortex. Bottom row: The dorsolateral prefrontal cortex (Blue; areas 9 & 46), anterior cingulate cortex (Orange; areas 24,25,32 & 33) and orbitofrontal cortex (Cyan; areas 11, 12, 47 – areas 13 & 14 not shown) marked on lateral (left) and medial (right) views of the frontal lobe. Image adapted from Tamminga (2004).

### 2.1.1 *Cytoarchitectural differentiation of frontal lobe sub-regions*

Structurally, the layers of the dorsolateral prefrontal cortex (DLPFC) exhibit a greater degree of granularity (6 layered granular cortex – eulaminate II; Figure 2.2) than those of the orbitofrontal cortex (OFC; mainly agranular, dysgranular and partially eulaminate I), as well as greater neuronal density and number (Dombrowski, Hilgetag & Barbas, 2001; Petrides & Mackey, 2006; Price, 2006). The pyramidal neurons of the DLPFC notably exhibit prevalent horizontal intrinsic axon projections – this has been proposed to form the neural substrate of working memory by sustaining persistent firing within the same cortical area (Gonzalez-Burgos et al., 2000; Wang et al., 2004; Zald, 2007). Fronto-polar neurons are relatively sparse in relation to the rest of the frontal lobe (Petrides & Pandya, 2004), and exhibit extensive dendrite arbours which might indicate a disposition for highly integrative processing (Jacobs et al., 2001). The ACC is notable by its lack of a fourth cortical layer, and its well-developed layer 5 that contains a distinctive type of spindle neuron (Betz, 1874; Ramon Y Cajal, 1900; von Economo & Koskinas, 1925; Nimchinsky et al., 1995) found predominantly in the ACC and frontal insular in humans (Seeley et al., 2012). Later called von Economo neurons, their large size and single basal dendrite may facilitate the rapid relay of simple signals to other brain regions, and therefore may allow fast intuitive assessment of complex situations (Allman, Watson, Tetreault, & Hakeem, 2005). In more posterior portions of the ACC, gigantopyramidal cells (which are essentially motor neurons), are involved in fine motor control (Allman, Hakeem, & Watson, 2002).



*Figure 2.2.* Cortex layer density and definition differences between orbitofrontal (OFC) and dorsolateral prefrontal cortex (DLPFC). Cortical layers are numbered I-VI in order of depth, BA: Brodmann Area. Figure adapted from Dombrowski et al. (2001).

### *2.1.2 Evolutionary segregation of frontal lobe sub-regions*

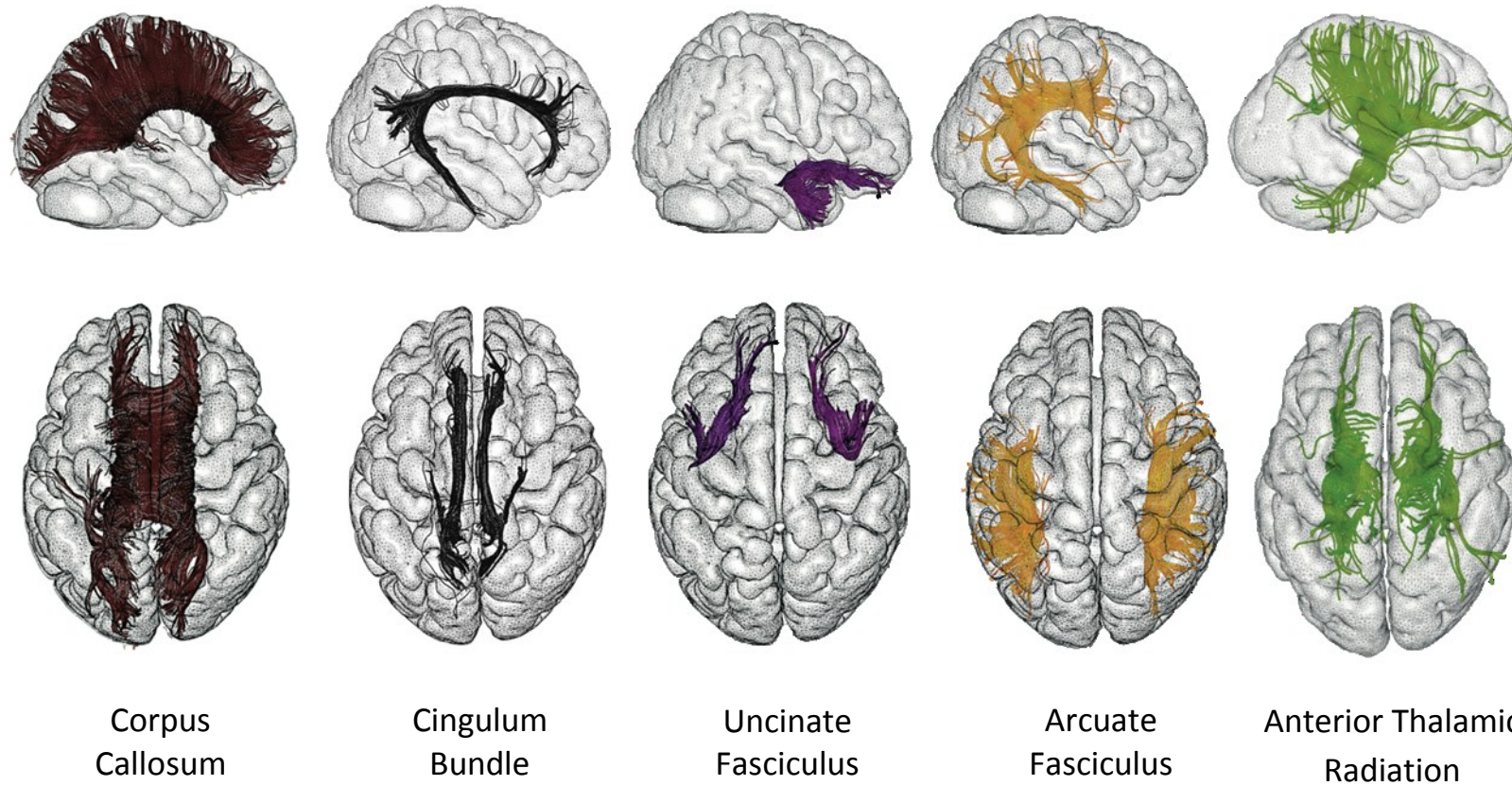
Evolutionary theory segregates frontal lobe regions as having emerged as the product of different phylogenetic trends (Sanides, 1969). According to this theory, the dorsolateral region evolved from the hippocampal or ‘archicortical’ trend and includes the hippocampus, cingulate gyrus and DLPFC with increasingly developed isocortex. Meanwhile, the orbitofrontal cortex is thought to have developed from the more primitive olfactory cortex with higher levels of complexity in the insula and OFC. Though Sanides (1969) suggests that the ACC is a more primitive part of our cerebral phylogeny, Allman and colleagues (2005) disagree. They argue that convergent evidence shows the ACC has undergone recent neocortical specialization

that allows a type of widespread connectivity with other brain regions present only in our most recent ancestors, indicating recent highly-selective evolutionary pressure. The frontal pole, although not a unique specialization of great apes and humans, is significantly larger in proportion to brain and frontal lobe size in humans when compared to apes. It is also subject to an increase in connectivity with higher-order association areas, compared to any other primate (Semendeferi, Armstrong, Schleicher, Zilles, & Van Hoesen, 2001).

### *2.1.3 Hodological differentiation of frontal lobe sub-regions*

Different areas of the frontal cortex have divergent profiles of connectivity with other brain regions; this is likely to constrain the types of information processing each region performs, offering another way in which frontal sub-regions can be differentiated (Barbas, 2000; Zald, 2007). The lateral PFC is connected to premotor regions via the superior and inferior frontal portions of the longitudinal fasciculus, which run parallel to the superior and inferior frontal sulci (Catani et al., 2012), and these branches of the fasciculus extend posteriorly to form long-range connections with the parietal lobe (de Schotten, Dell'Acqua, Valabregue, & Catani, 2012). Furthermore, a dorsal projection that arcs around the Sylvian Fissure connects temporal, parietal and lateral frontal regions. The OFC receives inputs from the amygdala, hippocampus, olfactory cortex and insula, along with auditory and visual information from temporal and occipital cortices via the uncinate and inferior fronto-occipital fasciculi (Catani et al., 2012; Catani & Thiebaut de Schotten, 2008; Petrides & Pandya, 2004; Yeterian Pandya, Tomaiuolo & Petrides, 2012). The ACC is

densely interconnected with most parts of the frontal cortex (Barbas, 1995) although it has become clear that dorsal regions of the anterior cingulate preferentially connect with dorsal frontal cortex, posterior regions are intimately associated with motor and pre-motor cortex, and anterior ventral regions with the OFC (Beckmann, Johansen-Berg, & Rushworth, 2009; Yeterian et al., 2012). Via U-shaped fibres from the cingulum bundle that, like the cingulate cortex, loop around the corpus callosum, the ACC is also connected to parietal, occipital and temporal lobes, including radiations into the parahippocampal gyrus (Catani & Thiebaut de Schotten, 2008; Mufson & Pandya, 1984). Furthermore, the OFC, ACC, and lateral PFC can be differentiated on the basis of their distinct connections to the mediodorsal nucleus of the thalamus (Klein et al., 2010). Figure 2.3 and Table 2.1 illustrate the pathways of major frontally-projecting white matter tracts in the brain.



*Figure 2.3.* 3D renderings of major long-range white matter tracts that extend to the frontal lobes. Lateral view (top row) and dorsal view (bottom row). Note that the anterior thalamic radiation is the anterior-most portion of the corona radiata (green). Composite image created from Catani & de Schotten (2008).

*Table 2.1.* The pathways of major long-range white matter tracts with frontal lobe connectivity.

<b>Tract</b>	<b>Connecting</b>	<b>References</b>
Corpus Callosum – Genu	Anterior right and left hemispheres (Prefrontal/premotor/supplementary motor)	Barbas & Pandya 1984 Catani & de Schotten 2008 Wakana et al. 2004
Corpus Callosum - Splenium	Posterior right and left hemispheres (Parietal/temporal/occipital)	Catani & de Schotten 2008 Seltzer & Pandya 1983 Wakana et al. 2004
Cingulum	Cingulate gyrus/ prefrontal & parietal cortices Retrosplenial cortex/parahippocampal gyrus	Catani & de Schotten 2008 Mufson & Pandya 1984 Wakana et al. 2004
Uncinate Fasciculus	Orbital frontal cortices with superior temporal gyrus	Catani & de Schotten 2008 Martino et al., 2011 Petrides & Pandya 1988 Wakana et al. 2004
Arcuate Fasciculus	Connects lateral frontal, parietal and temporal lobes	Catani & de Schotten 2008 Martino et al., 2011 Wakana et al. 2004
Anterior Thalamic Radiation	Anterior part of the internal capsule/corona radiata which is a major efferent tract carrying fibres between the PFC and thalamus. The anterior thalamic nucleus receives afferents from the hippocampus and anterior projections extend predominantly to the cingulate cortex and lateral PFC.	Catani & de Schotten 2008 Kahle et al., 2002 Wakana et al. 2004 Zhou et al., 2003

#### *2.1.4 Functional differentiation of frontal lobe sub-regions*

The distinct neuroanatomical characteristics of frontal sub-regions are likely to have implications for both their susceptibility to biological mechanisms responsible for decline in age, but also their processing capabilities. Indeed, these regional differences in structure are broadly concomitant with the general view of functional segregation within the frontal lobes that has arisen in neuropsychology. Convergent evidence from electrophysiological, lesion and functional imaging studies have been central to attempts to localize function, such that the combined strengths of each method can mutually outweigh their individual limitations to some extent. For example, the majority of electrophysiology work is conducted in animals, making the homologue of any observed effects difficult to identify (Michael Petrides, Tomaiuolo, Yeterian, & Pandya, 2012). Functional imaging studies that exploit magnetic inhomogeneities due to metabolism of oxygen or glucose can identify which areas of the brain might be involved in a particular task, but not which are necessary (Stuss & Levine 2002; Logothetis, 2008). Lesion studies are better situated to suggest which brain regions are necessary for performance, but there are several issues with this method too. Firstly, the locations of damage do not observe cellular or functional boundaries and therefore are often difficult to accurately categorise. Secondly, damage can arise via a number of different aetiologies which can add subtle complications to identifying which brain areas are affected. Thirdly, patients almost always lack pre-morbid cognitive measures. Finally, lesion groups in neuropsychological research are often categorised by the cortical area predominantly affected, and little consideration is (or necessarily can be) taken of the extent to which white matter is also damaged. As previously discussed, the network of short



and long-range connective fibres contained therein also facilitates information transfer between regions not necessarily related to the damaged cortical site – thus adding an additional level of complexity to lesion study interpretation.

However, neuropsychologists have been able to construct a picture of broad functional specificity by triangulating the recordings of individual or small fields of cells, larger-scale relationships between regional metabolic activity and cognition, and the effects of direct cell damage on behaviour, whilst acknowledging the inferential restrictions any single method may impose. In keeping with the dense reciprocal interconnectivity within the frontal lobes and their role as only one component in a distributed set of large-scale brain networks that facilitate complex cognition (Bressler & Menon, 2010; Mesulam, 1990), there are probably no behavioural measures that can exclusively tap the functioning of one region alone. However, a review of the current literature suggests that tasks do exist which may be more sensitive to the dysfunction of one frontal region than another, though how best to quantify the behavioural sequelae of region-specific insult within the frontal lobes is the subject of ongoing debate. A critical appraisal of the regional sensitivity of some promising paradigms follows.

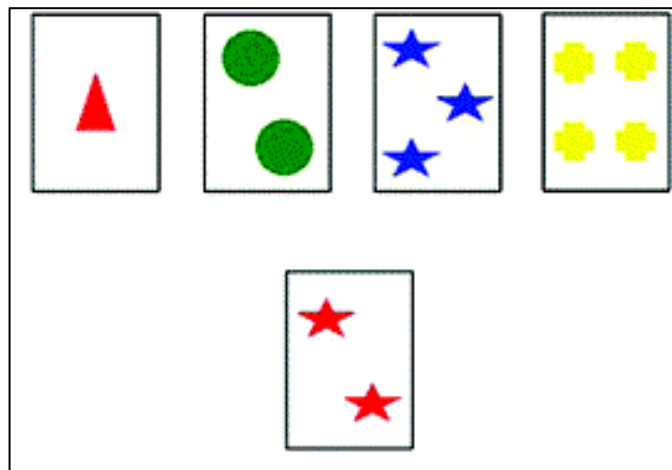
## 2.2 Dorsolateral Prefrontal Cortex

In line with its structural and connective features, the DLPFC has been consistently linked with working memory; that is, the ability to temporarily store and manipulate information (Logie, 1995). Tests that involve planning or monitoring behaviours are thought to rely heavily on this ability, and there is strong evidence from neuropsychology (in addition to the structural and connective evidence above) that the DLPFC is specialised for subserving this function. For example, DLPFC lesions impair the ability of primates (reviewed in Rodriguez & Paule, 2009) and humans (D'Esposito & Postle, 1999; Vérin et al., 1993) to hold the location of a target in mind for a short delay before making a response. Cells in the monkey DLPFC are most active during the delay between cue and response (Funahashi et al., 1993).

### *2.2.1 The Wisconsin Card Sorting Test (WCST; Grant & Berg, 1948, later modified by Nelson, 1976)*

This is a commonly-used test of set-shifting, requiring the participant to identify abstract categories and flexibly adjust their behaviour. In this complex test, the participant is given a pack of cards that contain designs which vary by 3 dimensions (colour, form and number). The participant must sort the cards they are given onto four key cards. These cards are deliberately ambiguous such that a card could share features in common with more than one key card, but the sorting criterion (based on either colour, or form, or number) is not made explicit (Figure 2.4). Rather, they must ascertain the sort rule via feedback from the experimenter. Once they have demonstrated they have correctly sorted a number of cards, the sort rule is changed.

A meta-analysis of 1,349 participants reported that WCST performance was significantly more impaired in participants with frontal damage than those with lesions to other non-frontal regions (Demakis, 2003). Regarding sub-regional specificity with the frontal lobes, participants who underwent DLPFC excisions showed impairment on this task compared to controls and those with ventral and medial frontal surgery (Milner, 1963). More recently, other reports also suggest that WCST performance is significantly impaired following lesions to the DLPFC, but not VMPFC (Bechara et al., 2001; Stuss et al., 2000).



*Figure 2.4.* A schematic of the Wisconsin Card Sorting Test, in which the participant must deduce the appropriate sort rule that pairs their current card (bottom row) with the key cards (top row) based on feedback from the researcher. Image reproduced from Deveney & Deldin (2006).

However, others report that DLPFC lesions do not necessarily impair WCST performance (Anderson, Damasio, Jones & Tranel, 1991; Golstein et al., 1993), and

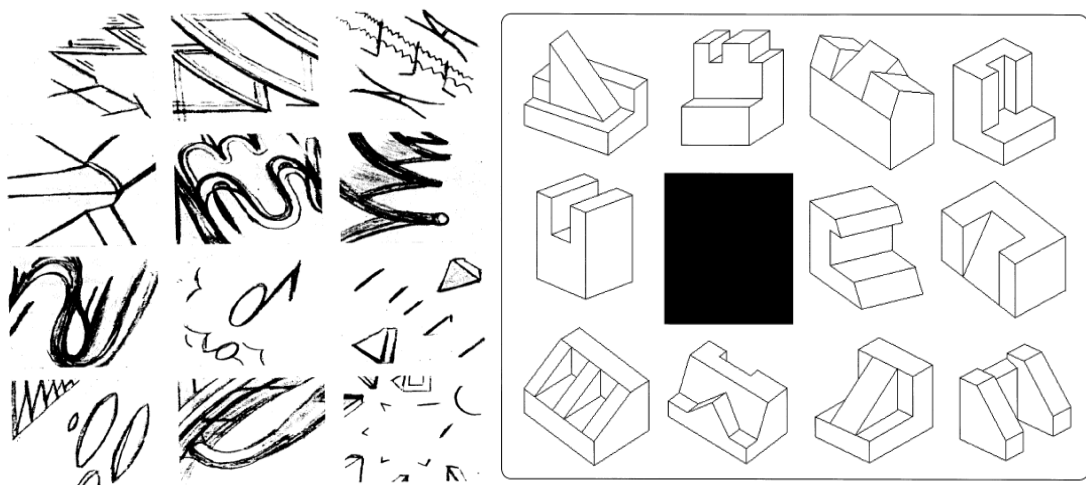
that additional damage to the ACC (Barcelo & Knight, 2002; Burzynska et al., 2012; Sarazin et al., 1998) and to the VMPFC can also impair task performance (Davidson, Gao, Mason, Winocur, & Anderson, 2008; Dias, Robbins, & Roberts, 1997; Stuss et al., 2000). Although it is likely that damage to other frontal regions impairs task performance by other cognitive mechanisms, such as decreased behavioural inhibition or sensitivity to negative or rewarding feedback (Dias et al., 1997; Stuss et al., 2000), it is difficult to conclude that the WCST is sensitive to selective DLPFC damage.

Functional imaging research corroborates the involvement of the DLPFC to some degree, but here too there are inconsistent findings. DLPFC activity has been reported in some studies during the WCST (Marenco, Coppola, Daniel, Zigun, & Weinberger, 1993; Rezai et al., 1993), but not in others (Berman et al., 1995; Cantor-Graae, Warkentin, Franzen, & Risberg, 1993; McDonald et al., 2006; Nagahama, Okina, Suzuki, Nabatame, & Matsuda, 2005). A meta-analysis of functional neuroimaging during WCST performance identified activity in both the DL and orbitofrontal regions (Buchsbaum, Greer, Chang, & Berman, 2005). The authors acknowledge the complexity of the task by examining various phases such as set-shifting and receipt of feedback which are likely to engage different cognitive processes. When they examined the set-shifting phase of the task in particular, they found increased activity in DLPFC, OFC and ACC. The effect of negative feedback during this task has recently been linked to increased activity in the DLPFC and ACC (Wilmsmeier et al., 2010) and VMPFC activity (Provost, Petrides, Simard, & Monchi, 2012). Thus, the task as a whole appears to lack sub-regional specificity; poor scores on the task can be attributed to decrements in various parts of cognition,

but it is still contentious which patterns of performance should be predominantly ascribed to which frontal sub-regions (Nyhus & Barceló, 2009).

### 2.2.2 Self-Ordered Pointing Task (Petrides & Milner, 1982)

The Self-Ordered Pointing Task (SOPT) is commonly used as a test of working memory and monitoring (Michael Petrides & Milner, 1982). Participants are presented with an array of items (such as words or pictures), and should select an item from the array they have not previously chosen (Figure 2.5). After each selection, the configuration in which the items are presented is re-arranged, forcing participants to remember the details of the items they have chosen, rather than the locations of their previous choices. The number of items displayed determines the number of selections participants are required to make before the trial ends (e.g. 8 items, 8 selections), and task difficulty can be manipulated by altering the array size, thus increasing the number of items to be stored in working memory. The main outcome measure is the number of times a previously-chosen item is selected, although reaction times may also be measured.



*Figure 2.5.* Examples of stimuli used in the Self-Ordered Pointing Task. The left panel shows the abstract designs used in Petrides and Milner (1982). The right panel shows 3D line drawings, and the previous locus of selection blocked out, used by Curtis et al. (2000).

Early Positron Emission Tomography (PET) research suggests that the DLPFC is predominantly involved in performance of this task; a study of healthy males found that the mid-DLPFC (BA 46) and dorsal ACC (dACC; BA32) was significantly more activated during the SOPT when compared to a task where pointing location was cued by the experimenter (Petrides, Alivisatos, Evans, & Meyer, 1993). Similarly, a more recent PET study reported a significant increase in rCBF in the right DLPFC (BA9/46) during an object-based SOPT. The task used here differed slightly to the standard SOPT in that it consisted of 11 monochrome 3D shapes, rather than abstract designs, which changed position after each selection. Importantly, the authors attempted to address the problem of participants' perseverative selection of the same location, which takes advantage of the position changes of the stimuli after each selection. By presenting a black square to mask the location of the previous choice, participants were no longer able to exploit this. Unlike the SOPT used by Petrides and colleagues (1993), this task elicited additional activations bilaterally in the fronto-marginal gyrus (BA 10/11) and left dACC, although only dorsolateral activations correlated strongly with task performance (Curtis, Zald, & Pardo, 2000).

In another variant of this task from the Cambridge Automated Neuropsychological Test Automated Battery (CANTAB; Owen, Downes, Sahakian, Polkey, & Robbins, 1990), participants are required to search for tokens in a series of boxes. Participants should avoid searching in a previously-selected box, and

therefore in this task it is the spatial location rather than the object-specific features that are to-be-remembered. Similar to the Petrides & Milner task, functional neuroimaging during performance of this CANTAB task identifies activation in the lateral prefrontal cortex and anterior cingulate regions (Owen, Doyon, Petrides, & Evans, 1996).

One structural study explored associations between the brain volumes of frontal regions and SOPT performance amongst a group of psychiatric outpatients with affective disorders (McLaughlin, Moore, Fulwiler, Bhadelia, & Gansler, 2009). The authors found a positive relationship between the volume of both right and left mid-DLPFC and SOPT repetitions, and no such relationship for the ventrolateral regions of interest. However, with no control group against which to compare the ROI volumes and cognitive performance, it is unclear whether or not findings relating SOPT ability with DLPFC size extend to a healthy population.

Evidence that the DLPFC is necessary for normal SOPT performance comes from several lesion studies. The performance of patients with unilateral frontal damage that mainly affected dorsolateral areas was compared to that of patients with temporal lobe damage and healthy controls. Participants were tested on four different self-ordered tasks, each using different types of stimuli (abstract images, representational drawings, high imagery and low imagery words), with the dorsal frontal group having performed significantly more poorly on each task (Petrides & Milner, 1982). Compression of the DLPFC via hyperostosis frontalis interna has also been reported to impair performance on self-ordered pointing tasks relative to controls (de Zubizaray, Chalk, Rose, Semple, & Smith, 1997), although both this

single case study and the previous report lack explicit comparison with other non-DLPFC frontal lesion groups.

Manes and colleagues (2002) undertook such a study using the CANTAB version of the SOPT, in which a group with circumscribed lesions involving the orbitofrontal areas was unimpaired relative to controls, whilst a dorsolateral group performed significantly more poorly than their OFC counterparts. A separate study also found that a patient group mainly involving DLPFC lesions performed significantly more poorly than an OFC group on the CANTAB task by returning to previously-chosen locations which did not contain a token (Berlin, Rolls, & Kischka, 2004). It is important to note however, that the OFC group were more likely to perseveratively return to boxes that had previously contained a token. This finding is likely to represent different forms of impairment on this particular task and highlights the difficulty in devising a test that can parse apart cognitive components. On the one hand, it is likely that the DL group performance was due to impairments in working memory and monitoring, whereas the behaviour of the OFC group suggests that they were unable to flexibly re-assign reward contingencies. As a result, it is possible that the presence of reward feedback in the form of a token may have implications for orbitofrontal processing, in contrast to the general absence of feedback during the Petrides & Milner version of the task.

### *2.2.3 The Tower Test*

This group of tasks is known under various names such as Tower of London (ToL; Shallice, 1982), Tower of Hanoi (ToH; Byrnes & Spitz, 1977), the Stockings of



Cambridge (SOC), the Delis-Kaplin Executive Function System (D-KEFS; Delis, Kaplan & Kramer, 2001) Tower. Items such as balls or discs are arranged in several locations, and must be manipulated (either manually or on a computer) from location to location in order to configure them into a target arrangement (Figure 2.6). The manipulations are subject to a set of rules that are explicitly outlined to participants at the start of the test (and should be clearly displayed throughout testing to reduce memory influences on performance). Deficits in planning and working memory ability are thought to be the predominant contributors to poor ToL performance. Early lesion studies demonstrated the sensitivity of this task to frontal lobe pathology (Shallice, 1982; Owen et al., 1990; Owen et al., 1995) and contemporaneous imaging studies suggested preferential recruitment of the frontal lobes during the performance of this task (e.g. Baker et al., 1996; Morris, Ahmed, Syed, & Toone, 1993). More recent convergent evidence points to the specific involvement of the DLPFC.



*Figure 2.6.* Various forms of the Tower test. Left: The Tower of London (Shallice, 1982); Middle: D-KEFS Tower, Right: Stockings of Cambridge (image from Feldman, Schuepbach, von Rickenbach, Theodoridou & Hell, 2006).

Although in essence the tower variants are all thought to tap planning and self-monitoring abilities (often related to the DLPFC), there are subtle differences between the tests that are worth noting. Tests such as the ToH and the D-KEFS Tower are similar in that they present participants with a series of discs of graded sizes and three pegs of uniform length. The rules are that you may only move one disc at a time, and a larger disc can never be placed on top of a smaller one. However, ToL and SOC-type tests provide pegs or ‘socks’ of differing length that can carry 3, 2 or 1 coloured balls of the same size, significantly reducing task difficulty. Some versions present initially simple problems requiring a small number of moves to achieve the goal before incrementally increasing the total minimum number of moves required, whereas others begin with a fully-constructed tower which has to be moved to a different location from the very first problem. Furthermore, some researchers include a planning phase in which participants are encouraged to either envisage the moves they plan to make in advance of carrying them out, or identify the minimum number of moves required to complete the task without physically attempting the problem. However, some evidence suggests that humans are not successful at planning ahead beyond a certain number of steps in this task (Phillips, Wynn, MacPherson, & Gilhooly, 2001), calling into question the validity of a planning phase for more complex problems.

The main outcome measure is the number of moves taken to achieve the target configuration (aggregated over a series of trials of increasing difficulty) and a broad time limit is often imposed, although the number of rule-breaks and time-to-completion have also been used as indices of performance. Further measures still can be calculated (such as mean first-move time or move-accuracy ratio) although it is

less clear from the literature how these metrics relate to frontal lobe metabolism and structural integrity. It has also been demonstrated that problem difficulty can be manipulated by the ambiguity of goal priorities (Newman, Greco, & Lee, 2009) – that is, in variants of the task such as the ToL and SOC, goal states can be complete towers (unambiguous), the three balls in separate ‘socks’ (ambiguous) or a partial tower. Ambiguous problems were shown to be more difficult than unambiguous problems, crucially whilst keeping the overall number of moves required at a constant level. As a result, the authors suggest that total number of moves should not be used as the only index of difficulty for relevant variants of this task.

Active clusters in the DLPFC during performance of tower tasks by healthy participants has been reported in numerous fMRI and PET studies with an equally consistent absence of orbital activation (Baker et al., 1996; Beauchamp, Dagher, Aston, & Doyon, 2003; Boghi et al., 2006; Cazalis et al., 2003, 2006; Dagher, Owen, Boecker, & Brooks, 1999; Dagher, 2001; den Braber et al., 2008; Elliott et al., 1997; Fincham, Carter, van Veen, Stenger, & Anderson, 2002; Fitzgerald et al., 2008; Just, Cherkassky, Keller, Kana, & Minshew, 2007; Lazon et al., 2000; Lazon, Rombouts, Scheltens, Polman, & Barkhof, 2004; Newman, Carpenter, Varma & Just, 2003; Newman et al., 2009; de Ruiter et al., 2009, Owen et al., 1998, 1996; Rasser et al., 2005; Rowe, Owen, Johnsrude, & Passingham, 2001; Schall et al., 2003; Unterrainer et al., 2004, 2005, Wagner, Koch, Reichenbach, Sauer, & Schlösser, 2006; van den Heuvel et al., 2003, 2005). The DLPFC is also known to receive extensive dopaminergic projections, and patient groups in which reduced dopamine is a defining characteristic have been shown to perform significantly worse than controls on the ToL (Culbertson, Moberg, Duda, Stern & Weintraub, 2004; Morris et

al., 1988; Owen et al., 1995, 1997). Indeed, one study examined the performance of PD patients on and off dopatherapy, and reported that the administration of dopatherapy significantly increased the BOLD response in the DLPFC and also significantly improved ToL performance (Cools, Stefanova, Barker, Robbins, & Owen, 2002). It is also proposed that there is some degree of hemispheric specialization, with the right side being involved in the planning aspects of the task, in contrast to the left side which is implicated in the execution of that plan (Newman et al., 2003; see Newman et al., 2009 for a review).

Tower performance does not appear to be affected by VMPFC lesions caused by aneurysms of the anterior communicating artery, which supplies blood to the ventral and medial PFC (Cicerone & Tanenbaum, 1997; Hornak, Rolls, & Wade, 1996; Mavaddat, Sahakian, Hutchinson, & Kirkpatrick, 1999). Conversely, patients with DLPFC lesions do exhibit deficits when compared to the performance of healthy controls (Gomez-Beldarrain, Harries, Garcia-Monco, Ballus, & Grafman, 2004; Mavaddat et al., 1999; Yochim, Baldo, Kane, & Delis, 2009), and those with orbital and ventromedial frontal lesions (Manes et al., 2002). However, two recent studies appear to contradict the assertion that DLPFC plays a central role in Tower performance. Vietnam veterans with either DL and VM lesions do not exhibit significant differences in their Tower overall score (Krueger et al., 2009), while others found that patients with right ventromedial lesions performed significantly worse than controls (Mazza et al., 2007). Interpretation of these findings should be undertaken with caution, given that the categorisation of ventromedial and lateral groups in the former study both explicitly included BAs 9 and 46, no tests were performed to compare performance of either group with controls. In the latter paper

too, their VM lesion groups included damage to BAs 10, 11, 12, 25 as well as 9 and 46.

As with other tasks, it is prudent to note that certain other brain regions are often identified as being involved in normal Tower performance. Activation of the dorsal ACC has been a relatively consistent finding in neuroimaging studies, consistent with its dense interconnectivity with DLPFC. For example, a study by Dagher et al., (1999) identified some additional task-related ACC activation, although this was shown to correlate with hand movements (right hemisphere; BAs 24 and 32) and task complexity (both hemispheres; dorsal area 24), both of which are certainly consistent with some of the proposed roles of the ACC, thanks to its dense connections with motor areas and its proposed role in autonomic regulation. Other studies have also attempted to explain reported ACC involvement by comparing the activation patterns of superior and normal performers (Cazalis et al., 2003, 2006). The authors found that only normal performers showed increased activation of the ACC. Beyond the frontal lobe, the basal ganglia has also been identified as a potential contributor to task performance (Beauchamp et al., 2003; Dagher et al., 1999; Newman et al., 2009; Rowe et al., 2001; van den Heuvel et al., 2003). Whilst it is currently unclear what contributions this region might make, it is thought to facilitate rule deduction and application during taxing reasoning tasks such as the tower (Melrose, Poulin & Stern, 2007; Newman et al., 2009).

## 2.3 Orbitofrontal Cortex:

Consistent with its architectural characteristics discussed in previous sections, the OFC is well-placed to integrate gustatory, olfactory, somatosensory, auditory and visual modalities from distributed brain regions, and feed the processed integration forward in order to guide future behaviour (Kringelbach, 2005). Animal models have demonstrated that neurons in the OFC are sensitive to the economic value of stimuli (Padoa-Schioppa & Assad, 2006)<sup>7</sup>, as well as proximity to reward during the learning of strategy implementation tasks<sup>8</sup> (Ichihara-Takeda & Funahashi, 2006; Simmons & Richmond, 2008), which would be necessary for tasks where the perceived valence of a given behaviour must be taken into account. Convergent evidence from electrophysiological, brain imaging and lesion studies suggests that damage to the OFC in monkeys and humans can impair the ability to flexibly alter their behaviour in response to a change in stimulus-reward associations (Rudebeck, Bannerman, & Rushworth, 2008). That is to say, it does not alter the ability to form stimulus-reward associations *per se*, but rather affects the flexible re-assignment of value to previously unrewarded stimuli (Izquierdo et al., 2004).

### 2.3.1 Reversal Learning Task (Rolls, Hornak, Wade, & McGrath, 1994)

In the reversal learning task, participants are presented with two options to choose between over a series of trials. One option is consistently associated with a reward,

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<sup>7</sup> Padoa-Schioppa and Assad (2006) found the *indifference point* for individual macaques by using the readings from OFC cell activity to inform them of the monkey's relative valuation of two different juices. This allowed them to manipulate the relative amounts of two juices on offer such that the subject was equally likely to choose either option.

<sup>8</sup> That is, when the subject must learn to switch strategies at a certain point based on reward feedback.

and the other with some form of punishment. Following selection of one of the options, feedback is given in the form of either reward or punishment dependent upon the selection made, and they must use this information to identify which option is the most beneficial choice in the next trial. Thus the first phase allows an initial stimulus-reward (S-R) association to be learned. Once a consecutive number of correct responses have been made (indicating encoding of the S-R relationship), this contingency is reversed, such that selecting the previously-rewarding stimulus now results in a loss or punishment. The main outcome variable is the number of trials it then takes for an individual to identify this reversal and correctly identify the new S-R association (indicated by a pre-set number of correct responses). Once this is achieved, the S-R association is switched again, and so on. In the original human version of this test (Rolls *et al.*, 1994), participants were then asked a series of questions at the end in order to gauge their understanding of the objectives:

*How could you gain and lose points in the test?*

*What were you thinking at the start of the test?*

*What happened later?*

Common variations of this task include the type of reward (virtual versus real money), type of images used, number of correct responses required for an S-R reversal, as well as the probability of each image giving a reward or punishment. For example, the original version reported by Rolls and colleagues has become known as

a deterministic contingency because one image will always be associated with a win, and the other will always be associated with a loss. However in probabilistic versions, the probability with which the stimuli will yield rewards and punishment can be manipulated, making the correct image (and the reversal itself) more difficult to detect. However, as a result of this more difficult version, longer training is often required.

The activity of cells in the OFC have been shown to be sensitive to changing reward contingencies; for example, recordings from the macaque OFC were shown to be sensitive to this reversal learning task, as cell-firing transferred from a previously rewarded stimulus to the newly rewarded one (Rolls et al., 1994; Thorpe, Rolls & Maddison, 1983). In humans, the first study to examine regional specificity of this task within the frontal lobes compared a group of 12 patients with ventral frontal lesions to 8 who had lesions outwith this area (including 2 with dorsolateral PFC damage; Rolls et al., 1994). Patients with orbital lesions were unable to alter their behaviour appropriately, contingent upon a change in stimulus-reward associations, when compared to a group of mixed non-orbital frontal lesions. In a deterministic version of the task, although the groups did not differ in their acquisition of the initial S-R relationship, the ventral patients took significantly more trials than their non-ventral counterparts to reach the criterion of 9 consecutive correct responses after the contingency first changed. The contribution of the OFC was replicated using a probabilistic task amongst patients with either orbital (BA10, 11, 12, 25) or dorsolateral and dorsomedial (BA9, 46/8, 9, 10) lesions (Berlin et al., 2004), where it was reported that the OFC group were shown to make more overall



errors (as measured by less money gained) and complete fewer reversals than either non-orbital or control groups.

The dissociation between the effects of dorsolateral and ventromedial damage on RL performance was explicitly studied using another deterministic task in which one pack of cards consistently concealed a \$50 win whilst the other yielded a \$50 loss (Fellows & Farah, 2005). Whilst both groups were comparable to healthy controls in their ability to identify the initial stimulus-reward acquisition, only the ventromedial group made significantly more reversal errors.

Using a probabilistic version of the test, another study compared the performance of groups with circumscribed surgical frontal lesions involving different frontal subregions (Hornak et al., 2004). The key finding was that individuals with unilateral orbitofrontal lesions performed as well as controls, whereas only bilateral orbitofrontal lesions (or those with dorsolateral lesions who did not attend to the crucial on-screen feedback) exhibited significantly poorer performance. Another study reported that a ventral group, where each patient had some degree of bilateral orbital damage, was impaired in terms of RL performance, and the authors ascribed the deficit to an inability to learn from specifically negative feedback (Wheeler & Fellows, 2008). Furthermore, performance by OFC patients on this task was compared to individuals with psychopathy (which is associated with ventromedial abnormalities; Shamay-Tsoory, Harari, Aharon-Peretz, & Levkovitz, 2010) and controls, and it was reported that both experimental groups showed a similar pattern of significant impairment in comparison to controls (Mitchell, Macrae, & Banaji, 2006).

Evidence from the domain of functional imaging also supports a central role of the OFC in reversal learning abilities. Using a probabilistic version of the task, in which the magnitude of the reward itself was also varied, significant activation of the OFC in relation to the receipt of a reward and punishment was reported (O’Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). Although some lateral PFC activation was also reported, it was shown that predominantly the OFC activation was positively correlated with the magnitude of the reward or punishment. The dACC was also reported to be activated in response to punishment and uncertainty, and this finding was replicated in another study, which also identified elevated VMPFC BOLD response on rewarding trials (Linke et al., 2010).

Significant activation of the lateral OFC has also been reported during acquisition of the new S-R contingency, i.e. when the participant changes response pattern (Cools et al., 2002)<sup>9</sup>. However, these studies have been criticised for their approach of *a priori* selected regions of interest and the absence of an affectively neutral baseline – rather, fMRI contrasts were based on trials within the same task, and so it could be argued that processing relevant to the reversal was continuing beyond the reversal trial itself (Remijnse, Nielen, Uylings, & Veltman, 2005). In an attempt to address these shortcomings, Remijnse and colleagues used a task in which participants were told in advance which selection to make, and were given neutral feedback (“selection made”). Using this as a contrast baseline, they observed activation in the DLPFC and anterior PFC in addition to the OFC, VMPFC and insula during general feedback processing, but only the OFC and ventral striatum

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<sup>9</sup> Cools et al (2002) were unable to image the most ventral parts of the OFC due to susceptibility artefacts.

were explicitly activated by reward and punishment, corroborating their role in the processing of valenced feedback (Remijnse et al., 2005).

The notion of the OFC as being dissociable from dorsolateral and dorsal cingulate regions during RL task performance has subsequently been supported (Ghahremani, Monterosso, Jentsch, Bilder, & Poldrack, 2010). In order to parse apart the neural correlates of reversal learning from those serving response inhibition, the authors compared frontal BOLD responses during a deterministic paradigm with those during the stop-signal task. The stop-signal task is a test of response inhibition, by requiring participants to respond as normal apart from trials on which they are presented with the stop signal (in this case, an auditory tone). While the OFC was engaged predominantly during reversal of learned associations (in line with its suggested role in reformulating S-R associations based on emotional valence), the dACC and IFG were activated in more general response inhibition and thus are likely to guide the specific actions required by the pertinent contingency. Likewise, Glascher, Hampton and O'Doherty (2009) demonstrated that the VMPFC is activated during reversal learning, irrespective of whether the required response is action-based or stimulus-based. When participants decided to change their behaviour from stay to switch, DL regions became significantly active as well as the OFC, possibly indicating a plan for the upcoming response which has been driven by identification of the extinct S-R contingency.

In an interesting variant of the reversal learning task, Kringelbach and Rolls (2003) presented participants with a choice between the faces of two individuals. Once selected, the individual either smiled or looked angry; the task of the participant was to keep track of the mood of both faces by selecting the happy person

as much as possible. The change in selection behaviour at reversal, cued by the angry face of the previously-happy person, was associated with activations in the OFC and dACC. Indeed, this was also the case when expressions other than anger were used to cue the reversal, suggesting that these areas may drive our ability to change behaviour in social settings.

It is therefore clear that the OFC is a key processing centre for the changing emotional valence of rewards and their effect upon subsequent behaviour. However, it is also one part of a much larger network of regions, each making a contribution to task performance either upstream or downstream (e.g. ACC, DLPFC and motor and pre-motor cortex, primary sensory areas, striatum, amygdala). Williams, Bush, Rauch, Cosgrove, and Eskandar (2004) demonstrate a central role for the dorsal ACC in integrating motor response with reward information. They showed increased firing of cells in human dorsal ACC in response to diminished reward during a variant of the RL task. Moreover, following cingulotomy the same patients make more response-selection errors than pre-surgery.

### 2.3.2 *Faux Pas task* (Stone, Baron-Cohen, & Knight, 1998)

One of the most prevalent theories regarding the emotional and social processes for which the OFC is necessary relates directly to those of reinforcement and reversal theory. The proposal is that social mistakes are made when an individual fails to correctly judge the potential social reward or punishment of a selected action (Kringelbach & Rolls, 2004). This view is well supported, not only by an

accumulation of data relating cells in the OFC with the encoding of stimulus-reward valence, but also evidence that OFC patients fail to recognise their own inappropriate behaviour compared to lateral frontal lesions (Beer, Heerey, Keltner, Scabini, & Knight, 2003; Beer, John, Scabini, & Knight, 2006) and fail to identify inappropriate behaviours in others (e.g. Happé, Malhi, & Checkley, 2001). An excerpt from Rolls et al., (1994) neatly illustrates socially inappropriate behaviours exhibited following orbital lesions:

*“Sexually explicit references, suggestive comments, or actual sexual advances were made to staff by cases 3, 8 and 10. Case 10 had also exhibited himself in the town centre. Cases 2 and 7 were overfriendly (case 7 swept a member of staff off her feet to hug and kiss her because he was in a good mood), case 3 was boastful, claiming he was more handsome and that his humour had improved since his accident (in fact his humour was childish and repetitive). Case 3 also tactlessly told a member of staff she was much less pretty than someone else. Case 4 practised karate kicks in the canteen and mimed the savage blows he would inflict on anyone who crossed him. Case 5 planned to kill the driver of the car that had hit him and asked the police to help him carry out his plan.” (Rolls et al., 1994, p1522)*

The Faux Pas task requires the participant to identify a social faux pas in a series of short stories. A faux pas (from the French false step) refers to a situation where someone says something without realising that the listener may not want to hear it, or may have been hurt by what was said. The original task includes 10 stories in which a faux pas is included, and 10 control stories, each of which is followed by some questions:

*(Faux Pas detection) Did anyone say anything they shouldn't have said?*

*(Faux Pas understanding) Who said something they shouldn't have said?*

*(Mental state) Why shouldn't they have said it?*

*(Mental state) Why did they say it?*

*(Empathy) How do you think X would have felt?*

*+ control questions relating to story comprehension*

Good performance on this task requires the participant to understand the mental states and beliefs of at least one and often two protagonists in order to apprehend the potential emotional impact of the situation. In order to reduce the potential memory load of this task, each story is displayed on a sheet in front of participants for their reference while it is being read, and while questions about the story are being asked. The Faux Pas task has been linked with the OFC, initially by Stone, Baron-Cohen & Knight (1998) who reported that VM, but not DL lesions, cause difficulties with detecting a social faux pas. The VM group had no difficulty in understanding the story content (as evidenced by unimpaired responses to control questions), and were also unimpaired on a false belief task or the empathy questions on the Faux Pas test, leading the authors to propose that the OFC may be central to the integration of understanding others' mental states with empathic information.

This lesion-specific pattern of spared and impaired performance was also supported by a series of studies showing significantly poorer performance on the Faux Pas test by individuals with ventromedial lesions in comparison to a DL group, those with more posterior damage and a group of healthy controls (Shamay-Tsoory, Tomer, & Aharon-Peretz, 2005; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003; Shamay-Tsoory, Tomer, Berger, Goldsher, & Aharon-Peretz, 2005). A separate study reported that individuals with medial prefrontal lesions were

significantly impaired specifically on Faux Pas question number 4, relating to the motivation behind the Faux Pas in comparison to a lateral frontal group, non-frontal group and healthy controls ( Lee et al., 2010). Furthermore, faux pas task performance is impaired in the frontal variant of frontotemporal dementia (fvFTD; Gregory et al., 2002; Lough, Gregory, & Hodges, 2001; Lough & Hodges, 2002; Torralva et al., 2007)<sup>10</sup>; a condition consistently associated with functional and anatomical abnormalities of the OFC (Diehl et al., 2004; Ibach et al., 2004; Salmon et al., 2003). A recent study suggests that performance differences on the Faux Pas task between Schizophrenics and controls correlates with regional grey matter reduction in the OFC (Herold et al., 2009).

Evidence from neuroimaging studies also suggests primarily medial and orbital involvement during social processing tasks (e.g. Gallagher et al., 2000; Jaillard et al., 2009; Keane, Calder, Hodges, & Young, 2002). Given the dense connections between the OFC and rostral ACC (Ongür & Price, 2000), the co-activation of these two regions is unsurprising, although one study suggests that lesions involving the dACC but sparing the OFC do not result in impairments on the Faux Pas task (Bird, Castelli, Malik, Frith, & Husain, 2004). However, the fact that patient G.T. in this case-study may have been less able to empathise with the characters in the stories (as corroborated by apparent emotional blunting reported by her husband) suggests that her emotional dysfunction may not have been fully gauged by the FPT, or that her pre-morbid performance may have been significantly better. Further qualitative examination of G.T.'s responses revealed indications of

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<sup>10</sup> The study by Gergory et al., (2002) highlights the effects memory load could have on task performance. The stories were not written out and available to participants for reference. The Faux Pas control questions were administered as 'memory' questions to both a fvFTD and Alzheimer's disease (AD) group. AD participants understandably performed poorly specifically on these questions.

somewhat concrete reasoning which also related to her anomalous ratings of embarrassment on another task examining transgressions of social norms.

No functional imaging studies of FPT have been undertaken, but Berthoz, Armony, Blair, and Dolan (2002) conducted functional imaging while participants were presented with neutral scenarios, or those in which social norms were violated. Contrasting activations of the former with the latter condition revealed orbital and medial frontal activity. In combination with the findings that first and second order ToM tasks were unimpaired in the report by Stone and colleagues (1998), Gallagher & Frith (2003) suggest that the OFC may be more involved in responding to potentially aversive reactions in others rather than the mentalising of others' states of mind. This is compatible with the connective and architectural profile of the OFC, suggesting it may integrate the emotional salience of social behaviours and events. This perspective is also corroborated by a recent meta-analysis of over 200 fMRI studies, which strongly implicates activity of the VMPFC more strongly than OFC during tasks that require participants to make inferences about interpersonal norms or the dispositions of others (Van Overwalle, 2009). Thus, the OFC may not be necessary for such mentalising tasks *per se*, but may contribute to our ability to assess their appropriateness.

### *2.3.3 Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994)*

This task was devised to simulate complex, real-life decision-making, in response to reports that patients with VMPFC lesions appear unable to assess the consequences of their own decisions. Participants are presented with four decks of cards, and told



that every time they choose a card from any of the decks, they have the chance to win money, but that they could also lose money. The object is to accumulate as much money as possible over the course of the test. Two decks contain a higher ratio of losses to wins, and two contain the converse. Several studies from the same research group provided evidence that lesions to VMPFC caused patients to choose from the disadvantageous packs more often than control participants or patients with lesions to other frontal areas (Bechara et al., 1994; Bechara, Damasio, Tranel, & Anderson, 1998; Bechara, Damasio, Tranel, & Damasio, 1997; Bechara, Tranel, Damasio, & Damasio, 1996).

By attempting to model more complex, real-life decision-making scenarios, the task's creators may have introduced the need for other types of cognitive processes such as strategy acquisition and risk computation, which might correspond to the DLPFC or other brain regions (Manes et al., 2002). In fact, several studies have found that lesions to other frontal areas to the exclusion of the VMPFC have also exhibited impaired performance on the IGT (Clark, Manes, Antoun, Sahakian & Robbins, 2003; Fellows & Farah, 2005; MacPherson, Phillips, Della Sala, & Cantagallo, 2009; Maia & McClelland, 2004; Manes et al., 2002). Functional neuroimaging studies also identify activation in the DLPFC and ACC during the IGT (Elliott, Frith, & Dolan, 1997; Ernst et al., 2002; Fukui, Murai, Fukuyama, Hayashi, & Hanakawa, 2005). One possible explanation for the contrast between the work of Bechara and colleagues and others may be that they explicitly selected patients based on a history of disadvantageous decision-making, which is likely to have significantly biased the outcomes of their studies (Fellows & Farah, 2005).

In summary, although early studies have suggested that the IGT predominantly measures the functioning of the VMPFC, more recent examinations do not support this. Rather - much like the WCST – the complexity of the task appears to require integrative processing from multiple frontal regions.

## 2.4 Anterior cingulate cortex

As discussed above, the anterior cingulate cortex (ACC) is intimately connected with motor and pre-motor regions, the DLPFC and OFC. From a structural perspective it is well placed to integrate motor, rule-based and visceral streams of processing, and is likely to have evolved specialization in apes and humans, keeping step with phylogenetic change in OFC and DLPFC. The dorsal ACC preferentially connects to the dorsal PFC and supplementary and motor regions (Beckmann et al., 2009), and electrical stimulation of more caudal regions of the ACC elicits integrated motoric responses (Talairach et al., 1973). The ACC appears sensitive to conditions under which more attentional resources are required to reduce systematic errors in behaviour, and specific cingulate innervations to DLPFC are thought to facilitate this (Medalla & Barbas, 2009). Prevalent theories regarding the cognitive role of the ACC suggest it may act as a conflict-monitor when multiple possible behaviours compete for selection (Botvinick, 2007), or that it tracks environmental volatility and unexpected events (Rushworth & Behrens, 2008). Whilst these two theories are not necessarily mutually exclusive (Botvinick, 2007), behavioural tasks that have been used to develop such cognitive explanations may be useful tools in gauging the normal functioning of the ACC.

### *2.4.1 Dorsal ACC – Stimulus Response Compatibility*

Stimulus-response compatibility (SRC) tasks are thought to elicit enhanced performance-monitoring by coactivating an automatic response tendency and one that is appropriate in the current context (Jonides & Nee, 2004). Participants are

required to make a response based on one dimension of a stimulus (e.g. colour, in the case of the Simon Task) while ignoring another equally salient dimension (e.g. stimulus location in the Simon Task). It has been noted that significantly greater reaction times (RTs) are taken to respond on trials where the stimulus characteristics elicit conflicting responses (incongruency effect) or on the subsequent trial following an incorrect response (post-error slowing). This response-slowing is thought to represent a triggered behavioural adaptation to prevent the repetition of errors, and a large body of evidence suggests a central role for the ACC in this type of behavioural identification and adjustment. Once this has been detected, it is thought that cognitive control processes are facilitated (subserved by the DLPFC) in order to minimise future errors (Miller & Cohen, 2001). The Stroop task (Stroop, 1935), Eriksen Flanker (Eriksen & Eriksen, 1974), Simon task (Simon, 1969) and motor Stroop (Lu & Proctor, 1995; Figure 2.7) are all experimental paradigms thought to create conditions of response competition, even though the source of the compatibility effects differs between tasks (Egner, 2008).

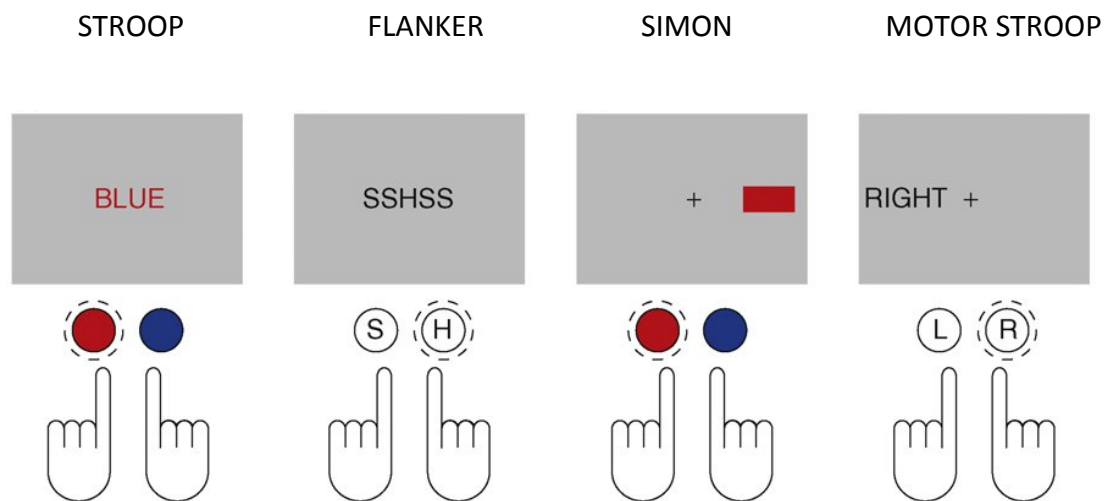


Figure 2.7. Stimulus-response compatibility tasks showing sources of conflict. For each task, the depicted stimuli presented to participants (inside grey boxes) is for the incongruent condition. Circles indicate response options, and the broken outline indicates the correct response. Image amended from Egner (2008). Note that different stimuli (e.g. arrows) and response dimensions (e.g. verbal or motor) can be used.

In the Stroop task, participants are required to respond based on the colour of the ink in which a word is printed, ignoring the colour that the word actually names. Thus, congruent trials are those in which both the word and the ink colour indicate the same response (e.g. “BLUE” printed in blue ink), and incongruent trials are those in which two responses are salient (e.g. “BLUE” printed in red ink). In the Flanker task, respondents must identify a central letter or object, ignoring the conflicting stimuli to either side that relates to the alternative response route. In the Simon task, the colour of the object rather than its conflicting location is the cue for the response, and in the motor Stroop it is the word itself that should determine action selection,

rather than its location on the screen. The conflict can arise in a number of ways and across numerous modalities, but a review of early functional imaging studies reported that the dorsal ACC was consistently activated in a number of tasks that involved inhibition of a prepotent response or commission of errors, irrespective of response modality (verbal or motor) or processing domain (spatial or verbal; Barch et al., 2001). In accord with this, direct comparison of BOLD activation patterns elicited during Stroop and Simon tasks are strikingly similar (Peterson et al., 2002).

Increased activity in the dorsal ACC and DLPFC on incongruent versus congruent conflict trial types has been reported in a large number of functional neuroimaging studies of healthy adults (summarised in Nee, Wager, & Jonides, 2007; and in Roberts & Hall, 2008). Likewise, functional imaging also indicates post-error ACC activity during these tasks (Braver, Barch, Grey, Molfese & Snyder, 2001; Carter et al., 1998; Carter & van Veen, 2007; Garavan, Ross, Kaufman, & Stein, 2003; Mathalon, Whitfield & Ford, 2003; Rubia, Smith, Brammer, & Taylor, 2003; Ullsperger & Von Cramon, 2001). A comparison of the coordinates from 14 neuroimaging studies reporting conflict-related activity with those reported following an erroneous response suggests that they originate from overlapping regions of the dACC (Ullsperger & von Cramon, 2004). This was subsequently corroborated using a version of the Simon task (Wittfoth, Küstermann, Fahle, & Herrmann, 2008). Electrophysiological recordings support the comparability of activity in the ACC related to conflict versus post-error slowing (Van Veen & Carter, 2002; Yeung, Botvinick & Cohen, 2004); activity which correlates with the BOLD response in the ACC (Mathalon et al., 2003). In addition, Kerns and colleagues report that increased

ACC BOLD response reflected the level of subsequent behavioural adjustment on trials following an incongruent trial and on post-error trials for both the Stroop (Kerns et al., 2004) and Simon tasks (Kerns, 2006). Thus, whilst the precise cognitive processes underlying ACC involvement remain a matter of some debate, the ACC activity related to post-error slowing and incongruent trials appear to exhibit similar characteristics, both of which are tapped by this category of task according to functional imaging.

However, disentangling the role of the ACC in these types of task, and judging whether this brain region is necessary for normal performance requires evidence from lesion groups. Post-error slowing appears to be unaffected following ventromedial lesions (Turken & Swick, 2008)<sup>11</sup>. It is clear from earlier lesion studies that the DLPFC is involved at some stage of task performance (Perret, 1974; Stuss, Floden, Alexander, Levine & Katz, 2001; Vendrell et al., 1995), although the fact that lesions to this region also impair participants' ability to name colours in a control condition of the Stroop suggests that the DLPFC may not be directly sensitive to incongruency and error (Floden, Vallesi, & Stuss, 2011). Rather, early lesion studies report that dorsomedial lesions in humans result in slowed responses to incongruent trials when compared to controls in SRC tasks (Richer et al., 1993). A study of 51 patients with focal lesions (Stuss, Floden, Alexander, Levine, & Katz, 2001) reported that dorsomedial but not ventral cingulate or orbital lesions resulted

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<sup>11</sup> Szatowska et al. (2007) report that resection of the right, but not left gyrus rectus to patients following anterior communicating artery (ACoA) rupture resulted in significantly larger difference in RTs between incongruent and neutral Stroop conditions, although it is not clear whether general slowing could be a factor, as proportionate data was not used, nor was a control for speeded RT. Also, those with ACoA ruptures that did not have a resection did not show this effect, which suggests the surgical resection may be causally related.

in incongruent response-slowness *and* increased error rates<sup>12</sup>. Dorsomedial lesions associated with demyelination in multiple sclerosis have been shown to account for a significant amount of variance in Stroop interference (Pujol et al., 2001). More recently, 8 patients with lesions involving the ACC showed slowed responses to incongruent stimuli, but only when preceded by a congruent trial on the Simon task (di Pellegrino, Ciaramelli, & Làdavas, 2007).

Cingulotomy patients show a greater incongruency effect when compared to controls (Cohen, Kaplan, Moser, Jenkins & Wilkinson, 1999) or when comparing pre- and post-surgery performance of the same individuals on the Stroop (Ochsner et al., 2001). Similarly, removal of epileptogenic tissue from a patient's ACC improved performance on the Flanker task from near-chance levels pre-surgery to near-perfect performance, and also resulted in the appearance of previously absent conflict-related activity in the medial PFC as measured by EEG (Cohen, Ridderinkhof, Haupt, Elger, & Fell, 2008). Another study reports a single individual whose rare selective lesion to dACC resulted in poorer error-correction and significantly slower responses on incongruent trials when compared to control subjects (Swick & Turken, 2002). Yen and colleagues (2009) recently undertook an evaluative follow-up of cingulotomy patients, in which they observed an initial increase in Stroop interference one week post-operatively, compared to baseline performance, although one month after excision the difference had dropped to a trend level of significance.

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<sup>12</sup> While a relatively large amount of data suggests that SRC tasks involve the ACC, primate studies do not replicate this finding. Whilst this has been used to suggest a misinterpretation of the human literature, a closer examination of the data suggests that there are crucial anatomical and evolutionary differences that make human and primate cingulate cortices incommensurable (Cole, Yeung, Freiwald, & Botvinick, 2009).



However, there are also conflicting reports of cases with cingulate lesions that exhibit no congruency or error-related effects on reaction time, compared to controls. Vendrell et al. (1995) reported that whilst ACC patients exhibited an increased number of errors compared to controls, their response slowing was not confined to just the interference condition, but also extended to the control colour-naming condition, indicating general slowing rather than a specific deficit in incongruent responding. Fellows & Farah (2005) reported that 4 patients with extensive cingulate lesions showed no significant differences in response-slowing either on incongruent trials or post-error, when compared to controls. However, it is crucial to note that small sample sizes of patients, but also of controls, may confound a synthesis of results between studies. Fellows and Farah (2005) note that a previous report of a single case (Swick & Jovanovic, 2002) as having shown general slowing would actually fall into the normal range when compared to the performance of their control group. In addition, contrary to a previous fMRI study reporting ACC activation irrespective of modality (Barch et al., 2001) it is possible that lesion location within the cingulate may have different effects on performance across different modalities. For example, a patient with a unilateral lesion limited to the posterior portion of the dACC showed increased errors and larger interference effects when motor but not verbal responses were required in response to coloured words (Turken & Swick, 1999).

There are clearly inconsistencies in the literature regarding both the regional specificity of functional activations within the anterior cingulate, lesion location and the behavioural profile in relation to SRC tasks. Indeed, the methods for precise localization of lesions in this small region may also confound cross-study

comparison – in this particular case it could be that supplementary motor regions of the cingulate rather than posterior ACC regions were predominantly affected – more generally this has particular implications for small anterior-posterior regions such as the ACC. As is common in lesions studies, the damaged site is transferred into standard co-ordinates<sup>13</sup> such as Montreal Neurological Institute (MNI) or Talairach and Tournoux (as is the case with the latter paper) where landmarks such as the anterior and posterior commissures are commonly used to aid spatial normalisation.

However, as will be discussed in more detail in the following chapter, the use of such systems are not sympathetic to the individual differences in gyrfication, which are likely to be a more accurate indicator of underlying anatomical (and therefore probably functional) significance than the method of using distant subcortical landmarks (such as the anterior commissure) across subjects. In a structure such as the ACC whose trajectory is primarily posterior to anterior (and whose underlying structure and connectivity alters along its course – Beckmann et al., 2009; Paus, Petrides, Evans & Meyler, 1993), small individual variations in the spatial relationship between the cingulate sub-region and anterior commissure are likely. Thus, noise introduced by the inconsistent classification of cingulate regions (e.g. pre-motor rather than dACC) could well contribute to inconsistencies in the behavioural profiles reported in relation to lesion site (and also functional activation).

Another potential form of noise arises from the fact that the medial wall of the frontal

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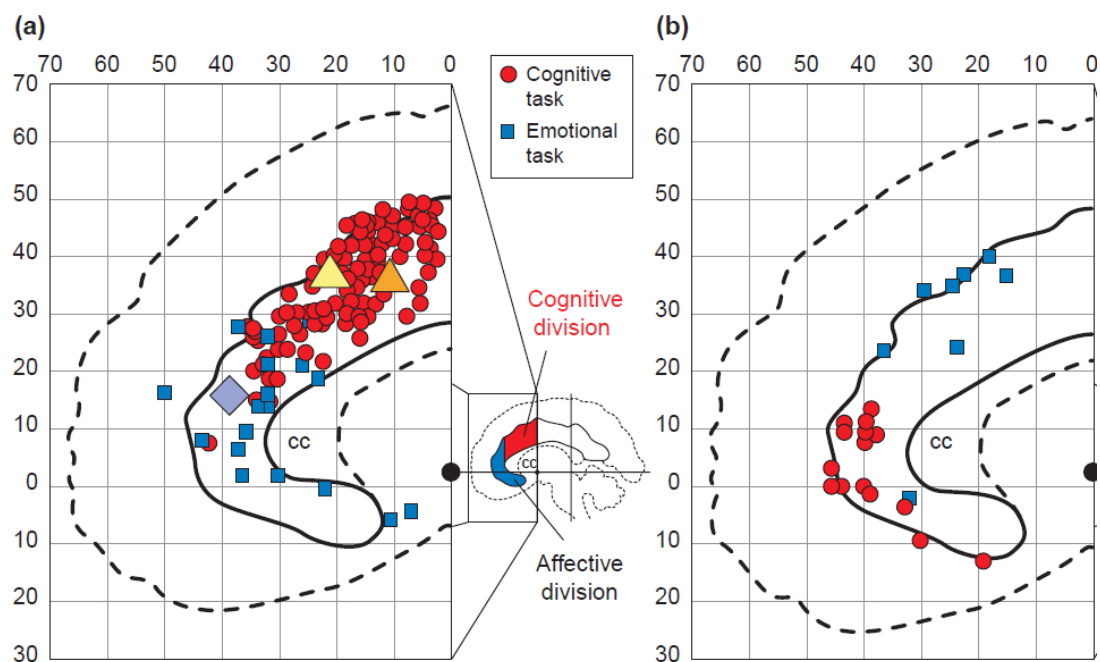
<sup>13</sup> Note that the method of transfer can also differ between reports. Because the lesioned region no longer exists (and pre-lesion scans very rarely exist), assumptions must be made about the spatial characteristics of the area that has been damaged. Most commonly the lesions are traced directly onto a template brain or onto the contralateral hemisphere of the same participant. The former introduces variance due to an inevitable discord between the micro and macro topographical variance between the subject and template, whereas the latter is more likely to have far more commonality and therefore will more accurately represent the characteristics of the missing regions. However, given that results from the latter method will be registered to a template at a later stage (and thus introduce similar problems of concordance), it is unclear precisely how much of a benefit this method is.

lobe is subject to large variability in gyrification, which further diminishes the reliability with which sub-regions may be identified from composite MR images (a. Fornito, 2004; Paus et al., 1996). Finally, the extent to which the white matter tract beneath the cingulate (cingulum bundle) is damaged is likely to vary between studies, but this is not always alluded to in studies of cingulate cortex lesions. Damage to this area is likely to elicit very different types of behavioural sequelae compared to cortical lesion alone (Brotis, Kapsalaki, Paterakis, Smith, & Fountas, 2009), and so this factor could also contribute to discrepant findings between lesion studies in comparison to the consistency of the functional imaging literature.

#### *2.4.2 Ventral ACC – Moral Judgement (Greene, Sommerville, Nystrom, Darley, & Cohen, 2001)*

Although considered part of the same anatomical structure, the dorsal and ventral parts of the ACC exhibit different cytoarchitectural properties (Vogt, Nimchinsky, Vogt, & Hof, 1995) and patterns of connectivity, preferentially connecting with dorsal and ventral PFC respectively (Beckmann et al., 2009) although the entire cingulate cortex also shares common connectivity via the cingulum bundle (Catani & Thiebaut de Schotten, 2008). The vACC is also connected other non-frontal regions such as the amygdala, hippocampus, hypothalamus and insula (Devinsky et al., 1995). Concomitant with this perspective, vACC has been posited to play a similar role in behavioural monitoring under uncertainty or incongruency, but in a different subset of tasks involving emotional stimuli. An informative meta-analysis of 132 data points from 64 functional imaging studies demonstrates a striking pattern of

activations (Figure 2.8a) and de-activations (Fig 2.8b). During SRC-type tasks as discussed above (dubbed ‘cognitive’ tasks by the authors), dACC shows a pattern of activation whilst vACC shows deactivations. In contrast, performing tasks involving emotionally salient stimuli appears to elicit the opposite pattern (Bush, Luu, & Posner, 2000). This has subsequently been corroborated by another meta-analysis of around 200 functional imaging studies (Van Overwalle, 2009).



*Figure 2.8.* Functional activations (a) and de-activations (b) during cognitive and emotional task performance plotted in common spatial coordinates (Bush, Luu & Posner, 2000). Performance of normal participants on a variant of an SRC task in which participants are required to count the number of words and ignore the number that the words name : yellow triangle. Within the same subjects, the counting SRC variant activates dACC (orange triangle) whereas the same task with emotional stimuli activates vACC.

Subsequent evidence appears to corroborate the involvement of the vACC in incongruent or high-conflict emotional stimuli, such as during moral appraisals and judgements where controlled reasoning processes and the emotional context of social and moral norm violation may sometimes compete in decision-making (Greene, Morelli, Lowenberg, Nystrom, & Cohen, 2008; Jorge Moll, Zahn, Oliveira-Souza, Krueger, & Grafman, 2005). This task was initially developed to investigate the position that both logical and emotional cognition influences our moral reasoning and decision-making; this became known as the dual process theory. The research was initially motivated by a difficulty in explaining the difference between two seemingly similar scenarios:

*“A runaway trolley is headed for five people who will be killed if it proceeds on its present course. The only way to save them is to hit a switch that will turn the trolley onto an alternate set of tracks where it will kill one person instead of five. Ought you to turn the trolley in order to save five people at the expense of one? Most people say yes. Now consider a similar problem, the footbridge dilemma. As before, a trolley threatens to kill five people. You are standing next to a large stranger on a footbridge that spans the tracks, in between the oncoming trolley and the five people. In this scenario, the only way to save the five people is to push this stranger off the bridge, onto the tracks below. He will die if you do this, but his body will stop the trolley from reaching the others. Ought you to save the five others by pushing this stranger to his death? Most people say no.*

*Taken together, these two dilemmas create a puzzle for moral philosophers: What makes it morally acceptable to sacrifice one life to save five in the trolley dilemma but not in the footbridge dilemma?”* Greene et al. (2001), p.2105.

In its original form, the participant is presented with a series of 60 dilemmas (Greene et al., 2001). A question follows each one, asking the participant whether or not they would endorse a suggested course of action in order to resolve the dilemma by simply answering yes or no. The scenarios typically fall into two categories:

moral and non-moral. The action required to achieve the depicted resolution in moral scenarios varies in its severity, but will often require the participant to contravene personal moral boundaries (i.e. doing direct harm to other people, such as pushing someone off a bridge). The value of the outcome is also manipulated, (e.g. thousands of lives will be saved), providing various levels of conflict between the desire to observe personal moral boundaries and to benefit the greater good. By contrast, non-moral scenarios contain no moral content, but rather present participants with both actions and outcomes that have low moral or emotive salience<sup>14</sup>. In healthy participants, levels of endorsement typically decrease with the extremity of the personal moral violation required. Likewise, the response time taken to arrive at a decision increases with the level of conflict elicited (the severity of the course of action required vs. the moral value of the potential outcome).

A further degree of distinction can be made within the moral category, whereby the type of action required is manipulated as either personal (e.g. causing direct physical harm to someone) or impersonal (e.g. pressing a switch or throwing a lever). However, studies vary in the way that they differentiate within personal-moral scenarios. Stories can be categorised in terms of high and low conflict based on reaction times (e.g. Greene et al., 2001), based on independent ratings of emotional salience (e.g. Koenigs & Tranel, 2007), or in terms of the type of moral conflict induced (Kahane & Shackel, 2008). Further variants of the task format itself include visual representations (Harrison et al., 2008), or short sentences or scenarios in which

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<sup>14</sup> Although responses to non-moral scenarios are not central to the frontal regional specificity of this test, it is important to note that some of the non-moral decisions are arguably not dilemmas at all (Kahane & Shackel 2007).

one must simply judge whether or not a moral violation has occurred (e.g. Moll et al., 2002).

Example of a moral dilemma (low conflict):

*You are visiting the sculpture garden of a wealthy art collector. The garden overlooks a valley containing a set of train tracks. A railway workman is working on the tracks, and an empty runaway trolley is heading down the tracks toward the workman. The only way to save the workman's life is to push one of the art collector's prized sculptures down into the valley so that it will roll onto the tracks and blocks the trolley's passage. Doing this will destroy the sculpture.*

*Is it appropriate for you to destroy the sculpture in order to save this workman's life?*

Example moral dilemma (high-conflict):

*Enemy soldiers have taken over your village. They have orders to kill all remaining civilians. You and some of your townspeople have sought refuge in the cellar of a large house. Outside you hear the voices of the soldiers who have come to search the house for valuables. Your baby begins to cry loudly. You cover his mouth to block the sound. If you remove your hand from his mouth, his crying will summon the attention of the soldiers who will kill you, your child and the others hiding out in the cellar. To save yourself and the others, you must smother your child to death.*

*Is it appropriate for you to smother your child in order to save yourself and the other townspeople?*

Using fMRI in normal healthy participants, the authors reported the increased engagement of the MPFC (medial BA 9/10) and decreased activity of BA46 during decision-making for moral-personal tasks when compared to moral-impersonal and non-moral conditions. This finding has been subsequently replicated (Greene,

Nystrom, Engell, Darley, & Cohen, 2004). An increase in reaction times was also reported between judgements approving of personal harm to others compared to judgements that disapproved these actions, but a subsequent re-analysis of the data suggests that this was an artefact of very fast disapproval reaction times on a select few dilemmas (McGuire, Langdon, Coltheart, & Mackenzie, 2009).

Further fMRI evidence suggestive of two complimentary moral decision networks has been reported using different moral dilemmas to those developed by Greene and colleagues, but which were still based on standard philosophical scenarios (Schaich Borg, Hynes, Van Horn, Grafton, & Sinnott-Armstrong, 2006). The authors reported that ventromedial regions were more active during elevated moral content, whereas dorsolateral regions were preferentially recruited for non-moral decisions (Figure. 9). In addition, they observed that whilst the DLPFC was more active during moral scenarios where individuals had to process the numerical consequences of their actions, the network that was activated when processing the intention of doing harm to others activated the OFC, along with the right Middle Frontal Gyrus (BA8). Similarly, Moll and colleagues (Moll et al., 2002a) reported that the VMPFC was also activated during the judgement of emotionally-charged moral sentences, whilst only the lateral OFC was recruited during evocative non-moral scenarios. The VMPFC has also been implicated in processing morally-salient images (Harenski & Hamann, 2006; Moll, de Oliveira-Souza, Bramati, & Grafman, 2002b).

Greene and colleagues (2004) also reported activation of the Anterior Cingulate Cortex (BA32) during decision-making in more difficult scenarios. This is consistent with a large body of evidence suggesting a role for the ACC in conflict



processing, given its connections with both DLPFC and OFC (e.g. Beckmann et al 2009), and its involvement in sensitivity to social pain (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006). Two more recent studies developed cartoons based on the original scenarios, and also reported that the ventromedial areas (including ventral ACC) were significantly more active whilst judging emotional situations when compared to non-emotional situations; contrasting with increased DLPFC activation in the non-emotional condition (Perez-Alvarez, Timoneda, & Reixach, 2007; Pujol et al., 2008)<sup>15</sup>. Another study which involved judging vignettes based on difficult/personal moral dilemmas, also reported significant ventromedial activation (including ventral ACC), although it is important to note that the activations were compared with a resting state rather than with impersonal or non-moral stories (Harrison et al., 2008). Using a slightly different task, in which subjects had to judge whether or not a social norm had been violated based on a two sentence passage, the involvement of both DLPFC and VMPFC in moral decision-making was replicated (Prehn et al., 2008). The authors also reported that increased recruitment of the DLPFC appeared to result in poorer accuracy in identifying social violations, which they interpreted as reflecting the use of inappropriate neural resources for the task at hand.

The consistent reporting of involvement of the VMPFC in moral decision-making has been explored in further detail, by manipulating the order in which the outcome of the action (neutral or negative) and the protagonist's intention (did they intend harm or not?) of each scenario was presented to participants (Young & Saxe,

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<sup>15</sup> It is important to note that these studies were both examining activations in adolescents, and therefore may not be fully representative of adult neural responses.

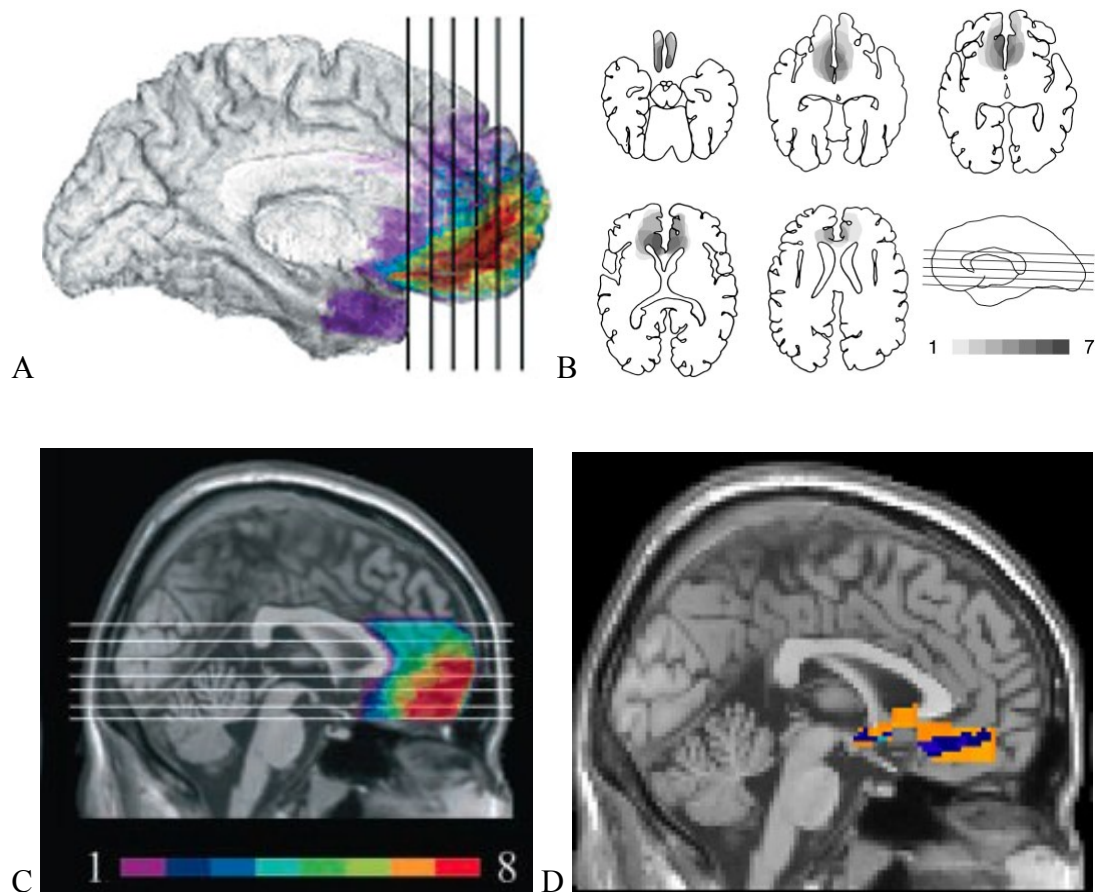
2008, 2009). Participants were required to make a judgement about whether an action was permissible for a series of scenarios. The VMPFC was significantly more active when the latter, morally-relevant feature of the action was displayed, irrespective of its position in the sequence in the presentation of the scenario, whilst the temporo-parietal junction and precuneus were activated during the encoding and integration of this belief-relevant information when having to make judgements after the outcome of the action had been revealed.

Thus, most of the functional imaging literature to date appears to support the idea that two cognitive streams occupy mutually-competing roles in moral decision making. Whilst the DLPFC's contribution to moral decision-making represents the exertion of controlled cognitive processes, the VMPFC drives more implicit emotional responses. This dual contribution is ostensibly supported by the report that responses to ontological (but not deontological) dilemmas were selectively slowed when faced with a simultaneous monitoring task to increase load on 'cognitive' processes (Greene et al., 2008). However, in apparent opposition to this received wisdom, Shenhav and Greene (2010) report that participants exhibiting a more utilitarian profile are associated with *increased* activation in the OFC, specifically in lateral areas (Figure 9). As the authors note, this contradiction may be reconciled by the differences between the experimental tasks, as well as the way the data is analysed: whilst in previous studies, participants are required to make a concrete yes or no judgement about the acceptability of a suggested action, the present study was designed to examine the economics of moral decisions by systematically varying the moral value of action/inaction in the context of variable probabilities of risk.

Therefore, they suggest this could reflect differences in the way the scenario variables are manipulated and consequently represents a different task demand.

Three lesion studies provide further evidence to support the role of the VMPFC in moral cognition (Ciaramelli, Muccioli, Làdavas, & di Pellegrino, 2007; Koenigs & Tranel, 2007; Moretto, Làdavas, Mattioli, & di Pellegrino, 2010). In each study, groups with lesions primarily overlapping on the subgenual ACC and BAs 10, 11 and 12 were significantly more likely to endorse a utilitarian solution to high-conflict moral dilemmas than controls (Figure 9). In the Koenigs et al. (2007) paper, performance was compared to an additional brain-damaged control group comprising 3 with lateral PFC damage, one with dorsomedial PFC damage and a further 8 with non-frontal pathology (Koenigs, personal communication) whose scores did not differ from controls. However, neither of the other studies contained a control group composed entirely of lesions to other frontal lobe regions.

Further evidence to implicate the VMPFC in accurate moral judgement comes from patients with Frontotemporal Lobar Degeneration (FTLD; Grossman et al., 2010). Participants were presented with brief social scenarios such as running a red light at 2am when either i) driving a sick child to hospital or ii) being observed by a police car. When compared to controls, the FTLD group endorsed moral rule violations with a negatively valenced feature or outcome significantly more than controls, and also showed atrophy in the VMPFC, which was activated when healthy participants performed the task (Figure 2.9).



*Figure 2.9.* Lesion overlaps in studies by A) Koenigs et al., 2007, B) Ciaramelli et al., 2007, C) Moretto et al., 2010. D) Activations by healthy control participants during a moral judgement task are shown in orange. Atrophy of FTLD group compared to controls is shown in blue from Grossman et al. (2010).

The performance of clinical populations has also been examined using this paradigm. A recent study examined the neural correlates of moral decision making in a group of 17 psychopaths of varying severity (Glenn, Raine, Schug, Young, & Hauser, 2009). They found that individuals who were rated particularly highly on the interpersonal factor of psychopathy (callous and manipulative) exhibited a reduction in activation in the VMPFC during the moral decision making scenarios developed by Greene and colleagues. However, the absence of a control group makes it hard to generalise these neural correlates to a normal population. Moreover, the moral

decisions that participants made are not reported (and would be of little use without a control group for comparison) and so does not allow interpretation of these findings in the context of behaviour. In fact, another study comparing the pattern of responses in moral decision-making between psychopaths and controls reported that there was no difference in their moral judgements (Cima, Tonnaer, & Hauser, 2010). Whilst this may suggest that emotional processes are not causally necessary for normal performance on such tests, it is important to bear in mind that the functional differences reported by Glenn et al. (2009) may reflect the motivational state of participants (i.e. seeking to deceive vs. giving honest responses); controls and psychopaths may have explicitly been attempting to do different things, rather than reflecting an implicit difference in processing during moral decision-making.

## 2.5 Summary & Conclusions

Given the complexity of tasks such as the Iowa Gambling task and the Wisconsin Card Sorting Test, it is plausible that complex interactions between dorsal and orbital processing are required for successful performance. However, as Manes et al (2002) observe, tests which appear able to fractionate (to some degree) the more basic cognitive components involved in more complex tasks of decision-making hold promise for allowing some degree of functional specificity. As such, the Tower test and SOPT may offer some preferential sensitivity to DLPFC functioning as opposed to that of the OFC. Likewise, the Reversal Learning and Faux Pas tasks may offer sensitivity to OFC functioning rather than to that of the DLPFC.

Nevertheless, the intimate relationship between the ACC and other frontal sub-regions has clearly made it difficult to elucidate the specific contribution this region might make, over and above our coarse understanding of the DLPFC and OFC. Constraints on spatial localization from both lesion studies and functional imaging make it difficult to functionally differentiate ACC from other frontal regions. In the former, it is very rare to have lesions to ACC without proximal locations such as the DLPFC or OFC having some damage. In the latter, strategies for the co-registration of activation patterns in functional imaging is still unlikely to take sufficient account of individual differences in local morphology to allow localisation at the level of individual gyri (which may be of particular functional relevance – see Chapter3).

The dense interconnectivity of the ACC with other frontal areas is broadly reflected by the neuropsychological literature, which generally links DLPFC and

dorsal ACC regions to tasks such as the Tower, Simon task and the SOPT, and the OFC and vACC to Faux Pas, Reversal Learning and Dilemmas tasks. While it is absolutely plausible that these different sub-regions make unique processing contributions to task performance, the current literature suggests that, at worst, an anatomically pure test of frontal sub-regional function is unattainable (Nyhus & Barcelo, 2009), or at best such a task has not yet been developed. Consequently, although this thesis will refer to the tests as pertaining predominantly to one region, the probable involvement of other frontal and non-frontal brain regions is implicitly acknowledged.

## **Chapter 3: A Systematic Review of Manual Frontal Lobe Parcellation Techniques in Magnetic Resonance Imaging**

Work presented in the following chapter is taken from the following paper:

Cox, S.R., Ferguson, K.J., Royle, N.A., Shenkin, S.D., MacPherson, S.E.,  
MacLulich, A.M.J., Deary, I.D. and Wardlaw, J.M. (*in press*). A systematic review  
of brain frontal lobe parcellation techniques in magnetic resonance imaging. *Brain  
Structure and Function*, doi: 10.1007/s00429-013-0527-5

A supplementary table containing all reviewed parcellation methods and full  
references for this section can be found in Appendices A and B respectively. An  
additional excel spreadsheet which details all reviewed protocols, sub-regional  
boundaries and quality scoring accompanies this thesis in electronic format.



### 3.1 Abstract

*Introduction:* Manual volumetric measurement of the brain's frontal lobe and its sub-regions from Magnetic Resonance (MR) images is an established method for researching potential neural correlates of a clinical disorder or cognitive function. However, there is no consensus between methods used to identify relevant boundaries of a given region of interest (ROI) on MR images, and those used may bear little relation to each other or the underlying structural, functional and connective architecture. This presents challenges for the analysis, reporting and synthesis of such results. We therefore performed a systematic literature review to highlight variations in the anatomical boundaries used to measure frontal regions, contextualised by up-to-date convergent evidence from histology and functional neuropsychology.

*Methods:* We searched EMBASE and MEDLINE for studies in English reporting three-dimensional boundaries for manually delineating the brain's frontal lobe or sub-regional ROIs from MR images. Exclusion criteria were: exclusive use of co-ordinate grid systems; insufficient detail for single boundary to allow reproduction of technique; publication in grey literature only. All papers were assessed on a range of quality criteria relating to bias, reproducibility and protocol rationale.

*Results & Conclusions:* The 206 eligible papers covered a wide range of participant groups. There was a large degree of variability in the three-dimensional boundaries of all regions. Half of the reports did not justify their rationale for

boundary selection, and each paper met on average only three-quarters of quality criteria. For the frontal lobe and each sub-region (frontal pole, anterior cingulate, dorsolateral, inferior-lateral, and orbitofrontal) we identified reproducible methods for a biologically-plausible target ROI, sympathetic to the individual differences in putative function and cytoarchitecture. It is intended that this synthesis, in addition to suggestions for improvement of bias and quality, will guide the design of future volumetric studies of cerebral structure.

### 3.2 Introduction

The brain's frontal lobes are both cytoarchitectonically and functionally diverse regions, and there is a large body of research examining their contributions to a wide range of cognitive processes and clinical conditions. Regions of the frontal lobes are differentiated by laminar organisation dependent on neuronal density, presence of granule cells, glial content, afferent and efferent connectivity (Zald, 2007). Such differences have functional implications, broadly supported by evidence from both neuropsychology and cognitive neuroscience that either discrete lesions to, or blood-oxygen level dependent response in, a specific region can be related to behavioural symptoms or hypothesised function, due to the high degree of segregation in the parallel fronto-subcortical circuits (Cummings, 1993). As a result, attempting to reveal the 'neural correlates' of a disorder by scrutinising the structure of a particular sub-region in relation to a specific symptomatology has become a widespread practice, with the aim of providing insight into the developmental aetiology or pathogenesis. Structural abnormalities of the frontal lobe (or their absence) have been reported in psychiatric, behavioural and neurological disorders and also in normal development and ageing (e.g. Convit et al., 2001; Salat et al., 2001; Yucel et al., 2008). However, the methods used to define and measure frontal regions are highly variable among publications. This variability has critical implications for the analysis, reporting and synthesis of neuroanatomical abnormalities in clinical populations, and could explain areas of inconsistency amongst findings of the

reported neuroanatomical characteristics of a population (Zhou et al., 2005). A full review of such inconsistencies is beyond the scope of this review<sup>16</sup>.

### *3.2.1 Tools for brain measurement*

Methods to measure brain structure fall into two categories: manual and automated. Manual delineation of ROIs affords precise control over boundary placement on a slice-by-slice basis for the MR image of each participant. Although this confers a high degree of reliability and allows adherence to individual differences in brain morphology, it requires expertise in neuroanatomy and involves significant time investment. Automated methods can require less user input thereby reducing time-cost and making these methods potentially more feasible for studying large cohorts. It also avoids the potential for bias and reproducibility issues introduced by manual rater drift. However, choices throughout the processing chain may introduce other forms of systematic and non-systematic bias; even automated parcellation methods require user-driven input in the first instance. That is, the software for automated segmentation of a target samples must be based on a particular structural schema or atlas. As there is no standardised protocol to manually identify the ROIs in the first place, the parcellations derived from automated atlas-based methods can only be as good as the manually-delineated approach on which they are based. For example, the Desikan-Killiany atlas for Freesurfer (Desikan et al., 2006), the Harvard Brain Atlas (Kikinis et al., 1996) and anatomical labels for SPM (Tzourio-Mazoyer et al., 2002) derived from the manual schema outlined by Rademacher et al. (1992), and

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<sup>16</sup> The data compiled over the course of this review (and the available supplementary material) may provide the basis for further reviews explicitly dealing with the effects of boundary variability on reported results and inconsistencies on a syndrome-specific basis.

subsequent modifications by Caviness et al. (1996) and Tzourio et al. (1997). The frontal lobe divisions for each of these are included in this review. In addition, different methods of spatial registration (which attempt to account for individual differences in brain morphology and size) can yield markedly different outcomes. Thus, choices of atlas selection and registration method significantly influence automated parcellation results (Bohland et al., 2009; Pantazis et al., 2010), and also offer no direct control over the positioning of ROI boundaries for each individual. Consequently, although the remainder of this article is concerned with the methods used in manual parcellation of the frontal lobes, the findings extend to automated methods that are predicated on a manually-derived atlas.

### *3.2.2 Approximating cellular field locations*

In manual parcellation, the approximation of cellular field locations on the cortex using only neuroanatomical cues from an MR image gives rise to a complex set of issues. These issues described below are likely to be the main source of variability between methods for frontal lobe parcellation. There is little doubt that distinct subregions of the frontal lobes can be defined histologically by distinct patterns of cell distribution over the cortex, as evidenced by the general accord between many influential brain cartographers over the last century. When examining the frontal lobes, Brodmann (1909), Campbell (1905), Smith (1907), von Economo and Koskinas (1925), Sarkisov (1949) and Petrides and Pandya (1994) amongst others, each identify the following subregions: an anterior tip, a region anterior to the central sulcus, and intermediate regions on the lateral and ventral convexity of the frontal

cortex based on patterns of cell distribution (summarised schematically in Figure 3.1). However, more detailed comparison of these maps reveals subtle differences in the way in which sub-regions relate to cortical topography, making it difficult to derive a clear and robust set of rules to apply to the topography of the MR image to be parcellated. Discrepancies between cytoarchitectural maps are partly due to different concepts of cortical organisation and different histology methods (Zilles and Amunts, 2010), but it also reflects the high level of individual differences in frontal lobe morphology, both at the micro and macro scale. Small sample sizes are typical in studies of cortical cellular fields, such that a single study (and resultant map) is unlikely to have captured much of the possible variation in morphology. As a result, differences between study samples can also partially account for differences between these maps. It is understandable, then, that this margin for interpretation has resulted in a variety of approaches for frontal lobe parcellation.



More recent studies of neuroarchitecture have gone some way to addressing the issue of individual variability in selected ROIs. These studies are relevant for two reasons. Firstly, they address one of the basic assumptions of manual parcellation; that the relationship between underlying cell structure and gross morphology is more or less stable across individuals. Secondly, they enable a more robust method for identification of ROIs by using sulcal and gyral landmarks. The importance of the first point cannot be overstated, as without a generally stable relationship between macro- and micro-anatomical variation, cortical parcellation would be futile. Examinations of cortical fields such as Brodmann Areas (BAs) 17, 41, 3b, 4 (Rademacher et al., 1993), 4, 6, 17, 18, (Fischl et al., 2008), the functional activation of the Frontal Eye Fields and sensory-motor regions (Frost and Goebel, 2012) have all been shown to hold a strikingly consistent position with specific gyri across a modest number of individual brains. Although other regions such as the fusiform face area, Broca's area (Frost and Goebel, 2012), orbitofrontal regions (Ongür et al., 2003), BAs 9 and 46 (Rajkowska and Goldman-Rakic, 1995) and BAs 44 and 45 (Fischl et al., 2008) show some inter-individual variability of position on the folds of the cortex, general observations about their likely location across individuals are still sufficiently robust to allow a meaningful measure to be derived from the sulcal and gyral pattern evident on an MR scan (Fischl et al., 2008)<sup>17</sup>. This suggests that not only can one be relatively confident about the relationship between topography and underlying structure, but that parcellation approaches should be sympathetic to the individual variability in gyrification rather than using gross geometric boundaries

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<sup>17</sup> These studies too are examinations across a small number of brains and so may not have fully captured population-wide variability.



derived from unrelated landmarks or coordinate systems (Devlin and Poldrack, 2007; Uylings et al., 2005).

Even with this proviso, variations in parcellation approach can be attributed to different configurations of the same gyri. For example, it has been observed that some individuals exhibit an additional cortical fold called the paracingulate gyrus on the anterior medial wall (Fornito et al., 2004), but decisions on how such variants should be measured (separately or as part of one or other adjoining region) also distinguish one approach from the next. Moreover, some regions are difficult to identify because no study has yet identified a sulcus that reliably indicates a sub-field boundary, so the boundary is sometimes determined using other easily-identifiable extrinsic landmarks that vary between methods.

### *3.2.3 Aims of the review*

The implications of the contradictory definitions of ROIs within studies of the frontal lobes are far-reaching. These underplayed methodological discrepancies confound assessment of the relationship between brain region and function or clinical symptom. Establishing an overview of putative neural correlates of a given disorder or function is fundamentally undermined by using standard nomenclature (e.g. “dorsolateral” or “orbitofrontal”) to label non-standardised brain measures. The current review aims to determine the range of frontal lobe sub-regional definitions that have been adopted, compare these with known relationships between architecture and morphology and comment on factors of study quality. This synthesis of studies investigating structure, function and connectivity offers useful guidance in

relating underlying cellular fields to topographical position for the most part, and also highlights gaps in our understanding for some ROIs in particular. Compromises between accuracy (does it make good biological sense?) and reproducibility (is it objective, feasible and applicable to all brains?) drive the commentary and identification of areas for future research.

### 3.3 Methods

#### 3.3.1 Study Identification

We undertook a systematic literature review of published articles reporting a manual tracing method of the human frontal lobe, following PRISMA guidelines (Liberati et al., 2009). Searching abstracts and article titles using MESH headings eliminated a number of relevant articles identified in a preliminary scoping of the literature. Consequently, a full-text search in both Medline and EMBASE was conducted (covering articles from 1946 to present) on 22<sup>nd</sup> September 2011 using the following search string: *(structural OR structure OR volume OR volumetric) AND (parcellate OR parcellated OR parcellation OR measure OR measurement OR estimate OR estimation) AND (frontal OR prefrontal)*. The references of all screened articles were searched for further relevant papers.

#### 3.3.2 Screening and Eligibility

All studies reporting a method for manual tracing the human frontal lobe or its sub-regions from landmarks on magnetic resonance images were included. Further inclusion criteria were: studies which reported three-dimensional boundaries for manually delineating the frontal lobe or sub-regional ROIs from MR images; and English language. Exclusion criteria were: exclusive use of co-ordinate grid systems; insufficient detail for single boundary to allow reproduction of technique; and publication only in grey literature (as defined by the Grey Literature International Steering Committee; [www.glisc.com](http://www.glisc.com)) due to the amount of detail required to describe a complete segmentation protocol. Information was reviewed from both

publication and supplementary material where available. Where a protocol was unpublished, the authors were contacted in the first instance, and the study excluded if there was no reply.

### *3.3.3 Data Extraction and Synthesis*

The following information was collected: boundary limits for ROI in frontal lobes, study population, sample size, age range, MR sequence used, magnet strength, slice thickness, image pre-processing steps, and inter- and intra-rater correlation coefficients.

### *3.3.4 Study Quality*

To quantify the steps taken by each paper to avoid bias and to justify and validate their protocols, the QUADAS quality assessment tool (Whiting et al., 2003) was adapted for the current review. The following criteria were used to rate reviewed publications: (1) Sufficient detail provided to reproduce the protocol. (2) Justification for selection of anatomical landmarks and sub-regional boundaries as evidence that the relationship between topography and neuroarchitecture had been considered. (3) The reporting of intra-class correlation coefficients (ICCs) was considered the minimum method for checking the reproducibility of the protocol in question. Ideally, both inter- and intra-rater metric, and measures of spatial concordance, should be reported. (4) Blinding to participant status where possible. (5) Robust rules accounting for topographical variation. Applicable for regions known to vary

significantly between individuals (e.g. cingulate and orbital regions – discussed in 3.4.3 and 3.4.6). (6) Summary statistics of volumes reported. (7) Demographics of the participant groups, including age, gender, number and clinical characteristics reported. Both of these final points are useful in identifying systematic biological variance both within and between participant groups, and whether or not the protocol may be appropriately applied to another population. Duplicate scoring was conducted independently by two raters (SRC & NAR) for a subset of papers (90) describing the posterior frontal lobe boundary only, and points of disagreement were discussed and resolved. For each publication, a score out of the eligible criteria (up to 7) was converted to a percentage as an indicator of quality.

### 3.4 Results

#### 3.4.1 Study Selection

A total of 1738 records were initially identified, and reduced to 1542 once duplicates were removed. Of these, 1312 reports did not meet the inclusion criteria mainly due to using automated structural methods, functional MR techniques, or animals. Papers that repeated the same method for the same participants were excluded. Studies applying the same protocol to different cohorts were not excluded as they contribute unique information concerning validity and reproducibility in a range of clinical populations or age groups. Further, their inclusion gives an undiluted picture of general publication quality for the entire spectrum of clinical topics studied using manual parcellation. The remaining 230 were potentially eligible for inclusion into the review. Twenty-four of these were excluded due to: lack of boundary information (n=13), regions not intended to be exclusively frontal (n=5), grey literature (n=1), and re-reporting previous results (n=5). This left 206 reviewed publications (Figure 3.2).

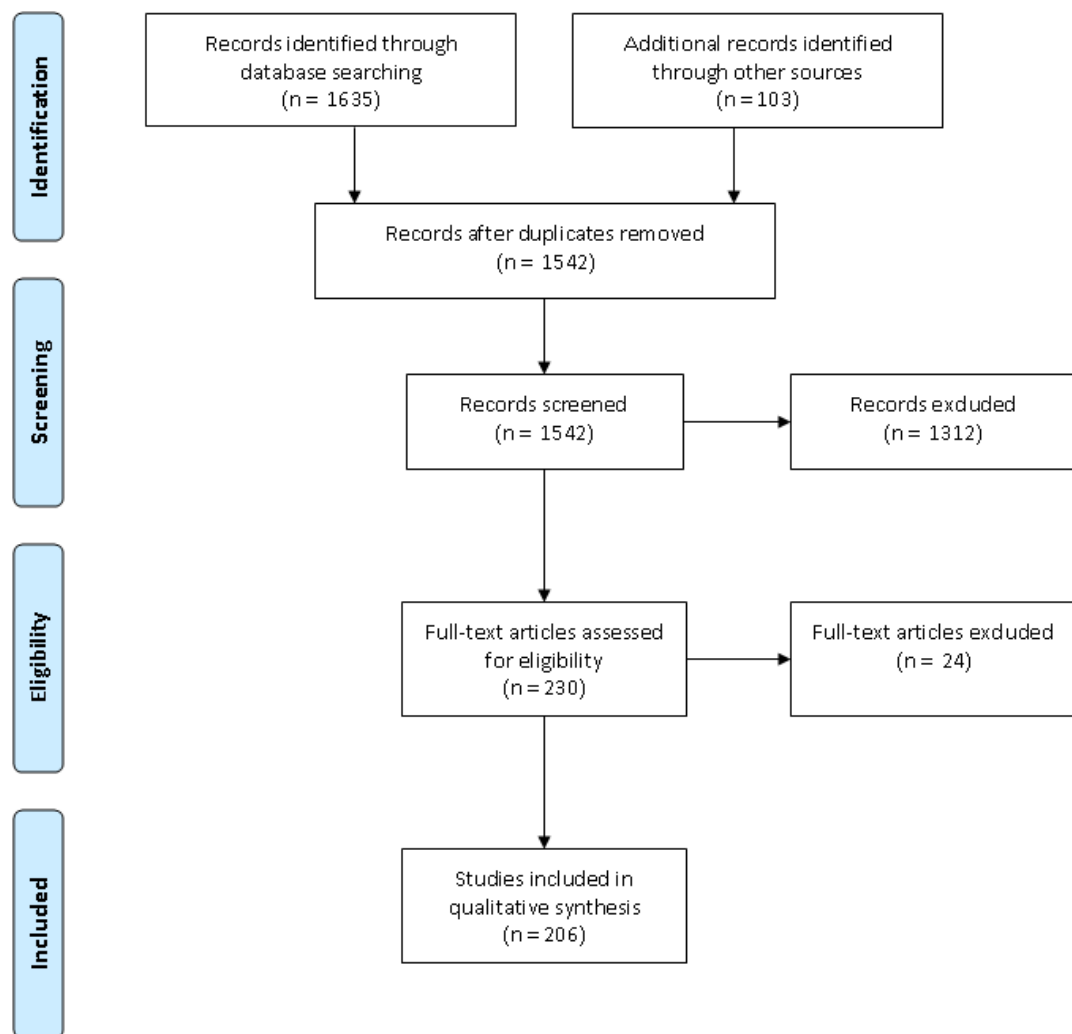


Figure 3.2. Systematic literature review flow diagram, adapted from Moher et al. (2009).

### 3.4.2 Study Characteristics

The 206 reviewed papers include 10,903 participants, with a mean of 29 per participant group (median = 22, range = 1-200). The main topics of interest were schizophrenia (25%), affective disorders (unipolar, bipolar, major and minor depressive disorders 13%), dementia (7%), and healthy adults of various ages (26%).

Study dates span 1988-2011, and MRI scanners range from 0.1T to 3T in magnet strength.

#### *3.4.3 Study Quality*

On average, papers satisfied about three-quarters of the quality criteria (median score = 73.21%, range = 16.67-100%); 50% of papers did not attempt to justify their boundary selections either explicitly or by citation. Reporting methods for controlling rater bias were also low, with 25% not reporting reliability measures, and 32% not reporting blindness to participant status. Amongst those papers that relied on topography to carry out the protocol, 31% failed to give explicit instructions on how to deal with known topographical variants, although only 4% did not provide sufficient detail for all necessary boundaries. Twenty-one percent did not report the raw volumes from their method, and almost 6% did not report the demographics of their participants.

#### *3.4.4 Synthesis of Results*

Two differences in the general type of approach to frontal lobe parcellation were noted. Firstly, geometrical cut-planes were used in most methods, combined with sulcal and gyral cues, or to demarcate large areas of lobe. The application of straight boundaries across the cortex clearly has advantages. As observed by Lacerda et al. (2003), this method is faster to execute and is more robust to rater subjectivity and difficulties caused by the highly variable sulcal patterning between brains that can lead researchers to exclude brains from analysis (e.g. Szeszko et al., 1999a, 1999b). Nevertheless, this approach is unlikely to offer sufficient sensitivity to capture subtle



sub-regional differences, and is not sympathetic to brain topography. Given the known relationship between cortical folding and underlying cytoarchitecture, landmarks that have been used to derive a limit geometrically are usually distant from the ROI (for example, using a coronal plane at the optic chiasm as the posterior extent of frontal cortex). Such landmarks are less likely to account for inter-individual variations in both brain size and shape, or the different effects of age and disease on the brain, potentially introducing error into the resultant measurements. Thus, using gyrification as a cue to underlying cellular composition (where possible) is a way in which such ambiguities can be controlled.

Secondly, the way in which white matter has been assigned to lobar sub-regions was found to vary amongst protocols. Of those articles reviewed, two approaches established a central point in each hemisphere and used radiating lines to the cortex to designate each segment of white matter to its corresponding cortical area (Convit et al., 2001; Sanfilipo et al., 2000). Other approaches quantified the cortex and sub-regional shallow white matter by drawing lines between key sulci (van Elst et al., 2003; MacLulich et al., 2006; Sanches et al., 2009; Schenker et al., 2005; Semendeferi et al., 1997) or separating CSF, grey and white matter.

A common misconception is that difficulties in reconciling anatomical findings across publications are due to differences in nomenclature (as observed by Bohland et al., 2009), rather than underlying differences in the method of ROI measurement. However, the reviewed papers used fairly consistent names to identify broadly similar ROIs. Each frontal sub-region will be discussed in turn under commonly used nomenclature, starting with the posterior frontal lobe boundary, then the frontal pole, anterior cingulate, dorsolateral, inferior-lateral and orbital. Each

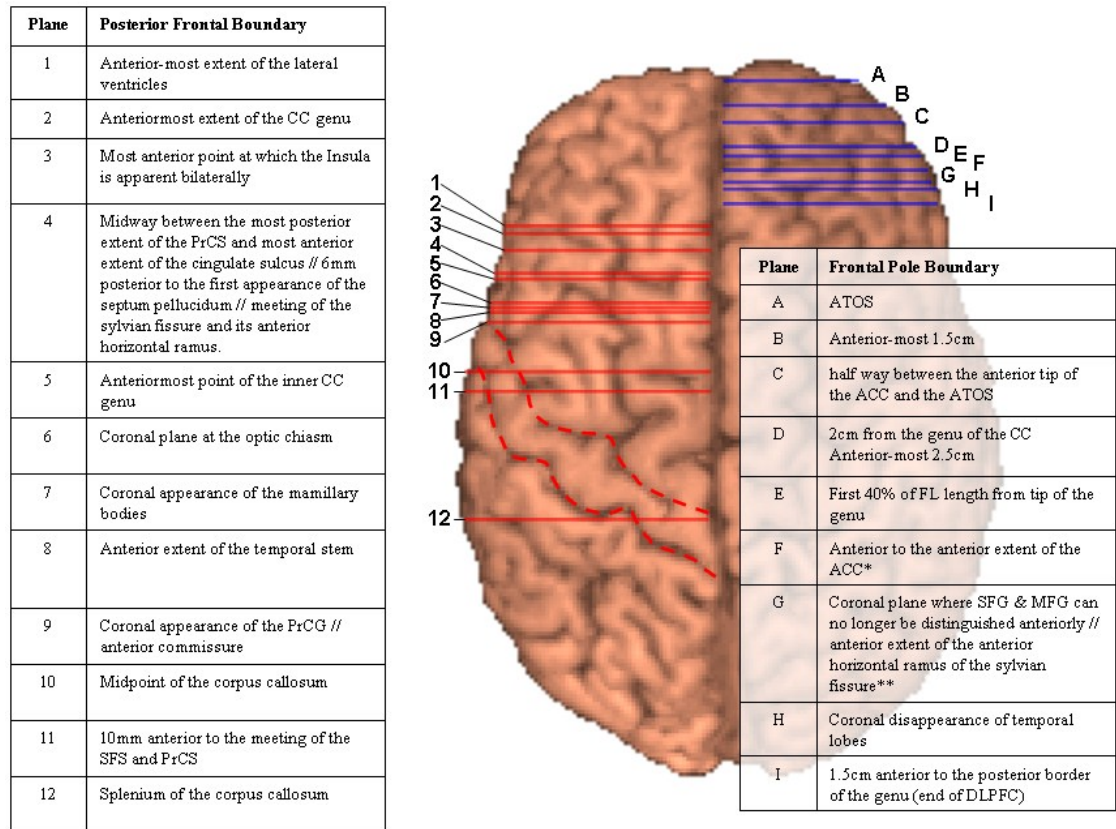
region below contains a brief introduction, results and short discussion. For ease of reference, only the papers from which a given protocol originated will be cited in the proceeding text, although full details of all the reviewed papers are available as supplementary material, and online at [\[www.bric.ed.ac.uk/research/imageanalysis.html\]](http://www.bric.ed.ac.uk/research/imageanalysis.html).

#### 3.4.4.1 Posterior Frontal Boundary

*Introduction.* At its posterior-lateral edge, the frontal lobe is situated anterior to the central sulcus. Also known as the central fissure of Rolando, this deep sulcus runs from the medial wall, over the lateral convexity until its ventrolateral termination at the sylvian fissure, separating the frontal lobe from parietal tissue. The precentral gyrus itself contains the primary motor cortex (BA4), immediately anterior to the precentral sulcus (PrCS) and supplementary motor area (SMA; BA6; Duvernoy, 1999). The differentiation between frontal and prefrontal lobe is traditionally made on the lateral surface, with the latter excluding both motor and supplementary motor regions (Semendeferi et al., 2001). The frontal lobe is ventrolaterally separated from the temporal lobe by the sylvian fissure, and on the ventral aspect is divided from the insular cortex (considered by some to be an entirely separate lobe; Stephani et al., 2011) by the circular sulcus of the insula.

*Results.* Amongst the reviewed publications, there were a number of variations in the use of lateral, medial and ventral aspects of the posterior frontal lobe boundary. We identified 19 different methods, using 15 different landmarks, for establishing the posterior frontal boundary (Figure 3.3), which has clear implications

for between-study comparison. The central sulcus was commonly adopted as the overall posterior boundary. The absence of a clear topographical landmark makes identifying the anterior limit of the supplementary motor area (and therefore the posterior extent of the prefrontal region) problematic. This has led to common use of the precentral sulcus (PrCS) as the most posterior boundary for defining the prefrontal (as opposed to frontal) lobe. Thirty-one papers reported that their measures began anterior to the PrCS. Although use of either central or pre-central sulcus was common, it can be challenging to determine their course when visualising the brain in 2D slices, as reported by several authors (Coffey et al., 1991, Lyoo et al., 1998 and Pantel et al., 1997). Common strategies to overcome this were the use of simultaneous tracing in multiple slice orientations or software that allows ‘painting’ onto 3D renderings to be visualised as a guide during tracing onto standard 2D slices were used.



*Figure 3.3.* Variation in boundary selection shown on a 3D rendering of an MRI of a young healthy male. Left hemisphere shows posterior frontal boundaries, Right hemisphere shows frontopolar boundaries. \* medial FP border for the Rademacher/Caviness protocol, \*\* lateral FP border for the Rademacher/Caviness protocol, “//” marked plane corresponds to multiple landmarks. Caudal and rostral broken red lines follow the course of the Central and PreCentral sulci respectively. Fronto-marginal sulcus not shown.

Given the difficulty in accurately identifying caudal aspects of the frontal lobe where such methods are unavailable, imposing a coronal cut-plane as the posterior boundary was also found to be a common method. The slice just anterior to, or in which the genu of the corpus callosum appeared was cited by 45 papers as the frontal lobe posterior boundary. The use of two coronal cut planes, one above the body of the corpus callosum where the central sulcus traverses the midsagittal line and one below the genu that intersects the anterior point of the inner surface of the genu, were applied in studies after Crespo-Facorro et al. (1999). Pantel et al. (1997) used the splenium of the corpus callosum but only in the superior slices where it appeared; above the mamillary bodies, a horizontal line from the lateral sulcus (Sylvian fissure) to the midline was used. Other studies used a coronal plane at the midpoint of the corpus callosum (Jernigan et al. 1991; Bartzokis et al. 1993), or a coronal plane a set distance anterior to the most anterior coronal extent of the temporal stem (after Wible et al. 1995). Coronal cut planes have also been employed at the anterior commissure (Bjork et al., 2009; Bremner et al., 2000; Filipek et al. 1997; Nifosi et al., 2010), anterior extent of the lateral ventricles (Coffey et al. 1998), bilateral appearance of the insula (Bäckman et al., 1997; Ginovart et al., 1997), the optic chiasm (Coffey et al., 1991; Lyoo et al. 1998), the mamillary bodies (Cowell et al., 1994), or 6mm posterior to the septum pellucidum (Noga et al., 1995). Several papers (Convit et al., 2001; Gold et al., 2005) attempt to distinguish the supplementary motor area from the prefrontal lobe by identifying the coronal plane that equally divides the distance between the cingulate sulcus and the precentral sulcus.

Although the majority of cut-plane methods use the selection of distant, sub-cortical landmarks to position cut-planes for the posterior frontal boundaries, explicit attempts to combine cortical topography and cut-planes have also been applied. Kates et al. (2002) selected a coronal slice at the appearance of the precentral gyrus, allowing the exclusion of the supplementary motor area between this plane and the precentral gyrus, based on relevant cortical folding and presumed underlying cytoarchitecture. However, the extent of variation in the angle of the precentral gyrus as it ascends from the dorsal aspect of the brain is unknown.

A number of cut planes have also been used to limit the most posterior extent of the ventral frontal lobe. The substantia perforata is a landmark used for many of the papers after Rademacher et al., (1992) to define the posterior boundary of the orbital regions, although Szeszko et al (1999a) report difficulties in identifying this. They suggest instead using the most posterior coronal slice in which the olfactory sulcus maintains its characteristic shape, although this, too, may be subject to interpretation. However, the majority of studies that utilise the central or precentral sulcus to guide frontal lobe segmentation stated the use of the circular sulcus of the insula as the ventral boundary, following traditional anatomical and functional convention.

*Discussion.* Therefore, whilst the method by Kates et al. (2002) may be a promising approach because it avoids the difficulty in following the central or PrCS in two dimensions and takes account of local topography to some degree, further work would establish whether the area of frontal lobe excluded is equivalent in each

individual. The lateral ventricles vary greatly in size within a healthy population, and as such would be a significant determinant of the resultant volumes if using these boundaries (Blatter et al. 1995). Measures obtained using these landmarks has further potential to be influenced by ventricular variation caused by pathology or ageing.

#### 3.4.4.2 Frontal Pole

*Introduction.* Designated as area 10 by Brodmann, the anterior tip of the frontal lobe, known as the frontal pole (FP) has been identified as a cellularly-distinct sub-region by a large number of brain cartographers (Brodmann, 1909; Campbell, 1904; von Economo and Koskinas, 1925; Hof et al., 1995; Ongur et al., 2003; Petrides and Pandya, 1994; Sarkisov, 1949; Semendeferi et al., 2001; Smith, 1907; Uylings et al., 2010). In addition to its structural distinctiveness, it is phylogenetically the most recent addition to the cerebrum (Semendeferi et al., 2001), is subject to an unusually long period of development and maturation (Burgess et al., 2006; Dumontheil et al., 2008) and thought to make functional contributions to higher cognitive processes such as analogical reasoning and self-referential thought (Benoit et al., 2010; Volle et al., 2010), and general intelligence (Gläscher et al., 2010; Jung and Haier, 2007). The relation of FP function to a wide variety of stimulus- and task-related processes, and activity when the mind wanders and when engaged in a demanding cognitive task (Dumontheil et al., 2010) supports the theory that it acts as a ‘gateway’ through which the balance between stimulus-oriented and stimulus-independent thought is controlled (Burgess et al., 2006; Gilbert et al., 2006).

The frontal pole is a clearly distinct sub-region, and like the posterior frontal lobe boundary, volumes of some or all FL regions are dependent upon the FP boundary. If this region is ignored, the resultant measures (of the frontal gyri for example) potentially include excess noise resulting from distributing the anterior portion of the frontal lobes between multiple regions. A further complication of ignoring this region then arises, as the anterior-most portions of the frontal gyri in the coronal plane become more difficult to differentiate, making continuing sub-regional parcellation challenging and potentially unreliable.

*Results.* The results of the systematic review revealed that, of the 71 papers reporting sub-regional volumes extending to the anterior-most portion of the frontal lobe, 47 (66%) did not include a measure of the FP. Amongst the remaining 24 studies (34%) that did, we identified 14 distinct posterior boundaries<sup>18</sup>. As displayed in Figure 3, this variability can have a striking effect on the reported size of the frontal pole.

Analysis of the variety of approaches shows that a commonly adopted method to deal with the lack of a clear landmark was to orient all brains to a standard alignment, and then use a single cut-plane in the coronal orientation to signify the FP boundary, based on a consistent and readily-identifiable feature. It is the selection of the feature itself that differs between studies. Several used a coronal plane positioned a fixed distance from a particular boundary (Planes B – Wible et al., 1997; D – Sanfilipo et al., 2000, Tisserand et al., 2002; and I – Gilbert et al., 2001). Others used a coronal plane at the anterior extent of the temporal lobes (Plane H – Rankin et al.,

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<sup>18</sup> Note that some of these papers account for the presence of the frontal pole but do not measure its volume.



2004, Rosen et al., 2002), the termination of the anterior horizontal ramus of the Sylvian fissure (Plane G – Sanches et al., 2009), the anterior-most extent of the ACC (Plane F – Convit et al., 2001), or the anterior termination of the olfactory sulcus (ATOS; Plane A – John et al., 2006, McLaughlin et al., 2009; Nakamura et al., 2008). Finally, Iordanova and colleagues (2006) used the fronto-marginal sulcus (FMS) to define the posterior fronto-polar limit, including the transverse fronto-polar gyri into measure of the superior and middle frontal measures.

*Discussion.* Whilst imposing a plane at a fixed distance from a landmark affords a high degree of reproducibility, imposing a rigid dimension (e.g. x most anterior slices) on each individual's frontal pole fails to take into account individual differences in global and local brain size and morphology. A similar issue can be said to apply to methods that use distant, unrelated landmarks such as the anterior extent of the temporal lobes (Rankin et al., 2004, Rosen et al., 2002). The use of the termination of the anterior horizontal ramus of the Sylvian fissure to identify the lateral FP boundary (Sanches et al., 2009), or the FMS for the dorsal limit (Iordanova et al., 2006) are preferable in terms of proximity; however, it has not been made clear how these sulci relate to underlying structure. Although a reliable cortical landmark (Ono et al., 1990), the FMS as a dorsal FP boundary does not correspond readily with numerous maps of cytoarchitecture on the medial wall (see Figure 3.4). Moreover, this landmark was used to limit the tracing of the lateral frontal gyri by Iordanova and colleagues (2006) and so no ventral boundary was proposed.

Use of the anterior-most extent of the ACC (Convit et al., 2001) seems to concur more readily with reported cytoarchitecture, in that no reports have yet suggested that the frontopolar cortex encroaches on the cingulate gyrus. This

structure presents a proximal, clear and logical boundary for the most anterior medial point that we can be fairly certain does not represent BA10, though how much more anteriorly this cellular field actually lies in different people, or how it relates to the lateral surface has not currently been reported in vivo.

Finally, the ATOS could be a promising feature for delineating the FP, based on the correspondence of this feature to the FP boundaries reported by Brodmann (1909), Sarkisov (1955), von Economo and Koskinas (1925), Ongur et al. (2003), Semendeferi et al. (2001) and Hof et al. (1995). Furthermore, it is the least variable (Chiavaras et al., 2001; Uylings et al., 2010) and earliest of the orbitofrontal sulci to appear during development (Chi et al., 1977) suggesting it may be a common feature between individuals. In spite of the weight of this supportive evidence cited by John et al. (2007), they are cautious to observe that whilst FP volumes using this approach show relatively little variance and correspond with a previous post-mortem measure of BA10 (Semendeferi et al., 2001), this cannot be taken as the ‘true’ limit of FP, and the ATOS may not necessarily be appropriate in other populations. We found that using the ATOS as a boundary in AC-PC aligned MRIs of 88 healthy 72 year old males yielded far more variable FP measures than for any other region (SRC – unpublished data; see Appendix E). Whether this finding is reflective of the small sample used by John et al. (20 young healthy volunteers), positional changes in the ATOS through generalised atrophy, or possibly the true nature of BA10 in the ageing brain, further work is needed to relate individual differences in morphology to underlying neuroarchitecture in a large and varied sample of individuals before the accuracy of FP measurement from MRIs can be improved. Just as with the posterior boundary of the frontal ROIs, this is also of key importance given the sizeable

volumetric impact that a shift in the frontal pole boundary has on the numerous other frontal ROIs with which this boundary is shared.

#### 3.4.4.3 Anterior Cingulate Cortex

*Introduction.* The anterior cingulate cortex (ACC) is the rostral portion of the cingulate gyrus running immediately dorsal to the corpus callosum, wrapping around its most anterior extent (genu), and is bound by the cingulate sulcus and callosal sulcus on the medial wall of the frontal lobes. This region is generally considered to comprise BAs 24 and 32, with BA25 positioned at the most posterior subgenual extent of the gyrus. Convergent evidence suggests that the ACC can be divided into at least two distinct segments with differing connectivity (Beckmann et al., 2009), receptor distribution (Palomero-Gallagher et al., 2009) and function (for a functional meta-analysis see Bush et al., 2000). The dorsal region is involved in goal-based action selection through its strong connections to lateral frontal and pre-motor regions, while the ventral region contributes to emotional processing and is preferentially connected to the ventral and medial frontal areas (Mansouri et al., 2009). This has made the ventral ACC a particular ROI for research into various affective disorders.

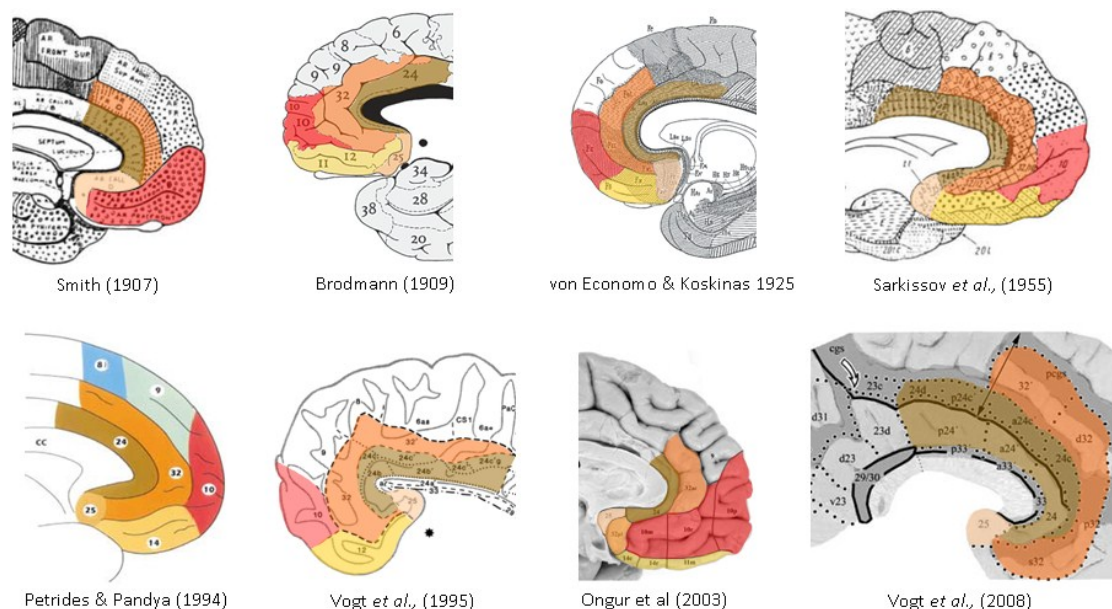
*Results.* We found 14 reports that incorporated the cingulate gyrus into a more gross sub-regional measure (Beyer et al., 2009; Bjork et al., 2009; Carper and Courchesne, 2005; Gur et al., 2000; Medina et al., 2008; Ratnanather et al., 2001; Sanfilipo et al., 2000; Semendeferi et al., 1997, Wilde et al., 2005). Amongst the remaining 59 papers measuring the cingulate, there were 26 distinct methods for

delineating the ACC and its subregions, using a total of 19 different boundaries, calculated from 12 landmarks. Two main points of variability between authors were: 1) the way in which a second cingulate or paracingulate gyrus (PCG) was considered; and 2) the selection of anterior and posterior limits. These are discussed below:

Firstly, the cingulate area is a site of considerable inter-person morphological variation, and authors have taken account of this in a variety of ways. A PCG is present in 30-60% of cases and there tends to be a greater likelihood of a PCG in the left hemisphere (Fornito, 2004; Ono et al., 1990; Yucel et al., 2001). Given that, where present, the PCG shares a boundary with the cingulate gyrus, it also tends to result in a 39% decrease in cingulate volume compared to individuals without a paracingulate sulcus when controlling for head size (Fornito et al., 2006). Its presence is also likely to impact the medial superior frontal gyrus volume as well as that of the frontal pole (particularly where the measure is taken as the anterior-most extent of the cingulate formation). Interest in the PCG is relatively recent and the functional implications of its presence are not well understood, it has been reported to associate with executive functioning (Fornito, 2004). Evidence suggests that the connectivity between other regions and the cingulate is comparable, irrespective of the presence or absence of a PCG (Beckmann et al., 2009; Devinsky et al., 1995).

Out of a total of 56 reviewed publications reporting cingulate boundaries, 13 do not mention the PCG (Ballmaier et al., 2004; van Elst et al., 2003; Flashman et al., 2001; Raz et al., 1995; Salat et al., 2001; Sowell et al., 2002; Woodward et al., 2006). Three treated the PCG as part of the cingulate region (Convit et al., 2001;

Ranta et al., 2009; Wible et al., 1995), 10 included it as part of the superior frontal gyrus on the medial aspect (Bremner et al., 1998; John et al., 2006; Lindberg et al., 2009; MacLulich et al., 2006; Suzuki et al., 2005; Szeszko et al., 1999a; Yamasue et al., 2004), though 27 treat it as a separate entity altogether (Bremner et al., 2002; Crespo-Facorro et al., 1999; Fornito et al., 2006; McCormick et al., 2006; Monkul et al., 2007; Noga et al., 1995; Paus et al., 1996; Rademacher et al., 1992; Riffkin et al., 2005; Takahashi et al., 2002).



*Figure 3.4.* Examinations of medial frontal lobe cytoarchitecture by various groups throughout the 20<sup>th</sup> century. Anterior cingulate is shown in brown, paracingulate in orange.

Secondly, both the sub-genual and posterior limit of the ACC vary between studies. Although cytoarchitectonic explorations of the region consistently discriminate between the anterior and posterior cingulate cortices (Figure 3.4), the boundary separating the two regions cannot be readily identified from clear proximal

landmarks in an MR image, resulting in an array of approaches (summarised in Figure 3.5). Whilst some simply do not divide the cingulate gyrus into two at all (Convit et al., 2001; Sowell et al., 2002; Tzourio et al., 1997), the most commonly adopted landmarks for the posterior extent make use of sub-cortical markers such as the anterior commissure (Bremner et al., 2002; Fornito et al., 2006; Kaur et al., 2005; Nifosi et al., 2010; Paus et al., 1996; Takahashi et al., 2002a; Tisserand et al., 2002; Yucel et al., 2008), the most anterior or dorsal extents of the corpus callosum (Bremner et al. 1998; Haznedaar et al., 1997; Ranta et al., 2009; Raz et al., 1995; Salat et al., 2001), the septum pellucidum (Noga et al., 1995) and mammillary bodies (Yamasue et al., 2004), whilst others have selected more proximal cortical features such as where the ascending ramus of the Sylvian fissure joins the cingulate sulcus (McCormick et al., 2006) or the dorsal termination of the precentral sulcus on the medial wall (Rademacher et al., 1992). This inconsistency is understandable, given that there is little cytoarchitectural information on variation in posterior ACC limit between individuals. Nevertheless, data from a probabilistic connectivity analysis appear to show that the cingulate area ventral to the central and precentral sulci on the medial wall contains connections to motor and premotor areas, whereas immediately more anterior cingulate regions connect to premotor and dorsal prefrontal cortex (Beckmann et al., 2009)<sup>19</sup>. This converges well with evidence from classical structural maps, suggesting that the posterior boundary lies in this vicinity and that local gyral patterns may better reflect this division.

The anteroventral extent of the cingulate gyrus also affects the consistency of reported cingulate volumes between studies. Figure 3.5 shows that several groups

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<sup>19</sup> Their dorsal PFC refers to middle frontal gyrus. The superior frontal gyrus was not used as a target for connectivity in this study.

have elected to trace the cingulate to its natural gyral extent; others use the appearance of the internal capsule or septum pellucidum. The use of the genu of the corpus callosum is widespread for limiting the cingulate gyrus or for excluding sub-genua cingulate regions altogether, though very few papers give an explicit justification for adopting this boundary.

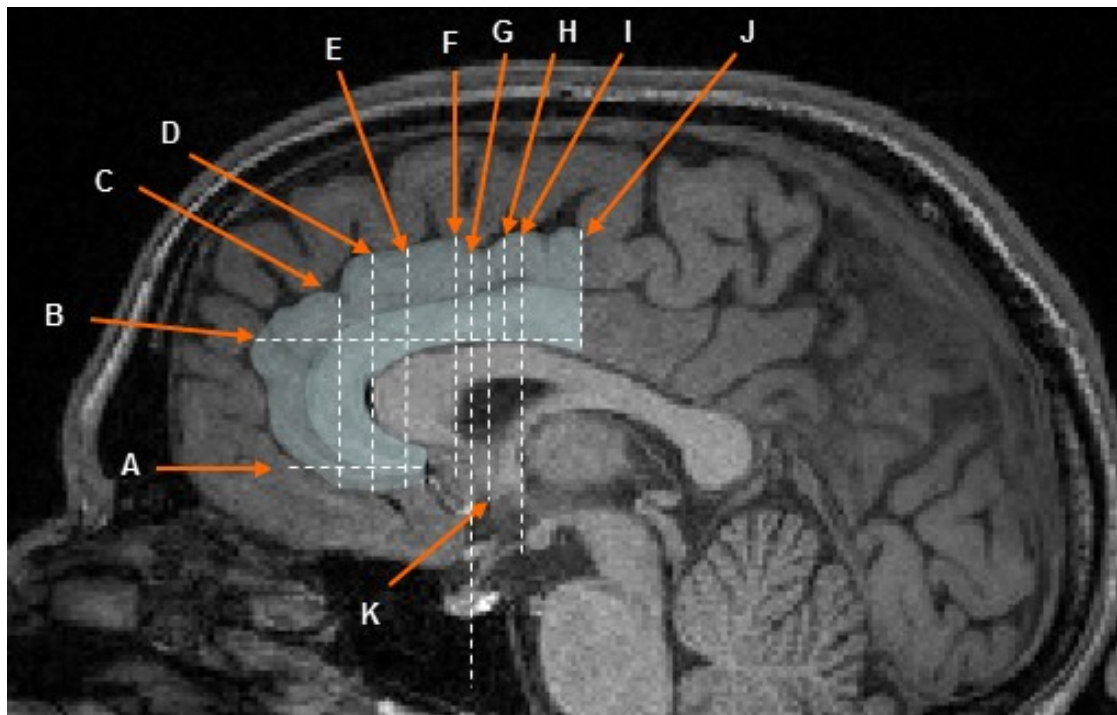
Convergent evidence from cytoarchitecture and tractography (discussed above) suggests that the anterior cingulate may be divided into sub-units, but the number and position of these is not clear. For example, Ongur et al. (2003) suggests that the sub-genua extent of the paracingulate stops near the superior rostral sulcus (similar to Smith, 1907 and Sarkisov, 1955), whilst the ventral cingulate gyrus only becomes divided in very posterior sections. This latter observation seems to be echoed by Brodmann (1909), von Economo and Koskinas (1925), and Petrides and Pandya (1994) although they each depict sub-genua continuity of the paracingulate with von Economo and Koskinas identifying four borders for the paracingulate only (see Figure 4). In contrast, Vogt et al. (1995, 2008) and Smith (1907) depict multiple cingulate regions on both ventral and dorsal aspects with a continuous paracingulate, which relates closely to recent connectivity analysis (Beckmann et al., 2009; Johansen-Berg et al., 2008), and broadly with previous reviews of neuropsychology data (Bush et al., 2000; Devinsky et al., 1995).

Amongst the various methods for cingulate parcellation identified in the review, several attempted to mirror the rostral ‘cognitive’ and ventral ‘affective’ cingulate divisions. Nineteen reported boundaries were derived from the corpus callosum (Asami et al., 2008; Botteron et al., 2002; Brambilla et al., 2002; Coryell et

al., 2005; Crespo-Facorro et al., 1999; Drevets et al., 1997; Fornito, 2006; Hastings et al., 2004; Hirayasu et al., 1999; Kegeles et al., 2003; Lindberg et al., 2009; McCormick et al., 2006; Nifosi et al., 2010; Rauch et al., 2003; Takahashi et al., 2003), and one used the anterior extent of the internal capsule (Bremner et al., 2002). Further differentiation between smaller sub-regions used a coronal plane extended both above and below the genu (Fornito et al., 2006; Takahashi et al., 2003), or the anterior extent of the internal capsule can be seen (Coryell et al., 2005; Drevets et al., 1997; Nifosi et al., 2010).

*Discussion.* In summary, the correspondence between multiple studies of the architecture, function and connectivity not only give some indication of appropriate anterior and posterior boundaries, but show that there is a reasonably stable relationship between distinct connectivity profiles and their location on the gyral surface across individuals. It is currently still unclear to what extent the geometrical partitioning of these sub-regions in manual tracing can take account of true individual variability in these boundaries and to what extent it is simply arbitrary. It is worth bearing in mind that although landmarks such as the corpus callosum and internal capsule appear to provide a convenient way of partitioning the ACC, the resultant volumes (and their reported correlations with symptoms) could represent differences in morphology of these extrinsic landmarks rather than the ACC itself. Particularly where small ROIs are concerned, even small fluctuations in boundary selection could result in a large percentage difference in the brain matter being measured.





*Figure 3.5.* Common anterior and posterior boundaries that have been used to delineate the ACC and its subregions, shown on a midsagittal MR slice of a young healthy male. A: Most ventral axial slice in which the globus pallidus, caudate and putamen can be clearly seen. B: Most dorsal axial slice where the CC divides the hemispheres. C: 16% of the distance between the CC genu and the tip of the frontal lobe. D: Coronal plane at the genu of the corpus callosum. E: Internal capsule separates caudate and putamen. F: Coronal plane at the posterior part of the CC genu. G: Most anterior coronal slice showing the temporal stem. H: Coronal plane at the most dorsal axial slice where the CC divides the hemispheres. I: Coronal appearance of the mammillary bodies. J: Coronal plane at the connection of the superior frontal sulcus and precentral sulcus / coronal plane at the dorsal termination of the precentral sulcus on the medial wall. K: Coronal plane at the anterior commissure.

#### 3.4.4.4 Dorsolateral Frontal Cortex

*Introduction.* Commonly referred to as the dorsolateral prefrontal cortex (DLPFC), BA 9 and 46 exhibit some variation in cortical positioning between individuals, based on the detailed examination of brains post-mortem (Rajkowska

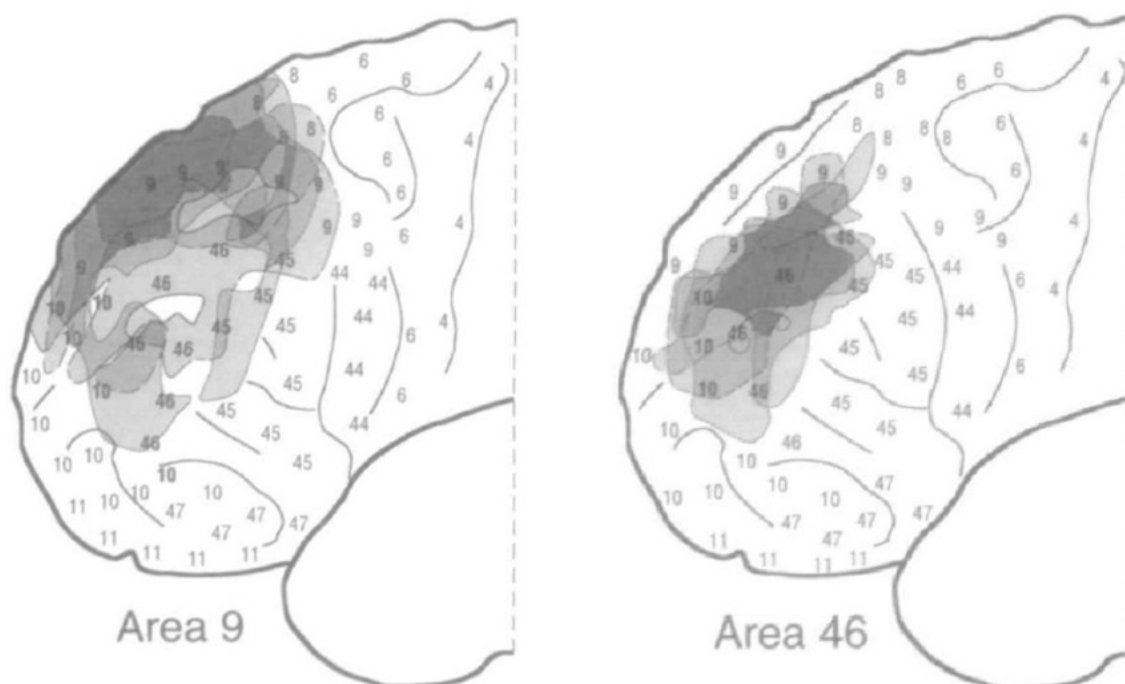
and Goldman-Rakic, 1995). Nevertheless, BA46 lies predominantly on the middle frontal gyrus (MFG), whereas BA9 lies mainly on the superior frontal gyrus (SFG; Figure 3.6). Evidence from functional imaging and lesion studies link this area with working memory (M Petrides, 2000), attentional control, switching (Cabeza and Nyberg, 2000; Shallice et al., 2008), planning (Unterrainer and Owen, 2006) and fluid intelligence (Deary et al., 2010; Jung and Haier, 2007).

*Results.* Dorsal and ventral borders of the DLPFC on the lateral wall vary between protocols. Whilst the superior and inferior frontal sulci were used consistently as boundary guides, combinations of two or even all three frontal gyri were used. We identified 55 papers reporting methods for measuring the lateral convexity of the frontal lobe. Of these, 7 explicitly combined SFG and MFG (Croxson et al., 2005; Gansler et al., 2009; McLaughlin et al., 2009; Rosso et al., 2010; Sanches et al., 2009; Seidman et al., 2006; Tisserand et al., 2002), although there were 22 that allowed measurement of the superior and middle frontal gyri separately (Crespo-Faccorro et al., 1999; Flashman et al., 2001; Iordanova et al., 2006; John et al., 2006; Rademacher et al., 1992; Ranta et al., 2009; Suzuki et al., 2005; van Petten et al., 2003; Wible et al., 1997; Zuffante et al., 2001).

In contrast, 6 papers separated the SFG and combined IFG and MFG, in contradiction to Rajkowska and Goldman-Rakic (Baaré et al., 1999; Bjork et al., 2009; Gilbert, 2001; Prasad et al., 2005; Seidman et al., 1994; Wilde et al., 2005). Twenty publications combined all three frontal gyri (Carper and Courchesne, 2005; van Elst et al., 2003; Head et al., 2002; Raz et al., 1995; Salat et al., 2001) or used geometrically derived boundaries without accounting for individual variation in topography (Harris et al., 1994; Hill et al., 2003; Medina et al., 2008; Nagel et al.,

2006; Ranta et al., 2009; Schlaepfer et al., 1994). It must be noted that Ranta et al. used cut planes following the trajectory of the superior and inferior frontal sulci, but this is not fully sympathetic to individual differences in the course of the frontal sulci.

Another significant variation is the differentiation of lateral and medial portions of the SFG. Methods explicitly dividing lateral and medial SFG identify relevant matter up to the lateral extent of the lateral ventricles from the midline (Bjork et al., 2009), lateral extent of grey matter at the lateral orbital sulcus (Gur et al., 2000), or a straight line into the grey matter at the superior margin of the inter-hemispheric fissure (Carper and Courchesne, 2005; Semendeferi et al., 1997; Suzuki et al., 2005; Tzourio et al., 1997). One alternative method used the longitudinal fissure for anterior slices and the deepest part of the MFG more posteriorly (McLaughlin et al., 2009).



*Figure 3.6.* Reconstructions of the variability of Brodmann Areas 9 and 46 based on 5 brains. Darker shades indicate a greater degree of overlap. Figures reproduced from Rajkowska and Goldman-Rakic (1995).

*Discussion.* There is some variation in the use of frontal gyri to delineate the DLPFC, although the extant data suggests combining superior and middle frontal gyri is biologically plausible (Rajkowska & Goldman-Rakic, 1995).

Neuropsychology suggests that the division between superior and medial SFG is important in task switching behaviours, where superior medial areas are explicitly implicated in activating novel, non-learned response operations (for a review, see Shallice et al., 2008). Nevertheless, it is unclear which regions of superior medial frontal cortex are involved due to the lack of spatial resolution afforded by lesion

studies and neuroimaging in this region. The method for defining medial and lateral SFG volumes is fairly reproducible, although more work is needed to establish a clear cytoarchitectural and functional basis for this approach.

#### 3.4.4.5 Inferior Lateral Frontal Cortex

*Introduction.* The inferior frontal gyrus extends ventrally from the inferior frontal sulcus and comprises the pars opercularis (BA44, also known as Broca's Area), triangularis (BA45) and part of the pars orbitalis (BA47; Petrides et al 2012). Posteriorly, it is bound by the precentral gyrus, and anteriorly by the frontal pole. In Brodmann's original designation, area 47 referred to a large cellular field extended dorsally from the pars triangularis to the medial orbital sulcus. However, more recent investigations suggest that this region can be divided by the lateral orbital sulcus (LOS) in order to achieve better concordance with Walker's (1940) map of the macaque frontal lobe which serves not only to preserve the correspondence to primate models from which a great deal of functional detail has been learned, but also preserves the lateral portions of the orbital frontal cortex which have been reported to exhibit distinct functions (see next section; Mackey and Petrides, 2009; Petrides and Pandya, 1994). Other cytoarchitectural studies do not agree on the number of lateral orbital subregions or their relation to orbital morphology (Ongur et al., 2003; Uylings et al., 2010). In terms of functional contribution, the left IFG has been consistently associated with word comprehension and production (for reviews, see Costafreda et al., 2006; Bookheimer 2002), whilst the right IFG has been implicated in response inhibition (for a review, see Aron et

al., 2004). Also, the IFG is thought to be a core substrate of the mirror neuron system and the pathophysiology of disturbed action imitation and social reciprocity in autism spectrum disorders (Yamasaki et al., 2010). The IFG has also been implicated in thought disorder (reviewed in Nishitani et al., 2005) which has made this region of interest in schizophrenia research (e.g. Suga et al., 2010; Suzuki et al., 2005; Yamasue et al., 2004).

*Results.* All 28 papers reporting IFG measures used the inferior frontal sulcus as a guide for the superior boundary (and their anterior and posterior boundary selections are discussed in 3.4.1 and 3.4.2), but there was some disagreement regarding the ventrolateral limit. Seventeen publications used the anterior horizontal ramus of the Sylvian fissure to differentiate orbital regions from the IFG (Convit et al., 2001; Bremner et al., 1998; Knaus et al., 2006; Rademacher et al., 1992; Suga et al., 2010; Tisserand et al., 2002; Yamasaki et al., 2010) or as a landmark for an axial cut-plane (Baaré et al., 1999). As a result, the pars orbitalis was excluded from the IFG in these cases, whereas in other studies, it was included when the lateral orbital sulcus was used as the ventral boundary (Crespo-Faccorro 1999; John et al., 2006; Iordanova et al., 2006; Suzuki et al., 2005) or middle orbital sulcus (Salat et al., 2001). Although, in one case it was not clear how the pars orbitalis and OFC were divided (Tzourio et al., 1997).

A small group of papers also examined sub-regions of the IFG in isolation. There is some evidence to suggest that in this region too, researchers have been able to identify the functional differentiations that underlying differences in architecture suggest (e.g. Figure 3.1). Based on a meta-analysis of functional studies reporting activity during verbal fluency tasks, a significant difference in the reported loci of

activation was found between phonologic and semantic verbal fluency tasks, with the former activating dorsal regions on the left IFG, and the latter activating ventral regions (Costafreda et al., 2006), whilst the orbitalis is thought to facilitate semantic retrieval (Sabb et al., 2007). This supports the possibility of functionally meaningful parcellation of the IFG. There is consensus that this can be done by using the horizontal and vertical rami of the Sylvian fissure. Yet here too, morphology patterns are highly variable between individuals. Tomaiuolo et al. (1999) examined the variability of the pars opercularis in 54 brains and reported a large degree of variability, but that the vertical ramus of the Sylvian fissure was a consistent and reproducible landmark in 106 of the 108 sampled hemispheres. Likewise, the distinct cytoarchitecture of the triangularis and orbitalis regions can be consistently distinguished by the anterior horizontal ramus of the Sylvian fissure, based on a combination of MRI and histological methods in a total of 27 brains (Uylings 2010).

*Discussion.* The variance in ventral IFG boundaries reflects confusion concerning cellular architecture of the pars orbitalis (Uylings et al., 2010), and whether its inclusion (partial or otherwise) in the IFG is justified. It also reflects the wide array of topographical variations exhibited by the orbital surface of the frontal lobes (Chiavaras and Petrides, 2000; Lacerda et al., 2003). Consequently, the ventral limit of the IFG is a compromise between approximating the presumed distribution of cellular fields and ensuring consistent identification of the boundary on MR scans.

Further parcellation of the IFG into sub-units shows some consensus. However, the difficulty in accurately identifying the anterior horizontal ramus has been highlighted both in histological and volumetric studies. Ono et al. (1990) observed that this sulcus was not present in some of the brains they examined.

Difficulty in identifying this landmark during parcellation (Foundas et al., 2001) has led to excluding participants apparently without a horizontal ramus (Szeszko et al., 1999a; Rupp et al., 2005). Furthermore, Fischl et al. (2008) demonstrated that BAs 44 and 45 have more inter-individual variability in gyral configuration than non-frontal regions; suggesting that correspondence between architecture and cortical location may also vary considerably.

Taken together, this evidence highlights the potential of measuring the IFG and its sub-regions, although the significant variability in cortical positioning and subtle nature of the functional contributions made by each portion may only be worthwhile in scenarios where these sub-regions are of particular interest, although sulcal variability in this area is problematic.

#### 3.4.4.6 Orbitofrontal Cortex

*Introduction.* The orbitofrontal cortex (OFC), comprising BA 11, 12 and medial parts of BA47<sup>20</sup> is on the ventral aspect of the frontal lobes immediately superior to the orbital part of the frontal bones, anterior to the insula cortex, and extending dorso-medially to the sub-genual cingulate sulcus (Uylings et al., 2010). Animal models, human imaging and lesion studies suggest this region combines the processing of taste and smell with representations of emotional valence and expected reward value of stimuli (Hof et al., 1995). Through its dense interconnectivity with other frontal and non-frontal regions, it influences decision-making from situations involving basic sensory reward to complex social and emotional interactions by

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<sup>20</sup> Though disputed by some, as discussed in the previous section.



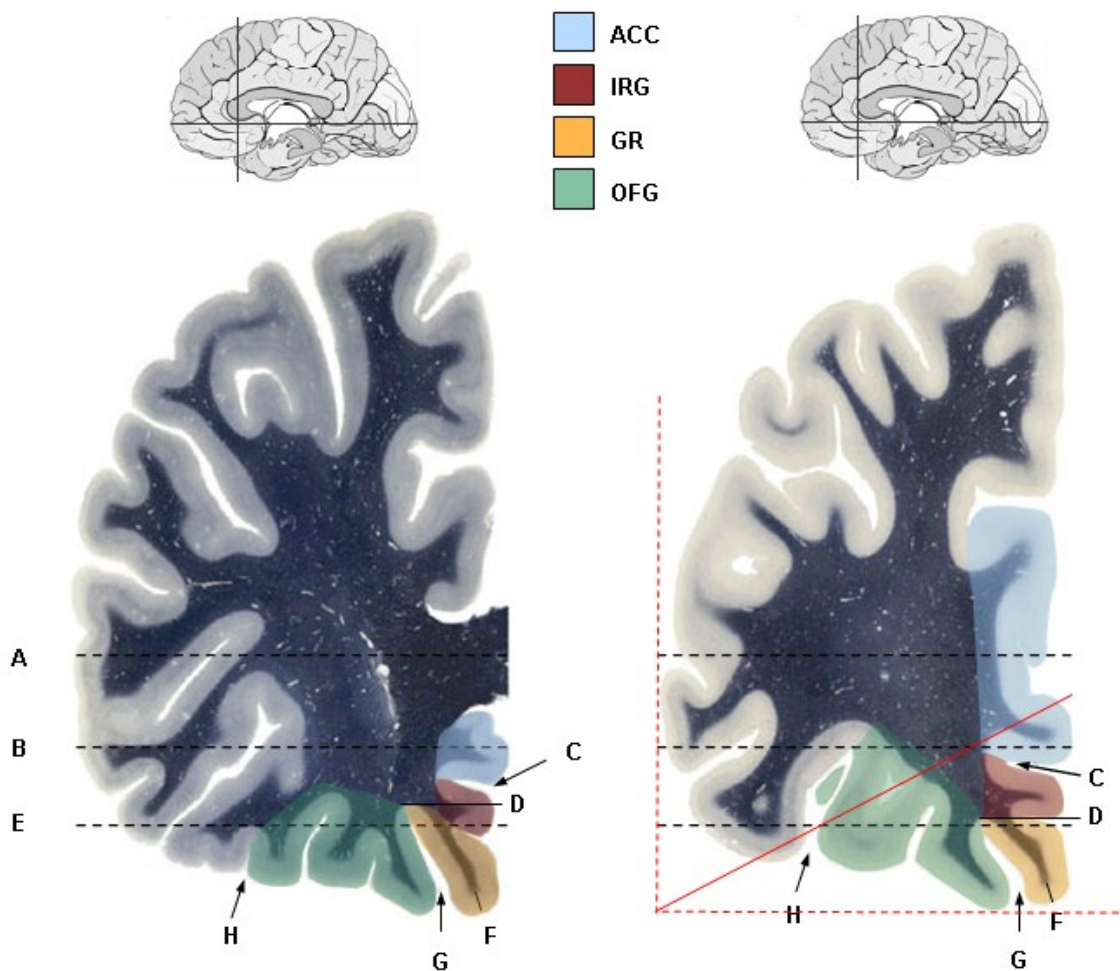
processing the emotional salience of potential actions (Rolls and Grabenhorst, 2008; Torralva et al., 2007). As a consequence, this region has been of particular interest in psychiatric disorders where affect is low or flattened (such as depression), schizophrenia in which olfactory insensitivity has also been observed (Moberg et al., 1997; Rupp et al., 2005), and obsessive compulsive disorder and bipolar disorder, in which OFC abnormalities have been reported in post mortem brains (Blumberg et al., 1999; Cotter et al., 2005; Rajkowska et al., 2005, 2007). However, reports of OFC volume from MRI in these disorders have been inconsistent in schizophrenia (as discussed in Nakamura et al., 2008) and bipolar disorder (see Najt et al., 2007), as are the selections of anatomical limits we have identified in this review.

*Results.* Amongst these methods, two points of contention were noted from our search<sup>21</sup>. Firstly, the medial extent of the orbital region varied significantly (Figure 3.7). The OFC extended onto the medial wall in 37 protocols using the superior rostral, cingulate or suborbital sulcus as the dorsal boundary (Baaré et al., 1999; Berryhill et al., 1995; Convit et al., 2001; Crespo-Faccorro et al., 1999; Croxson et al., 2005; Flashman et al., 2001; Rademacher et al., 1992; Szeszko et al., 1999; Rankin et al., 2004; Ranta et al., 2009; Rosen et al., 2002; Salat et al., 2001; Tisserand et al., 2002; Suzuki et al., 2005; Uylings et al., 2010; Wible et al., 1997). Other researchers imposed a limit on the medial wall at the depth of the olfactory sulcus (OS), although we found 7 different methods amongst 15 papers for identifying this. Three papers used the shortest straight line to the midline from the deepest point of the OS in coronal slices (Ballmaier et al., 2004). The dorsal disappearance of the olfactory sulcus was also used, defined as either most superior

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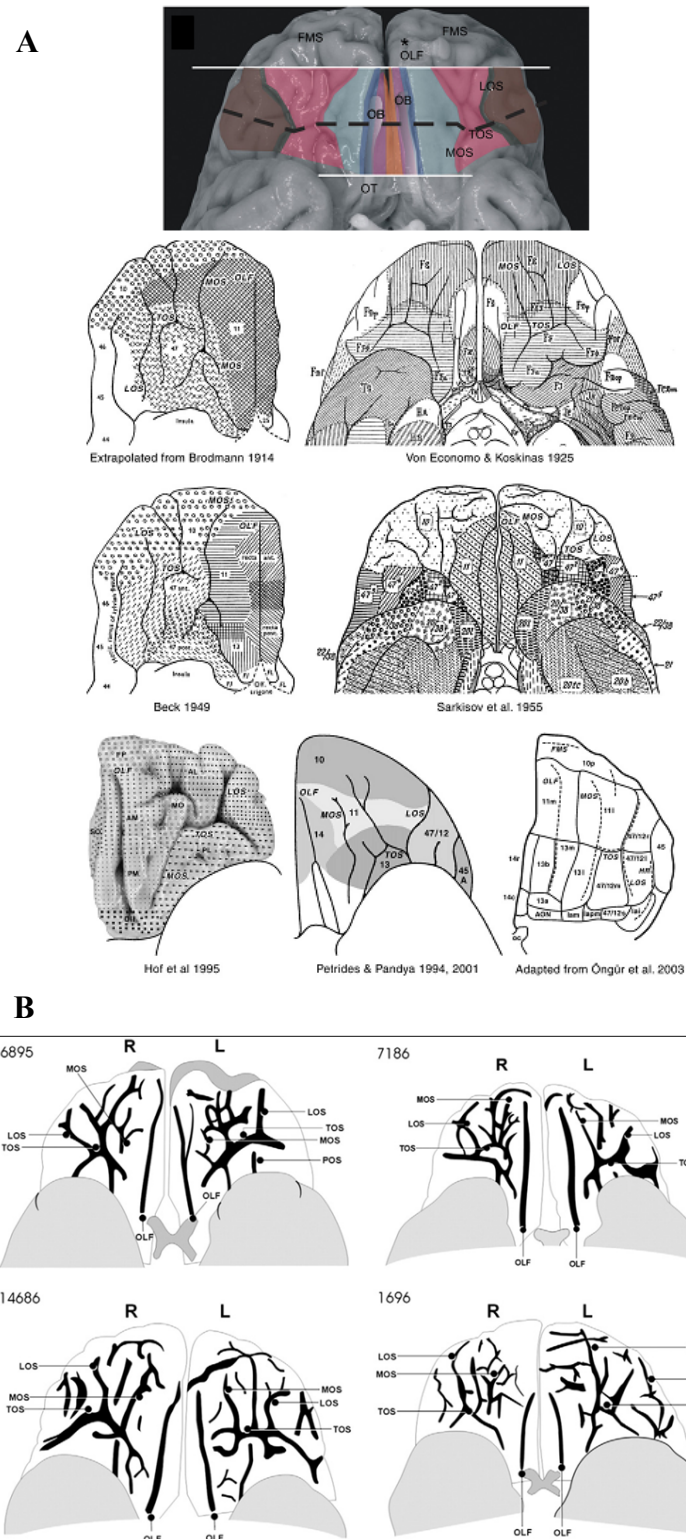
<sup>21</sup> In addition to the difficulty in identifying the lateral boundary between the IFG and OFC, and the posterior and polar boundaries discussed above.

axial slice in which >50% of the OS can still be seen (Bremner et al., 1998), where combined grey matter and CSF comprise less than three-quarters of the overall length of the OFC (Lai et al., 2000), or where grey matter ran its entire length (Wilde et al., 2005). Other geometric approaches applied an axial cut-plane at the most anterior extent of the genu of the corpus callosum (Medina et al., 2008) or the anterior commissure (Bjork et al., 2009; Gur et al., 2000). One further approach used the anterior cingulate sulcus until it intersected a geometrically-determined cut-plane more anteriorly. The plane begins at the genu of the corpus callosum. Its angle is determined coronally, as a line drawn from the intersection of horizontal and vertical lines at the lateral and ventral extents of the hemisphere to a point at the most ventral extent of the corpus callosum (Lacerda et al., 2003). Conversely, some studies excluded the medial wall by using the central fissure via a limit through the crown of the gyrus rectus (Semedeferi et al., 1997), or olfactory sulcus (Raz et al., 1995) as the medial boundary.



*Figure 3.7.* Two frontal coronal sections immediately posterior (left) and anterior (right) to the genu of the corpus callosum showing various boundaries for the lateral and medial orbitofrontal cortex. A: Axial slice at the genu of the corpus callosum. B: Axial slice at the anterior commissure. C: Cingulate sulcus. D: Shortest line to the midline from the deepest part of the olfactory sulcus / rostral sulcus. E: Plane at the axial termination of the majority of the olfactory sulcus. F: Grey matter limited by the central fissure. G: Olfactory sulcus. H: Lateral orbital sulcus. ACC: Anterior Cingulate Cortex. IRG: Inferior Rostral Gyrus. GR: Gyrus Rectus. OFG: Orbitofrontal Gyri. Red lines indicate the tangent lines (dashed) and locator line (solid) which runs from 5 slices below the anterior commissure to the tangent bisection (from the Lacerda 2003 protocol). Images modified from [www.thehumanbrain.info](http://www.thehumanbrain.info)

The second subject of variability between methods is in the further parcellation of the OFC. As discussed in depth by Uylings et al., (2010), the nomenclature, methods and criteria for architectural analysis of orbitofrontal composition are inconsistent for orbital sub-regions. Figure 3.8a demonstrates that there is consensus on a lateral/medial differentiation amongst cellular maps, and also partial support for an anterior-posterior boundary. These two directional trends also have support from functional studies, whereby lateral and medial OFC are involved in punishment and reward evaluation respectively, and the anterior-posterior divide corresponds to a spectrum of complexity from abstract to simple reinforcers (Kringelbach and Rolls, 2004 as cited in Uylings et al., 2010). Nevertheless, the ease with which subregions can be identified is dependent upon how consistent the main orbital landmarks are among brains. Unfortunately the cortical features on the orbital surface are subject to marked inter-individual variability (Chiavaras and Petrides, 2000; Nakamura et al., 2008; Uylings et al., 2010), as shown in Figure 3.8b.



*Figure 3.8. A: Various cytoarchitectonic maps of the orbitofrontal surface. B: Examples of the variability in orbital sulcal and gyral patterning. Reproduced from Uylings et al. (2010).*

Amongst the reviewed parcellation methods, we found that further parcellation of the ventral surface was achieved by dividing the straight gyrus from the orbital gyri either by using the olfactory sulcus (Ballmaier et al., 2004; Bremner et al., 1998; Crespo-Faccorro et al., 1999; Flashman et al., 2001; Nakamura et al., 2008; Rademacher et al., 1992; Szeszko et al., 1999a; Suzuki et al., 2005) or the crown of the gyrus rectus itself (Tisserand et al., 2002; Uylings et al., 2010). On the medial wall, two approaches further divide the gyrus rectus and medial OFC using a line bisecting the depth of the olfactory sulcus (Crespo-Faccorro et al., 1999) or the inferior rostral sulcus (Suzuki et al., 2005). Several studies of neuroarchitecture justify dividing the ventral surface of the OFC (see Figure 9 using the middle and lateral orbital sulci (Croxson et al., 2005; Uylings et al., 2010).

*Discussion.* As discussed in the previous section, contention over the status of the *pars orbitalis* is central to inconsistency in the lateral OFC boundary. Variability in the medial extent of the OFC is also apparent, although exclusion of the inferior rostral gyrus from orbital measures cannot be explained by cytoarchitecture. Further parcellation of the orbital gyri may also be possible, but the enormous variability of these gyri makes such detailed parcellation a technically demanding feat, particularly without information on cellular composition as an aid and the detailed knowledge and experience required to make sense of the variable orbital topography.

### 3.5 Discussion

This review has identified a large body of literature whose methods aim to quantify the volumes of the frontal lobe and its sub-regions from MR images. Against a backdrop of research linking cortical positioning with frontal cytoarchitecture, connectivity and function, we have described the marked variability with which different research groups have defined and reported each ROI. Such discrepancies may not be immediately apparent, but may underlie fundamental inconsistencies between reports of the neural correlates of various conditions. The variety of methods discussed range from those using geometry to divide the lobes into gross measures, to fine-grained parcellation of a single sub-region using available gyral cues, with the majority of methods using a combination of the two. For each of the frontal ROIs, we have identified the assortment of boundaries used and have mapped these out onto a single brain in order to illustrate the large degree to which a named single anatomical region can vary.

Nevertheless, it would be premature to conclude that detailed volumetric analysis of the frontal lobes is intractably complex at the sub-regional level. There is sufficient evidence to assume that some local gyral landmarks are common to all individuals. Further, these are most likely to allow a biologically meaningful measure sympathetic to presumed individual differences in neuroarchitecture. Likewise, analyses of variability in cortical folding and its implications have also been published. Observations on identification, measurement and potential effects on adjacent structures can offer useful guidance for protocol design. Crucially, for each region we identify some pre-existing boundaries that allow a reproducible method for a biologically-plausible target ROI based on the information discussed. It is hoped

that the synthesis of these in our review, in addition to comments on the need for measures to address questions of bias and quality, will guide design decisions in future volumetric studies of frontal lobe and other regions.

Given the difficulties in identifying papers by their methodology rather than subject of interest (exemplified by the large proportion of papers identified from manual reference searching, Figure 2), it is possible that not all relevant publications were identified in our search, thereby under-representing the true variability of methods. In addition, the current review cannot be considered a definitive guide to frontal lobe parcellation, as it refers mainly to manual methods. The use of automated approaches is widespread, and although some of the reviewed protocols are directly implemented by Freesurfer and SPM, we do not discuss non-atlas-based approaches to frontal lobe parcellation, nor their comparative merits and drawbacks.

For some regions – notably the frontal pole and anterior cingulate – further work is needed to help identify cellular field boundaries from structural landmarks. Such work may come in the form of traditional immunohistochemistry or elsewhere. For example, a technique by which myelination patterns can be objectively assessed *in vivo* across most of the cortex holds promise (Glasser and Van Essen, 2011). By generating a contrast between T1 and T2 weighted MR images, myelin maps were shown to enable the delineation of numerous cortical sub-regions which corresponded well with probabilistic cytoarchitectonic areas mapped onto the same surface. Exploitation of the microstructural qualities of the cortex can also be further enhanced by high-field imaging; the use of 7T magnetic fields and more sensitive receiver coils enables extremely detailed visualisation of intracortical myeloarchitecture. This technique accurately resolves the border between



somatosensory and primary motor cortex when compared to a post-mortem analysis of the same tissue (Geyer et al., 2011). Such an approach could not only allow further investigations into ‘problem’ areas such as the frontal pole and posterior border of the ACC, but also has potential for the guidance of manual or semi-automated parcellation in the future, whereby intensity signal changes can be mapped as sub-field boundaries across the cortex to complement the use of cortical morphology when identifying ROIs.

In the meantime however, topographical boundaries that appear to fit most plausibly with current knowledge of frontal lobe sub-fields are as follows. The posterior boundary of the frontal lobe, excluding the motor cortex can be traced on the lateral surface anterior to the precentral sulcus and extended medially to the cingulate or paracingulate sulcus, and ventrally at the insular sulcus in order to differentiate OFC from insula. In situations where one might wish to exclude pre-motor areas, or where 3D visualisation software is unavailable, use of a coronal cut plane at the most anterior extent of the precentral gyrus might be used for lateral aspects, and a coronal plane where the OFC and insula cannot be distinguished for ventral aspects of the frontal lobe. The frontal pole still presents practical difficulties, but the use of a coronal cut plane at the most anterior extent of the ACC appears plausible at this point<sup>22</sup>. Between these two points, the lateral convexity can be parcellated into the three main frontal gyri, (affording the option to combine SFG and MFG into DLPFC), using the lateral orbital sulcus to differentiate OFC and IFG. Medial and lateral portions of OFC and SFG can be separated using the crown of the most medial gyrus. The anterior cingulate can be measured from its most ventral sub-

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<sup>22</sup> Although the authors urge caution, as it remains unclear whether presence of a paracingulate might reflect true individual variation in frontopolar positioning.

genu extent to its posterior dorsal border in line with dorso-medial and lateral limits. Distinction between dACC and vACC can plausibly be made using a sagittal or coronal cut plane at the genu of the corpus callosum, although further work is clearly needed to establish relationships between topography and architecture for both posterior- and mid-cingulate boundaries. Authors may wish to pay closer attention to certain regions using finer-grained parcellations, expanding upon this guideline schema, although it should be noted that measuring smaller volumes often results in larger errors and poor reliability.

The reviewed studies have made crucial contributions to the development of frontal lobe parcellation. However, there is a need for consensus so that persisting differences in methods can reduce noise in the field and maximise future progress.

## **Acknowledgements**

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## Chapter 4: Cortisol

### 4.1 Introduction

It is clear that brain changes take place with increasing age, and that these changes also have an impact on cognitive functioning. The determinants and mechanisms underlying structural and functional decline in old age are relatively poorly understood, but one possible determinant may arise from individual differences in exposure to glucocorticoid (GC) levels. This hormone is essential for an organism's survival, but evidence from animal studies and human clinical groups suggests that prolonged exposure to elevated levels of GCs has detrimental effects on the brain and on cognitive function. Specifically, those regions of the brain that are involved in the normal regulation of GC production are also the likely foci of detrimental effects of prolonged exposure to elevated levels. Animal and human studies implicate the amygdala, hippocampus and areas of the prefrontal cortex in the regulation of GCs, and also as targets for the deleterious effects that accompany exposure to chronically elevated levels.

In humans and animals, there is evidence that levels of GCs increase with age, although this may be true for only a subset of the ageing population. In old age, lower hippocampal volume and poorer memory functioning have generally been reported in rodents, but the human literature is less clear-cut. Some studies identify similar findings for the hippocampus, although others report negative associations between memory performance and cortisol levels in the absence of related changes in hippocampal volume. Different areas of the prefrontal cortex have also been implicated as targets of GC-associated atrophic change, but it is unclear whether GC

levels in old age might be sufficiently high to confer structural and functional differences. In the human literature only two studies have examined frontal sub-regions and cortisol levels in old age, with conflicting results. To date there has been no examination of the potential functional sequelae of such change, and it is unclear which aspects of the complex GC secretion profile might best account for the variance in brain structure and function.

## 4.2 Glucocorticoid Physiology

The endogenous steroids glucocorticoids (GCs) are so-called because they are involved in the regulation of *glucose*, they are synthesised in the adrenal *cortex* and are a class of *steroid*. Their primary function is to prepare the organism for action in response to physical or psychological stressors. A stressor can broadly be defined as, “...an actual or anticipated disruption of homeostasis or an anticipated threat to well-being” (Ulrich-Lai & Herman, 2009). As part of the fight or flight response, GC secretion mobilises glucose and fatty acids, increases blood pressure and also leads to mild euphoria. In addition, it shuts down functions not essential for immediate survival, such as wound-healing, inflammation, immune responses and digestion (Sapolsky, Romero, & Munck, 2000; Seckl & Olsson, 1995).

As well as slower genomic effects, circulating GCs have been shown to exert rapid non-genomic effects on brain physiology and cognitive functioning.

Intravenous administration of GCs has been shown to reduce global EEG signal strength 15 minutes later in humans (Strelzyk et al., 2012), inhibit cerebral glucose metabolism in the rodent hippocampus (Kadekaro, Ito & Gross, 1988) and increase hippocampal extracellular glutamate concentrations (see Chaouloff & Groc, 2011 for a review). Variations in cortisol concentrations in young healthy humans affect complex cognition, detailed learning and memory (Arnsten, 2009; Lupien et al., 2002; Mujica-Parodi, Renelique, & Taylor, 2009; Newcomer, Craft, Hershey, Askins & Bardgett, 1994). They are also a key part of the diurnal - or circadian - rhythm which is involved in the normal functioning of various essential physiological systems (McEwen, 1998). A complete absence of GCs in the brain results in

pyramidal cell death in the dentate gyrus (Bye & Nichols, 1998), and can be fatal in some instances of Addison's disease in humans (Herbert et al., 2006).

Common to both reactive and diurnal healthy profiles is the characteristic increase in production during periods of need (either from evening nadir to wakening, or from rest to stress response) and a return to lower levels (either towards a nadir overnight, or a swift return to basal levels following resolution of the stressor; Roy, Kirschbaum & Steptoe, 2001). The regulation of these profiles is effected by the hypothalamic-pituitary-adrenal (HPA) axis. Signals from higher cerebral centres cause the paraventricular hypothalamic nucleus (PVN) to produce corticotropin-releasing hormone (CRH). This is detected by the pituitary gland which secretes adrenocorticotrophic hormone (ACTH), in turn stimulating an increase in GC production (Brown, 2000). Return to basal levels following the stressor, or gradual reduction over the course of the day as part of the circadian rhythm is thought to be achieved through a negative feedback loop; increased GC levels are detected by the pituitary and brain centres (by binding to specific receptors), inhibiting output in the adrenal cortex.

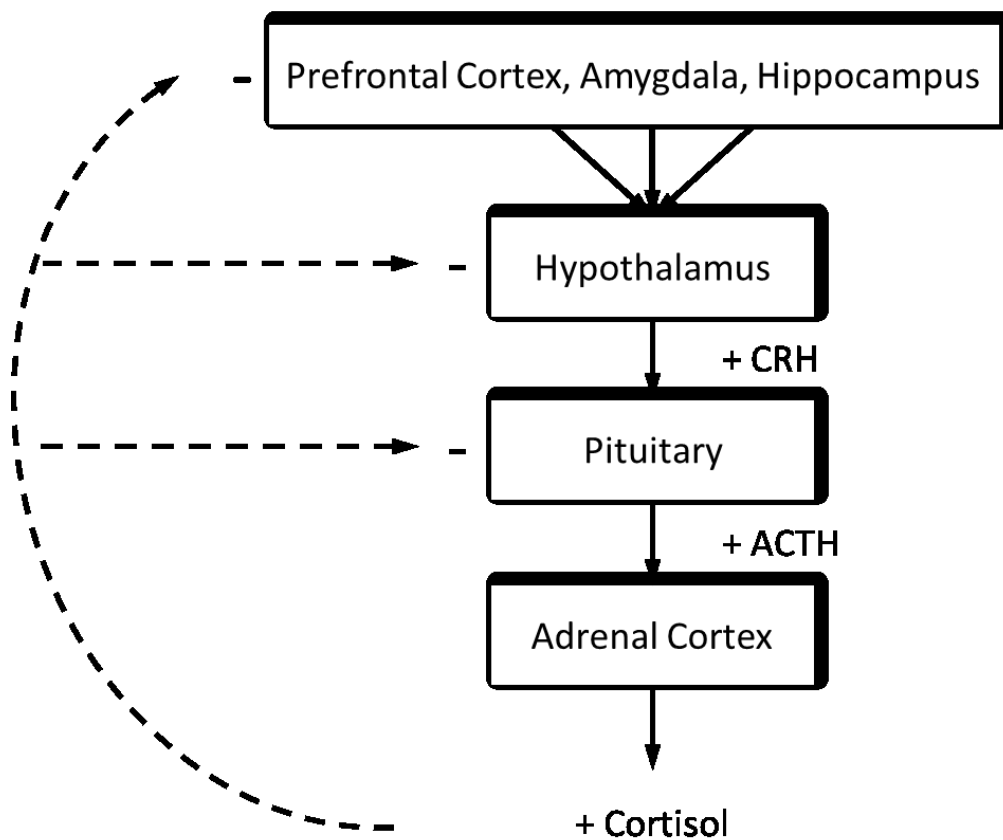
Glucocorticoids bind to two main types of receptors which are widely distributed throughout the body (McEwen, 1998). Mineralocorticoid receptors (MRs) have a much higher affinity with cortisol than do glucocorticoid receptors (GRs), and therefore only MRs tend to be occupied at low concentrations, whereas GRs are occupied with morning peak and/or stress levels of cortisol (Spencer, Young, Choo & McEwen, 1990). It is likely that MR receptors also play a role in negative feedback, but mainly for circadian regulation during low GC concentrations in the evening trough (Mattsson, Reynolds, Simonyte, Olsson, & Walker, 2009). Direct

evidence for the distribution and density of these receptor types in the brain is not comprehensive in either human or animal literature (Patel, Katz, Karssen, & Lyons, 2008), but there is evidence for preferential expression of both types of receptor in certain brain regions. Both MR and GR are found in the hippocampus (De Kloet, Vreugdenhil, Oitzl, & Joëls, 1998), and GR may be less preferentially expressed in primates than rodents in this region (Sánchez, Young, Plotsky, & Insel, 2000). Both receptor types are also present in the amygdala, hypothalamus and cerebellum (McMurry & Hastings, 1972), and are differentially expressed in prefronto-cortical regions, with lower density in the dorsolateral than ventral or medial areas in primates (Patel et al., 2001, 2008).

### 4.3 Brain Regions and Glucocorticoid Regulation

Our understanding of the key brain regions involved in GC regulation can further be gleaned from research examining the effects of selective lesions, exogenous steroid or receptor agonist administration on GC regulation (cortisol in primates, corticosterone in rodents). The emergent picture is that GC responses to direct physiological threats to homeostasis are facilitated by regions carrying visceral and primary sensory information, that directly innervate the paraventricular hypothalamic nucleus (PVN) such as brainstem loci, thalamus and other areas of the hypothalamus (Herman et al., 2003). Associated limbic brain regions such as the amygdala, hippocampus and prefrontal cortex can also indirectly influence the activation of PVN cells; although they have direct connectivity with other hypothalamic nuclei, direct innervation to PVN cells is notably absent (Fernandes, Tavares, Pelosi & Correa, 2007). For example, selective deletion of GR from the mouse hippocampus, amygdala and PFC resulted in higher diurnal levels, longer responses to psychogenic stressors, and a lack of feedback inhibition following exogenous steroid administration (Boyle et al., 2005; Furay, Bruestle & Herman, 2008). The amygdala is thought to enhance production of GCs through excitatory connections with hypothalamic nuclei, but both hippocampus and areas of the prefrontal cortex are thought to exert an inhibitory influence, predominantly during stress-induced activation of the HPA axis, as discussed below (Figure 4.1).





*Figure 4.1.* Schematic of the Hypothalamic-Pituitary-Adrenal Axis. CRH: Corticotropin-releasing hormone, ACTH: adrenocorticotrophic hormone. Dashed lines denote the negative feedback loop. Figure based on Nicolson (2007).

#### 4.3.1 Amygdala

In animals, stimulation of the amygdala increases GC levels, and damage to this region or steroid implant impairs reactive production (for a review, see Herman et al., 2003 & Herman, Ostrander, Mueller, & Figueiredo, 2005). In humans though, there is an absence of research linking the amygdala directly with cortisol levels or the BOLD response to psychological stressors (Dedovic, D'Aguiar & Pruessner, 2009). This may well be due to the contrasting types of stressor that subjects are exposed to in animal and human studies. The role of the amygdala in fear response is well-documented (Phan, Wager, Taylor & Liberzon, 2002), and animals are traditionally exposed to stressors that induce fear, whilst the reactivity in human studies is contingent upon perceptions of psychosocial threat, elicited by tests such as the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993)<sup>23</sup>. It has been suggested that these different types of stress activate the HPA axis through different neural mechanisms (Pruessner et al., 2008), and that individual differences in coping styles (i.e. perceptions of how stressful a situation is) could further confound comparison between human and animal work (Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009). In humans, amygdala stimulation does indeed increase ACTH production (Gallagher, Flanigin, King & Littleton, 1987) and cortisol (Rubin, Mandell & Crandall, 1966), but endogenous activation of this structure appears subject to individual differences. A recent neuroimaging study reported that those individuals who exhibited lower amygdala activation during an fMRI threat regulation task also showed reduced cortisol and behavioural stress (psychosocial resources) response to the TSST (Taylor et al., 2008), suggesting that the

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<sup>23</sup> In this test, participants are asked to give a speech or perform mental arithmetic in front of a panel of strangers, eliciting increased stress through perceived psychosocial threat.

psychological stressor may be perceived more as an actual fearful threat by those with poorer coping/psychosocial resources (Dedovic, Duchesne, et al., 2009). Thus it appears that the amygdala potentiates HPA activity indirectly, and may also be subject to up-stream modulatory influences from other brain regions (Dallman et al., 2003).

#### *4.3.2 Hippocampus*

As discussed in the previous chapters, the hippocampus is connected to prefrontal cortical areas and parts of the limbic system such as the amygdala. It is heavily implicated in terminating GC production through inhibition of HPA axis functioning (Sapolsky et al., 1986). As reviewed by Jacobson and Sapolsky (1991) and Herman et al. (2005), hippocampal stimulation inhibits HPA activity. Selective lesions to the rodent hippocampus have been reported to increase basal CRH and GC levels (Sapolsky, Krey & McEwen, 1984), but not in other studies (Tuvnes Steffenach, Murison, Moser & Moser, 2003; Bradbury, Strack & Dallman, 1993)<sup>24</sup>. Damage to this region can impair negative feedback in response to psychological (e.g. restraint stress) but not physical (e.g. ether or hypoxia) stressors (Herman, Dolgas & Carlson, 1998; Magarinos, Somoza & DeNicola, 1987). The diurnal rhythm flattens following hippocampal GC implants (Slusher, 1966), and GC output increases following hippocampal stimulation in rats (Casady & Taylor, 1976). The observation that GC hypersecretion following hippocampal damage is transient, and eventually returns to pre-morbid profile, has been shown in both rats (Fendler, Karmos & Telegdy, 1961)

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<sup>24</sup> Some studies have reported no GC hypersecretion resulting from hippocampal lesion, although it is possible that methodological differences between studies confounds direct comparison (see Herman et al., 2003)

and non-human primates (Sapolsky, Zola-Morgan & Squire, 1991), although Machado and Bachevalier (2008) reported that hippocampal lesions in rhesus monkeys did not alter cortisol levels at rest, under physical restraint, temporary isolation or various threatening scenarios.

In small samples of humans, hippocampal stimulation elicits a decrease in circulating cortisol levels (Rubin, Mandell & Crandall, 1966). Reactive cortisol levels negatively associate with hippocampal volumes in young healthy participants (Pruessner et al., 2005). Moreover, larger hippocampal volume was associated with reduced cortisol levels following administration of hydrocortisone; those with smaller hippocampi appeared less able to inhibit subsequent cortisol production (Tessner, Walker, Dhruv, Hochman, & Hamann, 2007). Hippocampal lesions have been reported to abolish the cortisol awakening response, but the authors found no association between hippocampal volume and cortisol secretion in either patients or controls (Buchanan, Kern, Allen, Tranel, & Kirschbaum, 2004). Overall, this evidence supports the idea that stressor-dependent neural correlates influence HPA activity, and that the hippocampus significantly contributes to negative feedback regulation by detecting GCs and inhibiting further production in animals. However, the evidence for a similar role in humans is less conclusive.

#### *4.3.3 Prefrontal Cortex*

Although studied in less detail than the hippocampus, the prefrontal cortex is also thought to modulate HPA axis activity in addition to its role in complex cognitive functioning. As outlined previously, the human prefrontal cortex comprises several

sub-regions. Just as their structural and connective profiles reflect distinct contributions to cognitive function, so too does the current evidence suggest that different sub-regions play different roles in HPA activity.

In rodents, lesions restricted to the prelimbic and cingulate areas of the mPFC result in increased levels of ACTH and corticosterone in response to stress (Diorio, Viau, & Meaney, 1993; Figueiredo, Bruestle, Bodie, Dolgas & Herman, 2003), suggesting an inhibitory effect on the HPA axis, in contrast to the decrease in GC output following ventral/infralimbic lesion (Radley, Arias, & Sawchenko, 2006). Furthermore, stress-induced activity in the infralimbic mPFC is positively related to PVN activity, whilst prelimbic mPFC activation shows the opposite relationship (Radley et al., 2008). GC implants to the prelimbic region result in decreased levels of ACTH and GCs in response to restraint stress and not to ether (Akana, Chu, Soriano, & Dallman, 2001; Diorio et al., 1993). Thus the animal literature describes a role for ventral areas in activating the HPA axis, and dorsomedial areas in its negative feedback regulation, predominantly during restraint stress.

A role for the orbital frontal cortex (OFC) in GC regulation is supported by work in monkeys. Alterations to cortisol output were stressor-specific following orbital lesions; cortisol reactivity to isolation from peers was blunted, but not during restraint or threatening situations (Machado & Bachevalier, 2008). Evidence for the involvement of frontal regions in cortisol regulation in humans is relatively limited and indirect. Much of the data come from functional neuroimaging studies which typically report BOLD response or glucose metabolism contrasts of a stressful and control task. A recent review of neuroimaging paradigms thought to elicit stress reported that decreases in OFC and hippocampal, as well as increased dorsomedial

prefrontal activation were the most consistent findings (Dedovic, D'Aguiar, & Pruessner, 2009). However, this review includes studies where the stress paradigm did not effect a significant cortisol increase, and some reviewed studies did not directly measure cortisol levels and relate these to the imaging contrasts. As a result, it is not entirely clear to what extent these activation patterns relate to HPA axis functioning.

There is a subset of recent studies that directly relate cortisol increases with brain activation patterns (Table 4.1). Increased activation of the right PFC<sup>25</sup> and left dACC was related to both higher self-report measures of stress and higher total cortisol output during a serial subtraction paradigm (Wang et al., 2005). Moreover, elevated dACC activity during a social stress paradigm<sup>26</sup> correlated both with a self-report measure of perceived stress and the percentage cortisol increase from baseline in response to the TSST (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007), while activation in the left dorsomedial and lateral PFC positively correlated with cortisol production only. A further study examined how glucose metabolism within the PFC varied with levels of salivary cortisol in response to a stressful task (TSST). Correlations with cortisol secretion were found in opposing directions dependent upon the location of activation (Kern et al., 2008). While increased dorsomedial and frontopolar PET activity was associated with lower cortisol reactivity (calculated as the difference between highest measure and lowest measure), activation of the right

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<sup>25</sup> The authors do not attempt to define this region more specifically – visualisation of the cluster suggests it lies in the ventral frontal pole. However, without seeing the individual activation patterns it is difficult to draw a conclusion about how best to categorise this cluster.

<sup>26</sup> “Cyberball” is a ball-throwing game played with other (simulated) players in which the participant gradually becomes excluded from the game (Williams et al., 2000). Contrasts compared inclusion to exclusion. Activity during this task has previously been shown to activate left dACC and right ventral PFC (Eisenberger et al., 2003).

superior, middle and dACC cortices all showed positive associations with the same cortisol measure.

*Table 4.1.* Human functional imaging (fMRI & PET) studies showing relationships between cortisol and activity in frontal sub-regions during a stressful task.

<b>Study</b>	<b>Region</b>	<b>Relationship</b>	<b>Paradigm</b>
Wang 2005	right FP	+	Arithmetic
	right dACC	+	
Eisenberger 2007	dACC	+	Cyberball/TSST
	left DMPFC	+	
	left DLPFC	+	
Wang 2007	right FP	+	Arithmetic
	left OFC	-	
Kern 2008	DMPFC	+	TSST
	FP	+	
	right DLPFC	+	
	dACC	+	
Pruessner 2008	dACC	+*	MIST
	right OFC	-*	
	vACC	-*	
	left MFG	-*	

\* relationship is implied through group differences in cortisol, but does not show direct correlations with cortisol levels. Some regional classifications have been adapted from the cited publication for purposes of comparison. MIST = Montreal Imaging Stress Task; TSST = Trier Social Stress Test.

Whilst increased resting-state EEG activity in ventral areas including the vACC and OFC correlated with a flatter diurnal slope in one study (Putnam, Pizzagalli, Gooding, Kalin, & Davidson, 2008), deactivation of the OFC in response to stress has also been observed in two recent studies. Wang and colleagues (2007) identified that along with increased right frontopolar activity, decreases in left OFC activity predicted both higher self-report measures of perceived stress and higher cortisol output. A separate study showed no significant correlations between cortisol output and any frontal activation, but significant peaks of activation in response to the stressful task were found in the dACC and cingulum bundle. Splitting



participants into those that showed a significant increase in cortisol during the task (responders) and those that did not (non-responders) revealed that responders had significantly reduced activation in bilateral vACC, right OFC and left middle frontal gyrus (Pruessner et al., 2008). There appears to be a broad pattern of findings in the functional imaging literature, linking medial and ventral structures with paradigms that increase perceived social stress. Yet, both the inconsistency of the precise loci within studies and the direction of association (activation versus deactivation) do not implicate clearly defined regions.

#### *4.3.4 White matter – the significance of negative feedback loop connectivity*

Although research has focussed extensively on cortical loci for GC regulation, the role of white matter is notably absent from the literature. Interconnectivity between the relevant cortical regions is explicitly discussed in many of the above-mentioned articles, yet overt examination of white matter tracts involved in GC regulation is comparatively sparse. However, it is clear that HPA axis regulation is performed by a large-scale brain network, within which information transmission is key. As a result, the quality of this transmission (reliant on tract integrity to some degree) may also affect the cohesion of the circuit and its operational efficiency. Given the involvement of the hippocampus, amygdala and medial prefrontal cortex, the cingulum bundle, uncinate fasciculus and fornix (Catani & de Schotten, 2008; Nolte & Angevine, 1995) are the limbic tracts most likely to facilitate HPA axis negative feedback from these regions.

One recent study reported associations between observational measures of behavioural stress reactivity, urinary cortisol levels and DTI and MRI measures amongst rhesus monkeys (Willette et al., 2012). Higher stress reactivity was associated with lower fractional anisotropy (FA) in white matter voxels thought to represent the anterior part of the cingulum bundle, and higher mean diffusivity (MD) in voxels in the anterior corpus callosum, uncinate fasciculus, and the cingulum bundle. Using cortisol and stress reactivity as main predictors, a multiple-regression voxel-wise analysis of FA and MD in *a priori* ROIs did not show any significant clusters for a main effect of urinary cortisol. However, an interaction of stress reactivity and urinary cortisol showed significant clusters for MD but not FA. This was confirmed by splitting the monkeys into high and low groups, based on behavioural observations in reaction to stressful events. Higher cortisol in the ‘high reactivity’ group exhibited lower MD in regions including OFC, dorsomedial PFC, amygdala, PVN, caudate and hippocampus. However, there was no such relationship in the ‘low reactivity’ group.

The study of Willette and colleagues (2012) is limited in several ways. The use of *a priori* voxel-wise comparison, rather than explicit tract measurement limits the authors’ power to accurately identify the implicated tracts within a given cluster. Furthermore, urinary cortisol was only measured at a single time point, and not in direct relation to a stressful event. Nevertheless, the identification of cortical clusters in regions known to have a high density of GR and MR receptors, and lower MD in white matter regions which connect these structures is biologically plausible.

#### *4.3.5 Hemispheric lateralization*

There is some evidence to suggest that supra-thalamic influences on the HPA axis may be partially lateralized. Lateralization of basic autonomic and life-sustaining functions has long been linked to the right hemisphere (Geschwind & Galaburda, 1985), and it appears that this is also true of the stress response, though the picture is slightly more complex. In rodents, chronic stress-induced remodelling in the mPFC appears to affect mainly the right hemisphere (Cerqueira, Almeida, & Sousa, 2008; Czéh, Perez-Cruz, Fuchs, & Flügge, 2008; Perez-Cruz, Simon, Czéh, Flügge, & Fuchs, 2009). On the other hand, induced hypercortisolaemia results in a decrease in left ACC volume (Cerqueira et al., 2005). Furthermore, lesions to the right or bilateral, but not left PFC induced lower cortisol levels before and in response to restraint stress (Sullivan & Gratton, 1999). It has been hypothesised that, in lower mammals including rodents, the left prefrontal cortex is involved in stress responses to immediate environmental demand, whereas the right is more linked with responses to longer-term stressful situations (Czéh et al., 2008). In humans, this theory of hemispheric specialization is supported, but may be reversed. Only patients with left-sided stroke exhibited an increased morning cortisol when compared to controls, while right-handed lesions were associated with a more blunted response during a mild cognitive stressor (Lueken et al., 2009). However, another patient study found that hemispheric laterality had no effect on cortisol output in their group of brain damaged patients (Tchiteya, Lecours, Elie, & Lupien, 2003). A higher cortisol awakening response also correlated with greater right:left asymmetry in measures of uncinate fasciculus fractional anisotropy (Madsen et al., 2012), and studies have identified lower structural metrics of the left prefrontal cortex with elevated mean

diurnal cortisol (Kremen, O'Brien, et al., 2010) and dexamethasone non-suppression (MacLulich et al., 2006). Thus, it is likely that hemispheric laterality is pertinent to GC-driven psychopathology, though the evidence to date remains too sparse to concretely link specific stress responses in humans with specific ROIs on the left or right hemisphere of the brain.

#### *4.3.6 Summary*

In summary, the above data provide evidence that the hippocampus, amygdala and PFC are key modulators of GC production and regulation. Animal studies suggest that pure physical challenge is primarily implicated at the level of the brainstem and amygdala (Fenoglio, Brunson & Baram, 2006; Ulrich-Lai & Herman, 2009), while psychological stress engages the amygdala, hippocampus and frontal areas (Dedovic, Duchesne, et al., 2009; Herman et al., 2003; Pruessner et al., 2008). Medial/orbital and dorsolateral regions of the human PFC appear to exert differential effects on HPA axis activation. The sub-regional specificity of this model for the PFC is based predominantly on human functional imaging. Although the functional evidence is only correlational in nature, some authors have posited that effective deactivation of limbic brain regions is necessary for the initiation of a stress response, whereas more dorsal ACC and lateral PFC activity could function to stimulate PVN activity and downregulate hippocampal inhibition (Dedovic, Duchesne et al., 2009; Herman et al., 2003; Pruessner et al., 2008; Figure 4.2). Whilst this appears to fit well with the human functional imaging data, it does not correspond well with previous animal studies which show that activity in infralimbic areas correlates with that in the PVN,

and lesions to this area result in decreased GC output (discussed above). There are several possible reasons for this apparent discrepancy, which are outlined below.

Although rodent models have often shown their usefulness for informing our understanding of human physiology, the human frontal lobe is quite different even to that of our closest ancestors. As discussed below, the detailed sub-regional mapping of function between rodent and human brain may not hold in all instances, and the assumption that the stress-response system is entirely evolutionarily-conserved (Joëls & Baram, 2009) may be flawed. As a result, attempts to glean human prefrontal stress functioning from animal models may not be sufficient at the fine grain of prefrontal sub-regions. Also, the types of stressors that are commonly employed in the animal literature differ significantly from those to which human participants are exposed. Fear-based induction of stress through paradigms such as restraint is commonly employed in rodent models, in stark contrast to the complex perception-based methods that simulate social exclusion, evaluation and/or negative emotions in humans. It is unclear whether the rodent brain can process such complex evaluative information, and so even analogous rodent paradigms may give little insight. Due mainly to practical and ethical constraints, lesion, implant and physical/fear/restraint paradigms in human research are also notably absent, and these differences call into question the degree to which cross-species comparisons can inform our understanding of specific frontal sub-areal roles in HPA axis function.



2011). Furthermore, the paradigms used in the human functional imaging literature vary in the types of stress they elicit and possibly in the effects of contrasting experimental and control conditions. For example, the paradigm used by Wang and colleagues (2005) reports results based on contrasts between serial subtraction (13 from a four-digit number (during which, experimenters prompt the participant for faster performance) and simple counting down from 1,000. In the MIST, control and experimental tasks differed not only in terms of difficulty, but in that negative feedback was only given in the latter, both via a mock performance meter suggesting scores were lower than average, and by the experimenter between trials, stating that the staff were all aware of the participant's poor performance. As a result, it is not possible to parse apart the contributions of task difficulty, social perceptions of performance and negative feedback to overall stress levels. The serial subtraction paradigm used by Wang and colleagues (2005) was considerably briefer than that of Kern et al (2008) and appears to give a much smaller cortisol response than the TSST (Kern et al., 2008). Likewise, the MIST elicits a much milder increase in cortisol (30-50%) when compared with the TSST (50-200%; Pruessner et al., 2010).

There is also evidence that human gender differences exist with respect to cortisol response and frontal activity during psychological stress. This further complicates the picture as some studies use mixed gender groups (Wang et al., 2005; Pruessner et al., 2008) and others do not (Kern et al., 2008) or studies do not take account of this in their analysis (Wang et al., 2007). For example, there appear to be distinct gender differences in neural activity during psychological stress, a trend towards different baseline levels of cortisol (Wang et al., 2007), and males and females show different patterns of cortisol secretion in response to different types of

stressor (Stroud, Salovey & Epel, 2002). In response to the TSST, men showed a significantly larger increase in cortisol from baseline than women (Eisenberger et al., 2007), and female salivary cortisol levels in response to stress are susceptible to both phases of the menstrual cycle and oral contraceptive use (Kirschbaum Kudielka, Gaab, Schommer & Hellhammer, 1999).

Finally, the cortisol metrics used in correlations with activation peaks are also variable across studies. Correlational analyses of functional brain activity and total cortisol output (measured using area under the curve), change in cortisol between baseline and stressor, percentage change, maximum percentage increase, slope, or by splitting groups into responders & non-responders have all been conducted. Although these are all rational ways in which one might wish to represent cortisol reactivity, meaningful synthesis of the current findings is impaired by the lack of standardisation.



#### 4.4 Deleterious Effects of Glucocorticoids: Implications for Cognitive Ageing

The ability to evaluate the potential threat of a situation and effect rapid and enduring physiological adaptations is of undoubted benefit for survival. While increased GC production in response to a social or cognitive stressor might reflect evolution lagging behind the socio-cultural development of *homo sapiens*<sup>27</sup>, a transient boost of this steroid is crucial for physical readiness and behavioural adaptation, and a characteristic diurnal pattern is necessary for homeostatic processes. However, chronic exposure to high levels of GCs can have deleterious effects on the brain.

In rodent models, a large number of studies have reported that prolonged exposure to repeated instances of restraint stress or exogenous steroids results in reduced synaptic and dendritic complexity in the hippocampus and mPFC, with dendritic growth in the amygdala (Cook & Wellman, 2004; Izquierdo, Wellman, & Holmes, 2006; McEwen, 1999; McEwen & Gianaros, 2010; Radley et al., 2004, 2006; Vyas, Mitra, Rao & Chattarji, 2002; Wellman, 2001). Chronic stress has been shown to also result in a volumetric change in these regions: for example, volumes and neuronal numbers of the rat cingulate and medial (infralimbic and prelimbic) PFC were found to be reduced following 4 weeks (but not 3 or 6 days) of chronic unpredictable restraint stress (Cerqueira et al., 2007). Disruptions to neuronal morphology are also likely to have implications for cognitive function (Kasai, Matsuzaki, Noguchi, Yasumatsu & Nakahara, 2003); GC-induced cognitive impairments have also been reported in memory tasks (Dachir Kadar, Robinson & Levy, 1993; Sousa, Lukoyanov, Madeira, Almeida, Paula-Barbosa, 2000) and PFC-

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<sup>27</sup> Given the putative short-term effects of GCs on some domains of cognition, stress-responses in situations that require these abilities would appear to be counter-productive.

specific abilities such as attentional set-shifting (Liston et al., 2006), although the latter paper also reported an *increase* in dendritic arborization in the OFC and no impairment on reversal learning after 21 days of restraint stress. Chronic socially-stressed tree shrews exhibited shrinkage of the apical dendrites in the CA3 hippocampal area (Magarinos, McEwen, Flugge, Fuchs, 1996), reduced volume on MRI, and poorer subsequent memory function (Ohl et al., 2000).

In primates, prolonged exposure to GCs is associated with a reduction in hippocampal volume (Sapolsky, Uno, Rebert, & Finch, 1990), impairing the survival of hippocampal neurons (Landfield, Waymire & Lynch, 1978; Sapolsky et al., 1986). In response to prolonged periods of social stress, GR receptor expression was diminished in the hippocampus, whereas MR expression was reduced in the orbital PFC when compared to no-stress controls (Patel et al., 2008).

In humans, the primary characteristic of Cushing's syndrome is a chronic excess of GCs, usually caused by adrenal or pituitary tumours, or through high-dose steroid administration (Patil et al., 2007). This condition therefore holds a great deal of potential to directly inform our understanding of excess cortisol exposure in humans. Cushing's syndrome has been associated with global cerebral atrophy, general cognitive impairment (Forget, 2002; Michaud, Forget, & Cohen, 2009; Starkman, Giordiani, Berent, Schork & Scheingart, 2001), specific hippocampal atrophy (Toffanin et al., 2011) and associated memory decrements which appear as little as 2-6 months after syndrome onset (Starkman et al., 1992; reviewed by Patil et al., 2007). Hippocampal volumetric reductions in Cushing's disease are partially reversible once GC levels are normalised (Starkman et al., 1999). This further supports the idea that GC-induced volume loss reflects dendritic, synaptic, glial and

possibly axonal re-modelling, rather than widespread cell-death (Fuchs & Flügge, 2003).

However, there are very few studies relating chronic GC exposure to white matter damage or alteration. A series of rodent studies observed that axon sprouting<sup>28</sup> in response to lesion in the entorhinal cortex is impaired by subsequent GR- (but not MR-) specific steroid treatment, and that this effect is dose-dependent (Scheff & Cotman, 1982; Scheff & DeKosky, 1983). Temporal manipulation of the initiation of treatment also showed that increased exposure to GCs prior to lesion led to less axon sprouting than when GCs were only administered post-lesion (Scheff & Dekosky, 1989).

#### *4.4.1 Glucocorticoid Hypothesis of Brain Ageing*

Observing that biomarkers of hippocampal ageing in rodents correlated with corticosterone levels (Landfield, Waymire & Lynch, 1978), Landfield et al. (1978) proposed that accumulated exposure to normal levels of GCs over the lifespan promote brain ageing, and exposure to higher levels (which may occur due to chronic stress) accelerates the process. The authors did not explicitly identify the nature of the interaction between age and GC levels (of which there are several possible variations – Figure 4.3; Porter & Landfield, 1998), but circulating GC levels and age were proposed to interact to facilitate cell-damaging processes. However, the findings of a recent genetic microarray study contradict the assumption that the GC

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<sup>28</sup> A plastic process via which the central nervous system responds to axonal loss following cell death or injury. It involves initiating the growth of additional axons from surviving neurons which re-establishes some degree of innervation, in patterns consistent with the local laminar environment (Deller et al., 2006).

and age interaction is entirely unidirectional (Landfield et al., 2007). They compared genes sensitive to hippocampal ageing with those in the hippocampus that are regulated by GCs. Consistent with Landfield's hypothesis, they found that the number of genes regulated by both age and GCs was greater than chance, but more genes were altered in opposite directions by age and GC than in the same direction. However, those genes that were regulated in the same direction by GCs and age were found in a few categories critical for brain ageing (Landfield et al., 2007). Although this study was confined to the hippocampus, it highlights the potential for GCs and ageing to interact in a more complex fashion in the brain. More specifically, they propose that, "*aging selectively increases GC efficacy in some cell types (e.g. neurons), enhancing catabolic processes, whereas aging selectively decreases GC efficacy in other cell types (e.g. astrocytes), weakening GC anti-inflammatory activity*" (Landfield et al., 2007, p.205). Thus, lifetime cortisol production may facilitate focal wear and tear, and individual differences in cortisol exposure throughout the lifespan may partially explain the variability in age-related brain atrophy and cognitive decline.

Further to this hypothesis, Sapolsky, Krey and McEwen (1986) posited the glucocorticoid cascade hypothesis of ageing. They state that damage to brain regions involved in negative feedback regulation of the HPA axis results in a failure to effectively terminate GC production when appropriate. This propagates elevated GC production beyond the period of need, and promotes further GC-induced damage to these brain regions. This was more recently re-named the neurotoxicity hypothesis, in order to put emphasis on excess GCs acting to reduce the ability of neurons to withstand toxic challenges or attrition (Gilbertson et al., 2002). Increasing age should

therefore be associated with a dysregulated negative feedback profile. Based on the evidence above, this should also translate to poorer integrity of regions to which GCs preferentially bind, and impaired subsequent functioning with age.

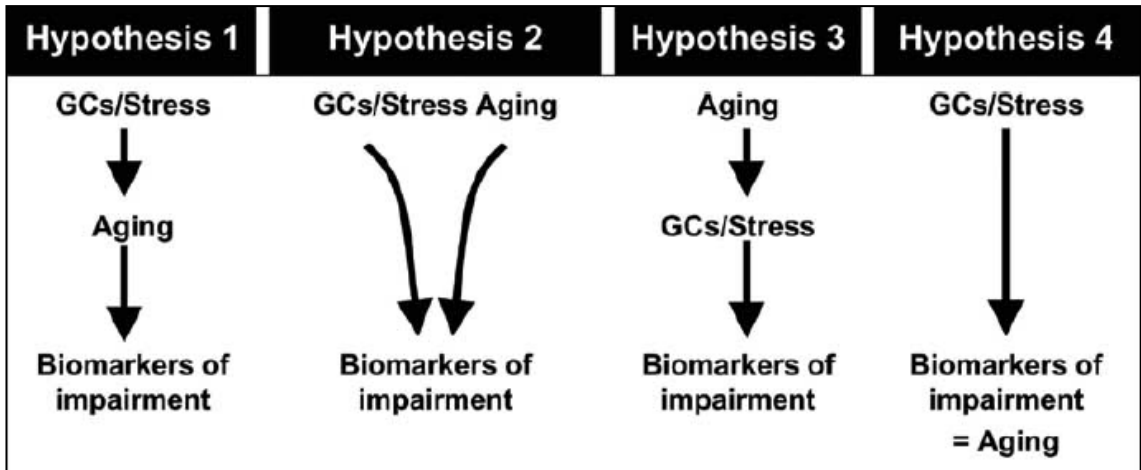


Figure 4.3. Possible ways in which glucocorticoids and ageing could interact, based on the initial glucocorticoid hypothesis of ageing (Landfield, 1978). From Porter & Landfied (1998), redrawn in Landfield et al., (2007). Subsequent evidence suggests that GCs and ageing do not always interact cooperatively, or always negatively, but vary dependent upon cell type (Landfield et al., 2007).

#### 4.4.2 Evidence for Age-Related Changes in Glucocorticoid Levels, Brain Structure and Function: Animals

Ageing in rodents has been associated with impaired reactive (Sapolsky et al., 1984; Segar, Kasckow, Welge, & Herman, 2009) and diurnal GC profiles (Issa, Rowe, Gauthier, & Meaney, 1990) when compared to younger controls, although late-life patterns of GC production vary between rodent strains and show increased heterogeneity (Kasckow, Xiao, & Herman, 2009; Segar et al., 2009). Old rats, adrenalectomised (ADX) at middle-age, showed considerably less age-related

hippocampal change and more closely resembled younger rats in performance on a reversal learning maze when compared to a non-ADX elderly group (Landfield, Baskin & Pitler, 1981). Reports from other laboratories also show cognitive impairment and hippocampal atrophy concomitant with higher GC levels in ageing rodents (Issa et al., 1990; Meaney et al., 1995; Sapolsky et al., 1986; reviewed in Landfield et al., 2007). Moreover, alteration of GC exposure from midlife has been shown to have a significant impact on the hippocampus and memory functioning. Suppression of GC secretion increases hippocampal neurogenesis in old age, and abates age-related memory decline, whereas increasing GC exposure at midlife has the opposite effect (Montaron et al., 2006). The emergent picture of ageing in rodents is one of increased HPA activity, hippocampal damage and cognitive impairment in a subset of animals.

This body of literature only reports either basal or reactive measures of cortisol and is focussed entirely on the hippocampus. However, there has been relatively little animal work examining ageing, GCs and the mPFC. In order to address these lacunae, one study used microdialysis to measure GC levels in the hippocampus and PFC in young and aged rats, both during restraint stress and under basal conditions (Garrido, de Blas, Del Arco, Segovia, & Mora, 2012). They found that although the old group showed higher cortisol levels in response to stress, when measured from plasma from an incision above the tip of the tail, there were no age-related differences in GC levels in the PFC and hippocampus. but that free basal levels were significantly higher for aged rats in both the hippocampus and PFC. Crucially, although cortisol levels in response to stress were no different between young and old rats, they found that basal plasma levels in response to stress were

significantly higher in aged rats, but that there was no age-related difference in GC levels the hippocampus or PFC. The dissociation between serum and brain GC levels (also reported by Yau et al., 2007) has implications for the ability of blood or salivary measures of cortisol to accurately depict the situation in the brain. This dissociation also supports the idea that additional containment mechanism(s) may protect the brain from exposure to high GC levels (Droste et al., 2009), and individual differences in containment may contribute uniquely to age- and GC-related brain changes. Although only performed with small groups ( $n < 10$ ) and with no link to structural change, the important implications of this study will be further explored at the end of this chapter.

#### *4.4.3 Evidence for Age-Related Changes in Glucocorticoid Levels, Brain Structure and Function: humans*

In humans, HPA axis dysfunction has been reported in numerous age-related diseases such as Alzheimer's disease (Huang et al., 2009; Landfield et al., 2007), depression and other mood disorders (O'Brien, Lloyd, McKeith, Gholkar, & Ferrier, 2004; reviewed in McEwen, 2005). However, the causal relationship between brain pathology and cortisol levels is unclear in these cases (Dedovic et al., 2010), and therefore it may be problematic to generalize this to all ageing humans. In healthy ageing, the majority of studies report that diurnal HPA measures increase with age, with a flatter diurnal pattern and increased mean daily output (Deuschle et al., 1997; Heaney et al., 2010; Luz et al., 2003; Yen & Laughlin, 1998), though others report no change in daily output (Edwards, Evans, Hucklebridge & Clow, 2001; Madsen et

al., 2012; Wolf, Convit, Thorn & de Leon, 2002), or a steeper diurnal slope with increasing age (Ice, Katz-Stein, Himes & Kane, 2004). Two studies showed a lower awakening response with increasing age (Heaney et al., 2010; Kudielka & Kirschbaum., 2003), one found a trend (Pruessner et al., 2005), but others found no such difference (Heaney et al., 2011; Pruessner et al., 1997; Wurst et al., 2000). Others still report age-differences in men only (Almeida, Piazza, & Stawski, 2009), or increased morning levels for men only, and higher evening levels in both men and women (Larsson, Gullberg, Råstam, & Lindblad, 2009). A detailed longitudinal study took 24hr cortisol each year over a period of 3 to 6 years for healthy elderly individuals, and reported that basal profiles did not appear to change in the same direction (Lupien et al., 1996). Rather, considerable variation in old age was reported, and three general groups were observed with increasing, decreasing and stable measures.

With respect to the reactive profile, it does appear that ageing confers a larger cortisol response in humans. A recent meta-analysis of human data compared the pre-test and reactive measures of cortisol from 625 older (69+/-6 years) and 670 younger (28+/-5 years) normal healthy adults (Otte et al., 2005). Older adults exhibited a significantly larger response to challenge (Cohen's  $d=0.42$ , 95% confidence interval, 0.26–0.57), although the authors report finding no age differences in pre-test cortisol measures.

In humans, studies directly comparing cortisol levels, measures of brain structure and cognitive function in old age are rare. Rather, the majority of studies report correlations between cortisol and *either* cognition *or* structural brain measures. Results of these studies in humans are summarised in Table 4.2. Higher cortisol in



old age appears to be associated with a decline in memory and general cognitive functioning. An early study reported that general cognitive functioning was negatively associated with dexamethasone suppression (Kalmijn et al., 1998). A highly detailed diurnal cortisol sampling approach took saliva measures on waking, and then +15, +30 and +45 minutes, and then four more samples at 3 hour intervals on two consecutive weekdays (Evans et al., 2011; Evans, Hucklebridge, Loveday, & Clow, 2012). They found that a general factor of cognitive performance was associated with mean cortisol (0-45mins after waking), mean cortisol 3-12 hours post-waking, the cortisol awakening response (30 minute minus waking sample) and the diurnal fall (from 30 post-waking minutes to final sample of the day). This pattern was also generally true for various indices of verbal memory ability and the Trail Making Test part B.

Using a different approach, the change in 24hour serum blood (sampled every hour on one occasion each year over four years) correlated with delayed verbal paired associate recall performance and selective attention - as measured by a visual search paradigm - but did not relate to performance on a large number of other cognitive tests (Lupien et al., 1994). Another low-powered study ( $n=14$ ) reported that increased cortisol in anticipation of a public speaking test impaired word-pair recall (Lupien et al., 1997). In contrast, a large cross-sectional study using 967 participants aged 50-70 years compared cortisol levels before, during and after cognitive testing on seven domains (language, processing speed, eye-hand coordination, executive functioning, verbal learning and memory, visual memory and visual construction; Lee et al., 2007). Measures of total cortisol output (AuC and mean), and pre-test levels were associated with poorer performance in all domains except for visual

reconstruction. Verbal memory decline in relation to higher basal cortisol measures has also been reported amongst post-menopausal women in several other studies (Beluche, Carrière, Ritchie, & Ancelin, 2010; Comijs et al., 2010; Seeman, McEwen, Singer, Albert, & Rowe, 1997). In a prospective study that followed individuals from age 85-90, no relationship between cortisol levels and verbal memory recall (immediate and delayed) was reported at baseline (Kuningas et al., 2007). Rather, the authors reported that higher cortisol correlated with poorer processing speed and MMSE score, and these associations were also true at follow up. Mean and evening cortisol levels predicted a 3 year decline in immediate and delayed verbal memory and executive functioning in another longitudinal ageing study (Li et al., 2006). MacLulich and colleagues (2012) found no association between 24 hour urinary cortisol and measures of verbal fluency, processing speed, verbal and spatial memory or reasoning either at baseline or follow-up 6 years later, or accelerated decline over time. However, another prospective study split a large ageing cohort in APOE e4 allele-carriers and non-carriers ( $74.5 \pm 7.2$  years,  $n = 911$ ; Gerritsen, Comijs, Deeg, Penninx, & Geerlings, 2009) and examined associations at 4 year follow up. For the whole cohort, higher evening levels and a flatter diurnal slope correlated with poorer memory functioning at both baseline and follow up, but cortisol levels were not associated with increased cognitive decline. Lower morning cortisol, higher evening levels and a flatter diurnal rhythm correlated with increased risk of verbal memory decline for e4 carriers only, but MMSE score or processing speed were not associated with cortisol levels either between groups or for the overall cohort. In contrast, another prospective study ( $n=538$ ) reported that only the group with the lowest quartiles of 12 hour urinary cortisol were at reduced risk of a 7 year decrease

in global cognition (Karlamañgla, Singer, Chodosh, McEwen, & Seeman, 2005). The remaining three groups each exhibited equally high risk of cognitive decline, though only 78 participants showed any decline at all over 7 years.

Several placebo controlled double-blind studies have examined the effects of various dosages of GCs on cognitive performance in old age (Coluccia et al., 2008; Porter, Barnett, Idey, McGuckin, & O'Brien, 2002; Wolf et al., 2001). Two of these studies reported that steroid administration had no effect on performance on a diverse battery of tests including executive function and memory measures (Porter et al., 2002; Wolf et al., 2001). However, another study found a significant dose effect on delayed memory scores amongst arthritis sufferers, which was not evident when the groups were split into those who were chronically medicated with cortisone (~5 years) and those who were un-medicated (Coluccia et al., 2008). Although the design ensures that the small sample size ( $n < 24$  in these studies) is maximised by exposing all participants to both placebo and dose conditions, the small numbers of participants and the use of exogenous steroids limit the generalizability of results from such studies to the natural reactive levels of the wider ageing population.

To examine relationships between cortisol levels and brain structure, a longitudinal study took 24 hour basal cortisol measures each year over a period of 5-6 years (Lupien et al., 1998). The group with increasing or high 24 hour basal cortisol levels ( $n=11$ ) exhibited lower hippocampal volume and poorer delayed, but not immediate memory recall when compared to the group who showed stable or decreasing cortisol ( $n=5$ ; Lupien et al., 1998). Elsewhere, increasing age was correlated with reduced hippocampal volume and a trend towards higher cortisol awakening response, but correlations between hippocampal volumes and cortisol

were not directly performed in the whole ageing group (Pruessner et al., 2005). Other studies show no significant associations between cortisol measures and hippocampal volumes in healthy ageing samples (Gold et al., 2005; Kremen, O'Brien, et al., 2010; MacLulich et al., 2005, 2006, 2012) or depression (O'Brien et al., 2004; Vythilingham et al., 2004).

More recently, there has been a shift of focus to include the frontal lobe in studies of cortisol levels in old age. Cortisol output (AUC) over 75 mins following CRH injection was measured in 54 adults (aged 51-75), along with nocturnal 12h urinary free cortisol, and cortisol following dexamethasone administration the night before testing (Gold et al., 2005). The only cortisol measure to show an association with brain volume was AUC in response to CRH injection which was associated with the visual assessment of global and frontal lobe atrophy, and showed a trend towards reduced volume of the frontal lobe but not hippocampus (Gold et al., 2005). However, as discussed previously, the frontal lobe is structurally and functionally heterogeneous, and may also be differentially sensitive to circulating GC levels. Another study combined measures of cortisol, cognition and brain structure from MRI in 97 males aged 65-70 (MacLulich et al., 2005). Only cortisol taken at 09:00, but not 14:30 or post-dexamethasone was found to correlate with a general cognitive factor, and delayed verbal memory and processing speed components. No measures of brain structure correlated with any cortisol metrics apart from a negative correlation between left temporal lobe and afternoon cortisol levels. However, within this same cohort, the 10 individuals who showed the lowest levels of suppression following dexamethasone administration were found to have smaller left ACC, (but not right ACC, bilateral SFG or hippocampi) compared to the 10 highest suppressors

– note that these ROIs were also manually-measured on MR images (MacLulich et al., 2006). In contrast, another study used the automated software Freesurfer to examine cortical thickness and hippocampal volume in relation to mean daily cortisol output - taken on the day of the scan appointment - in middle-aged males (aged 50-59yrs; Kremen et al., 2010a). Cortisol did not correlate with either ACC or hippocampal volume, but with the cortical thickness of bilateral SFG, right medial OFC, left MFG and left IFG. Wolf and colleagues (2002) found a group-wide association between 24 hour urinary cortisol and hippocampal volume in small group with a wide age range ( $n = 20$ , aged: 19-76 years. Cingulate gyrus volume did not correlate with 24 hour cortisol, but there was a negative correlation between baseline ACTH and both cingulate and hippocampal volumes for the whole sample. However, when the participants were split by age, there were no group differences in the cortisol-structure correlations for hippocampal volume, parahippocampal volume, orbitofrontal cortex volume, cingulate gyrus volume or total CSF (as a measure of global atrophy).

Few publications have examined relationships between white matter and GC levels in ageing. Increasing age in a group of rats was associated with increased diurnal corticosterone (DeKosky, Scheff & Cotman, 1984) and reduced axonal sprouting following removal of the entorhinal cortex (Scheff, Bernardo & Cotman, 1980), perhaps suggesting that higher cortisol levels impair white matter repair following insult. In humans, relationships between cortisol levels and white matter tract integrity in old age have not been examined. In a small group of young and middle-aged participants ( $n = 48$ , age  $37.4 \pm 19.3$ ), cortisol awakening response did not correlate with the FA of either the uncinate fasciculus or cingulum bundle

(Madsen et al., 2012). However, a higher degree of right vs. left FA asymmetry was associated with a higher cortisol awakening response for the uncinate, and in the opposite direction for the cingulum<sup>29</sup>. Yet, one recent study has reported that an index of cortisol sensitivity<sup>30</sup>, but not 24 hour urinary cortisol, in 41 men (aged 65-70 years at the time of initial study) correlated with periventricular white matter hyperintensities (MacLulich et al., 2012). This baseline measure of sensitivity showed a trend towards significance with white matter hyperintensities 6 years later. There are therefore no studies that have combined measures of reactive and diurnal cortisol in ageing humans with a detailed examination of frontal sub-regional structure, white matter tract integrity and neuropsychological function.

#### *4.4.4 Methodological Considerations*

Several methodological issues might underlie the discrepancies amongst studies exploring the possible impact of cortisol levels in human ageing. Firstly, cross-study comparison is undeniably hampered by the variable age ranges of participants. As shown in Table 2, age ranges span from 50-90 years of age across the different studies. Further, if only a subsample of the normal healthy population exhibit cortisol dysregulation with age, self-selecting cohorts of healthy ageing participants could contain a less representative proportion of those with cortisol hypersecretion. For example, amongst one of the larger longitudinal studies discussed above, participants excluded through non-response tend to be significantly older, have a higher incidence of poor health or health behaviours, and poorer cognitive performance and

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<sup>29</sup> These relationships were not mediated by a general brain asymmetry, determined by including a measure of global white matter asymmetry in their multiple linear regressions.

<sup>30</sup> The urinary ratio of tetrahydrometabolites of cortisol: tetrahydrometabolites of cortisone is thought to be an index of 11 $\beta$ -HSD1 activity. This is an enzyme that interconverts inactive cortisone into active cortisol.

significantly different cortisol profiles (Gerritsen et al., 2009). Additionally, the proportion of individuals that exhibit cortisol levels that are severely neurotoxic may vary between studies.

Just as with the functional imaging studies discussed earlier in this chapter, the use of cortisol metrics is not consistent across studies (Otte et al., 2005); these include maximum response, reactive or basal area under the curve, greatest reactive change from baseline, various single timepoint measures, longitudinal change in basal levels, diurnal slope, and levels sampled in response to dexamethasone or CRH administration (e.g. Table 4.2). In addition, the number, timing and frequency of sampling points is not uniform (Kraemer et al., 2006; see also Table 2), and this lack of standardisation makes synthesis of the literature difficult. Circulating levels of cortisol in serum and saliva appear to be well-correlated (Vining, McGinley, Maksvytis & Ho, 1983), suggesting that (aside from individual stress responses to blood sampling) either serum or saliva samples are acceptable measures of free cortisol levels. However, the finding by Yau et al (2007), and Garrido and colleagues (2010) of a dissociation between brain and peripheral serum levels of GC may suggest that neither saliva nor serum measures may entirely capture levels of cerebral GC exposure.

The concepts of cognitive organisation and the tests used to gauge function also vary; from the MMSE to various tests of verbal and spatial memory, to latent variables representing general cognitive ability. Furthermore, MacLulich and colleagues (2005) observe that previous ageing studies had not controlled measures of cognitive performance for an estimate of peak intelligence. It is therefore unclear how much of the individual differences in cognition were present due to

developmental factors, and how much might have occurred after cognitive peak, possibly due to cortisol exposure. Thus, by controlling for peak intelligence their results provide an estimate of the relationship between morning HPA axis functioning and ageing-related change in cognitive function.

It has been shown that a relatively brief period of stress can produce significant cerebral remodelling. Therefore the degree to which reported correlations between cortisol and brain structure in humans are the product of long-term, rather than short-term endocrine status is difficult to parse apart. The fact that brain changes in Cushing's disease are at least partially reversible raises further questions about the potential transience of cortisol's effects on the brain. However, it has recently been reported that the dendritic spines in the ageing rodent PFC are less plastic in the face of short-term stressors (Bloss et al., 2011). Were this finding to be replicated in primates, it could suggest that structural changes observed in old age in relation to cortisol may be at least partially related to long-term rather than short-term age-related changes in GC exposure.

Finally, administration of exogenous steroids in order to examine HPA axis negative feedback might not accurately reflect endogenous processes. For example, it has been suggested that the selective GR agonist dexamethasone shows a relative resistance to enzymatic processes that interconvert inert and active glucocorticoids in target tissues (Best, Nelson & Walker, 1997). Dexamethasone may also differ from cortisol in its mechanism of transport across the blood-brain-barrier and cannot account for any potential influence of MR on negative feedback (de Kloet, 1991; Mattsson et al., 2009). As a result, such studies may not be directly comparable with those measuring HPA axis reactivity in response to stress.



Table 4.2. Overview of relationships between cortisol vs. brain structure, and cortisol vs. cognition in healthy ageing humans.

Study	Age range	n	Cortisol	Cortisol vs. Structure		Cortisol vs. Cognition	
				Direction	Variable	Direction	Variable
Lupien (1994)	60-80	19	change in 24hr levels			-ve	explicit memory, selective attention
						ns	immediate & delayed verbal and visual recall, divided attention, VF
			mean final measure			ns	ns for all measures
						ns	ns for all measures
Lupien (1997)	62-83	14	reactive			-ve	immediate verbal memory
						ns	non-declarative/delayed memory
Seeman (1997)	70-79	1189	12hr urine (8pm-8am)			-ve	delayed verbal memory (females only)
						ns	visual memory, spatial memory, visuospatial ability, delayed memory (males)
	2.5yr follow-up	200	12hr urine (change)			-ve	delayed verbal memory (females)
						ns	ns for all other measures
Kalmijn (1998)	55-80	189	8-9am 9h post-DEX			ns	MMSE
						-ve	MMSE
Lupien (1998)	76.5±4.3	11	5yr change in 24hr levels	-ve	HCv	-ve	delayed memory
				ns	temporal gyri vol.	ns	immediate memory
Wolf (2001)	19-76	20	placebo vs. cortisol <sup>a</sup>			-ve	delayed memory (no age diff)
	(19-30) (59-76)	(9) (11)	(0.5mg/kg cort)			ns	immediate memory, attention, Stroop

Study	Age range	n	Cortisol	Cortisol vs. Structure		Cortisol vs. Cognition	
				Direction	Variable	Direction	Variable
Wolf (2002)	19-76 (19-30) (59-76)	20 (9) (11)	24hr urine     pre-test	-ve	HCv ( <i>no age difference</i> )		
				ns	parahippocampal gyrus vol.		
				ns	global atrophy		
				ns	cingulate gyrus vol.		
				ns	orbitofrontal vol.		
				ns	HCv		
				ns	parahippocampal gyrus vol.		
				ns	global atrophy		
Porter (2002)	69-82	16	placebo vs. cortisol <sup>a</sup> (20mg hydrocortisone)			ns	digit span, spatial span, RAVLT, pattern recognition, spatial recognition, continuous performance test
Gold (2005)	51-75	54	AUC-CRH <sup>b</sup>   12h nocturnal 15h post-DEX	+ ve	global atrophy (vis)		
				+ ve	frontal atrophy (vis)		
				-ve trend	frontal lobe vol.		
				ns	HCv		
				ns	ns for all		
				ns	ns for all		

Study	Age range	n	Cortisol	Cortisol vs. Structure		Cortisol vs. Cognition	
				Direction	Variable	Direction	Variable
Karlamangla (2005)	70-79	538	12hr urine (8pm-8am)			-ve	SPMSQ score 7 years later
			1430h 10h post-DEX	-ve <i>ns</i>	left temporal lobe vol. <i>ns for all</i>	<i>ns</i> -ve trend	<i>ns for all</i> processing speed
MacLulich (2005)	65-70	97	0900h	<i>ns</i>	HCv, temporal lobe & frontal lobe vol.	-ve	g, processing speed, logical memory
MacLulich (2006)	65-70	20	10h post-DEX (hi vs lo groups)	-ve <i>ns</i>	left ACC right ACC, bilateral SFG, HC vol.		
Li (2006)	78 ±7.1	79	11pm			-ve	3yr change in immediate and delayed verbal memory, TMTb, Stroop, MMSE.
			3yr Mean			<i>ns</i>	BVRT
						-ve	3yr change in delayed recall, TMTb, Stroop, MMSE
						<i>ns</i>	BVRT, immediate recall
Lee (2007)	50-70	967	before cog. test			-ve	6 domains (language, processing speed, eye-hand coordination, executive function, verbal memory, visual memory)
			during cog. test			<i>ns</i>	<i>ns for all</i>
			after cog. test			<i>ns</i>	<i>ns for all</i>
			end of lab visit mean			<i>ns</i> -ve	<i>ns for all</i> 6 domains as above

Study	Age range	n	Cortisol	Cortisol vs. Structure		Cortisol vs. Cognition	
				Direction	Variable	Direction	Variable
Lee (2007) cont...			AUC			-ve	6 domains as above
Kuningas (2007)	85	460	morning (<11am)			-ve	MMSE, processing speed
						-ve trend	Stroop
						ns	verbal memory
	85-90 follow-up	460	morning (<11am)			-ve	MMSE, processing speed, Stroop
						ns	verbal memory
Coluccia (2008)	41-65	24	placebo vs cortisol <sup>a</sup> (5mg prednisone)			-ve	immediate & delayed verbal memory
	59.4±1.5	13	5yr prednisone	ns	HCv	ns	immediate & delayed verbal memory
	50.3±2.2	11	no prednisone		global CSF		
Gerritsen (2009)	75.5 ±6.8	911	waking+30 <sup>c</sup>			-ve	verbal memory 4yr change (immediate & delayed) – <i>APOE e4 only</i> .
						ns	MMSE, processing speed
			bedtime			-ve	verbal memory (immediate & delayed) – <i>whole sample</i> MMSE, processing speed

Study	Age range	n	Cortisol	Cortisol vs. Structure		Cortisol vs. Cognition	
				Direction	Variable	Direction	Variable
Gerritsen cont....			diurnal slope			-ve	verbal memory 4yr change (immediate & delayed) – <i>APOE e4 only</i> .
						-ve	verbal memory (immediate & delayed) – <i>whole sample</i>
						ns	MMSE, processing speed
Beluche (2010)	65-90	197	morning			-ve	semantic fluency, TMTb (males only)
			diurnal slope			ns	BVRT, MMSE
						-ve	semantic fluency (females only)
	4yr follow-up	162	morning			ns	BVRT, MMSE, TMTb
						-ve	TMTb (females)
						ns	BVRT, MMSE, semantic fluency
						ns	MMSE, BVRT (females), TMTb (females), semantic fluency (males)
Kremen (2010a)	50-59	388	mean <sup>d</sup>	-ve	bilateral SFG, right medial OFC, left lateral surface <sup>e</sup>		
				ns	HC vol.		
Comijs (2010)	65-88	1154	11am			-ve	immediate & delayed verbal memory (males & females)

Study	Age range	n	Cortisol	Cortisol vs. Structure		Cortisol vs. Cognition	
				Direction	Variable	Direction	Variable
Comijs cont...			11am			-ve	processing speed (females only)
						ns	MMSE (males & females)
						ns	6 year change in MMSE, processing speed and memory
Evans (2011 & 12)	60-91	50	0-45min post-waking			-ve	verbal recognition, TMTb (trend), g (trend)
			3-12hr post-waking			ns	immediate & delayed recall, VF
			diurnal mean diurnal fall (peak-trough)			-ve	delayed verbal memory (trend), g (trend), TMTb (trend)
			CAR			ns	all others
						ns	ns for all
						-ve	g, immediate verbal memory, verbal recognition, TMTb
						ns	all others
						-ve	g, TMTb, VF
						ns	all others
MacLulich (2012)	65-70	41	24hr urine	ns	HC vol., ventricular volume, WMH	ns	verbal fluency, DSST, BVRT, logical memory, visual reproduction, Raven's matrices
	+6 years		24hr urine	ns	ns for all	ns	ns for all

<sup>a</sup> placebo controlled double-blind crossover <sup>b</sup> Area under the curve of cortisol output 75 mins after CRH injection. <sup>c</sup> Cortisol Awakening Response, taken monthly over 1 year. <sup>d</sup> Mean level of awakening+30minutes, 10am, 3pm and 9pm. <sup>e</sup> Cortical thickness. AVLT: Auditory verbal learning test, BVRT: Benton visual retention test; CAMCOG: cognitive examination from the Cambridge examination for mental disorders in the elderly, CAR: cortisol awakening response; DEX AUC: Cortisol area under the curve after Dexamethasone; DSST: digit-symbol substitution test, HCv: hippocampal volume, RAVLT: Rey auditory verbal learning test, SPMSQ: short portable mental state questionnaire (Pfeiffer, 1975); TMTb: Trail making test part B, VF: Verbal Fluency, WMH: white matter hyperintensities.

## 4.5 Conclusions

In summary, GCs are a vital component in both normal homeostasis, and our ability to respond to perceived challenge. Brain regions that contain a high density of GR and MR – to which GCs preferentially bind – are thought to play a major role in regulating HPA axis activity. Brain regions including the hippocampus and PFC exert indirect influence upon the process of GC production and have been shown to contribute to the negative feedback system that reduces GC synthesis. This system can therefore be characterised as a large-scale distributed brain network, yet the importance of the axonal connectivity between these regions has been generally underplayed in both human and animal research to date.

Although an essential hormone, rodent and primate/human studies demonstrate that elevated and chronic GC exposure can disrupt cognitive performance and the structure of brain regions implicated in GC regulation. In rodent models, the hippocampus and mPFC show dendritic remodelling and de-arborisation even following a relatively short exposure to extreme levels, whether achieved via exogenous administration or stress. The widespread reduction in brain volume in Cushing's disease is likely to represent such remodelling, and gives strong evidence for the detrimental effects of chronic hypercortisolaemia in humans. Concomitant memory impairment is also a relatively consistent finding in both animals and humans, although it is interesting to note that the detrimental effects of chronic GC exposure appear to be, at least partially, reversible.

Higher diurnal and reactive GC levels have been associated with increasing age, although this is not true for all aged animals and humans (e.g. Issa et al., 1990;

Landfield, 1978; Lupien et al., 1996, 1998). It has been hypothesised that GCs are a determinant of cognitive ageing, as chronic (and possible increasing) levels of GC production with increasing age facilitate neurotoxic processes in certain tissue types. Thus, those individuals who exhibit higher levels in old age are more likely to be susceptible to GC-driven brain changes and accompanying cognitive deficits.

Research has primarily focussed on the hippocampus, and the animal literature consistently reports high GC levels with age relate to smaller hippocampi and impaired cognitive function. Some evidence points to a similar pattern in ageing humans, although some studies did not find correlations between hippocampal volume and cortisol measures. Others still have reported negative cortisol-memory associations in the absence of a cortisol-hippocampus relationship, but it is notable that one large study did not find any link between cortisol levels and either immediate or delayed verbal memory recall (Kuningas et al., 2007) whilst another study only reported such an association when genetic status was taken into account (Gerritsen et al., 2009).

The animal literature also identifies the frontal lobes as a target of GC-driven remodelling, and suggests that the medial prefrontal cortex is particularly vulnerable. To date however, only two studies in ageing humans fractionate the frontal lobes into sub-regions, but their results are conflicting: one identifies associations with the left ACC, but not SFG (MacLulich et al., 2006), whilst the other implicates a reduction of bilateral SFG thickness, along with most of the left fronto-lateral surface (Kremen et al., 2010a). In terms of associations between cortisol levels and frontal lobe functioning, several findings report poorer performance on tests that have been broadly linked with anterior cerebral functioning. Higher levels of cortisol (using



various metrics) have been reported to correlate negatively with measures of executive function, general cognitive ability, and the Stroop task (a test often associated with the DLPFC and ACC).

Apart from the methodological inconsistencies between studies, few studies combine measures of diurnal and reactive cortisol measures with measures of brain structure and function. Sub-regional examinations of the frontal lobe in particular are lacking, and have not examined cognitive functions subserved by these regions. Moreover, the significance of white matter integrity for GC regulation and its susceptibility to chronic GC exposure in old-age has been comparatively overlooked. There are suggestions from animal models that white matter may be affected by chronic GC administration as well as higher GC levels in old age, and that the symmetry of limbic fibre bundles is related to endocrine functioning in young healthy humans. However, no studies have directly examined cortisol and the integrity of white matter fibres in old age.

## Chapter 5: Methods

### 5.1 Participants

The Lothian Birth Cohort 1936 (LBC1936; Deary, Whalley & Starr, 2009) comprises individuals who were all born in 1936 and most of whom took part in the Scottish Mental Survey of 1947 when they were 10.5 to 11.5 years old. At a mean age of 69.5 years ( $SD = 0.8$ ), these healthy, community-dwelling individuals were also mostly living in the Lothian area of Scotland when recruited for this first wave of follow-up testing (June 2004 – May 2007). The Lothian Health Board initially identified 3810 people on the Lothian Community Health Index (CHI) that were born in 1936 and contacted 3686 of them on behalf of researchers. In combination with advertisements placed in the two Edinburgh-based newspapers, the total of 1226 individuals were interested and eligible to participate in the study, from which 1091 eventually completed participation in this first wave of follow-up tests.

Wave 1 contained this same mental test they sat at age 11, in addition to other cognitive and medical tests, genetic sequencing and rich background data which are detailed elsewhere (Deary et al., 2007). Three years later, at a mean age of 72.5 years ( $SD = 0.7$ ), 866 returned for a second follow-up wave which repeated many of the same tests, but also included a comprehensive set of brain MRI sequences on the majority of participants ( $n=730$ ) at a mean age of 72.7 years ( $SD = 0.7$ ). This effort has produced one of the richest and most unique datasets in cognitive ageing and epidemiological research. A particular strength of this design is the value of age 11

IQ as a covariate and the multiple waves of testing which are both important in understanding the complex causal interplay of numerous potential determinants of cognitive ageing. Adding cortisol measures and neuropsychological tests to the existing MRI and cognitive variables from this second wave of testing forms the basis from which research questions in this thesis are addressed. The selection and recruitment of participants (who had just completed Wave 2 testing at the outset of this thesis) are detailed below.

#### *5.1.1 Selection Criteria*

For the current study, a subset of LBC1936 members was identified as potential participants according to the following selection criteria:

- Male. The extant literature indicates gender differences in cortisol excretion (e.g. a meta-analysis of 45 studies; Otte et al., 2005), and in its relationship with cognition in old age (e.g. Beluche et al., 2010). Thus, separate male and female groups would be required to adequately explore the main hypotheses of this thesis. Given that a sample size of 100 is required for adequate power (see section 5.1.2), a sample of 200 would have been required to adequately address the central questions of this thesis for both males and females. Time constraints on the MRI image analysis and additional cognitive testing of 200 participants meant that a single-gender approach was taken. A male-only sample was selected in order to maintain some comparability with other studies relating cortisol to frontal lobe measures (MacLulich et al., 2005, 2006; Kremen et al., 2010a).

- A score below 11 on the depression subscale of the Hospital Anxiety Depression Scale (Snaith, 2003). Scores above this level denote probable presence of depression (Snaith, 2003).
- Not taking antidepressant medication. Although the use of antidepressants has been shown to yield some positive improvements in cognitive impairment associated with depression, it does not appear to cause complete normalization (Culang et al., 2009), leaving residual decrements in processing speed and executive abilities (Jeste et al., 1996) which may vary dependent upon the precise drug and dosage used (Doraiswamy et al., 2003). Furthermore, it may also impact on the expression of glucocorticoid receptors in the brain, and the way in which cortisol crosses the blood-brain barrier (Pariante, Thomas, Lovestone, Makoff, & Kerwin, 2004). Consequently, individuals currently prescribed such medication are likely to have altered cognitive performance and atypical cortisol profile and/or sensitivity.
- Not taking regular glucocorticoid medication in the last 2 years.
- No self-report of stroke from LBC1936 notes.
- No brain MRI-related issues. Following the MR examination that each participant underwent, their scans were examined by consultant neuroradiologist Prof. Joanna Wardlaw, and any incidental findings were referred to geriatrician Prof. John Starr to determine whether a GP referral would be necessary. Suitability for this study was defined as an absence of serious neurological event, as identified by both the initial referral to Prof. Starr, subsequent referral to a GP, and comments on the outcome which were written on the participants' LBC1936 notes. Excluded participants were those

whose scans contained evidence of large brain infarcts, meningiomas, frontal or temporal cysts or extensive siderosis, frontal infarcts, and also those who had self-reported stroke or mini-stroke. Permissible findings include tiny non-frontal infarcts, microbleeds, clinically insignificant atheroma and white matter lacunes. This list was checked, and then cross-referenced with a list detailing incidental findings and comments on scan quality (such as movement artefacts) which was compiled by superintendent radiographer Elaine Sandeman at the Brain Research Imaging Centre, Western General Hospital, Edinburgh.

- Free from neurodegenerative disorders.
- Not a heavy consumer of alcohol (excluded if >50 units per week / average of 7 units per day).
- Mini Mental State Exam (MMSE; Cockrell & Folstein, 1988) scores of 24 or above.

Participants who met these criteria were then selected if they had been scanned less than 1.5 years prior to the current testing start date.

### *5.1.2 Recruitment*

Power was calculated using the nQuery Advisor programme by Prof. Ian Deary. A linear regression analysis in which four prior covariates have accounted for 60% of the variance would provide 80% power to detect an additional contribution of 3% to the explained variance for a sample of 100 subjects (alpha set at .05). Using `pwr.r.test` from the `pwr` package in R (version 2.13.1), 100 subjects would provide

80% power to detect correlation coefficients of medium effect size (0.28; after Cohen 1992) with alpha set at .05. A total of 118 eligible members of the LBC1936 were then mailed an information sheet (4<sup>th</sup> - 22<sup>nd</sup> October 2010; Appendix C), which gave details of the proposed study and informed them that they would be telephoned by a member of the CCACE office in the coming weeks to gauge their interest. Once their participation had been confirmed, their details were passed to SC in order to answer any further questions and arrange appointments for testing. Appointment calls also allowed participants' health details to be checked and updated if not current. A recruitment flowchart shows the stages of screening and recruitment (Figure 5.1). A pack was then mailed to respondents which contained the following:

- 1 x Confirmation Letter
- 1 x Sample Collection Record Sheet
- 1 x Salivette labeled **“MORNING”**
- 1 x Salivette labeled **“EVENING”**

In order to minimise the lag between their MRI scan and neuropsychological testing, the recruited participants were slightly older than average for the LBC1936 with a mean age of 73.10 years (SD = 0.40) at the time of LBC1936 wave 2 of cognitive testing. Their mean age at MRI scanning was 73.30 years (SD = 0.37) and they were 74.48 years (SD = 0.32) when they attended the further appointment at which cortisol sampling and additional neuropsychological tests were administered.

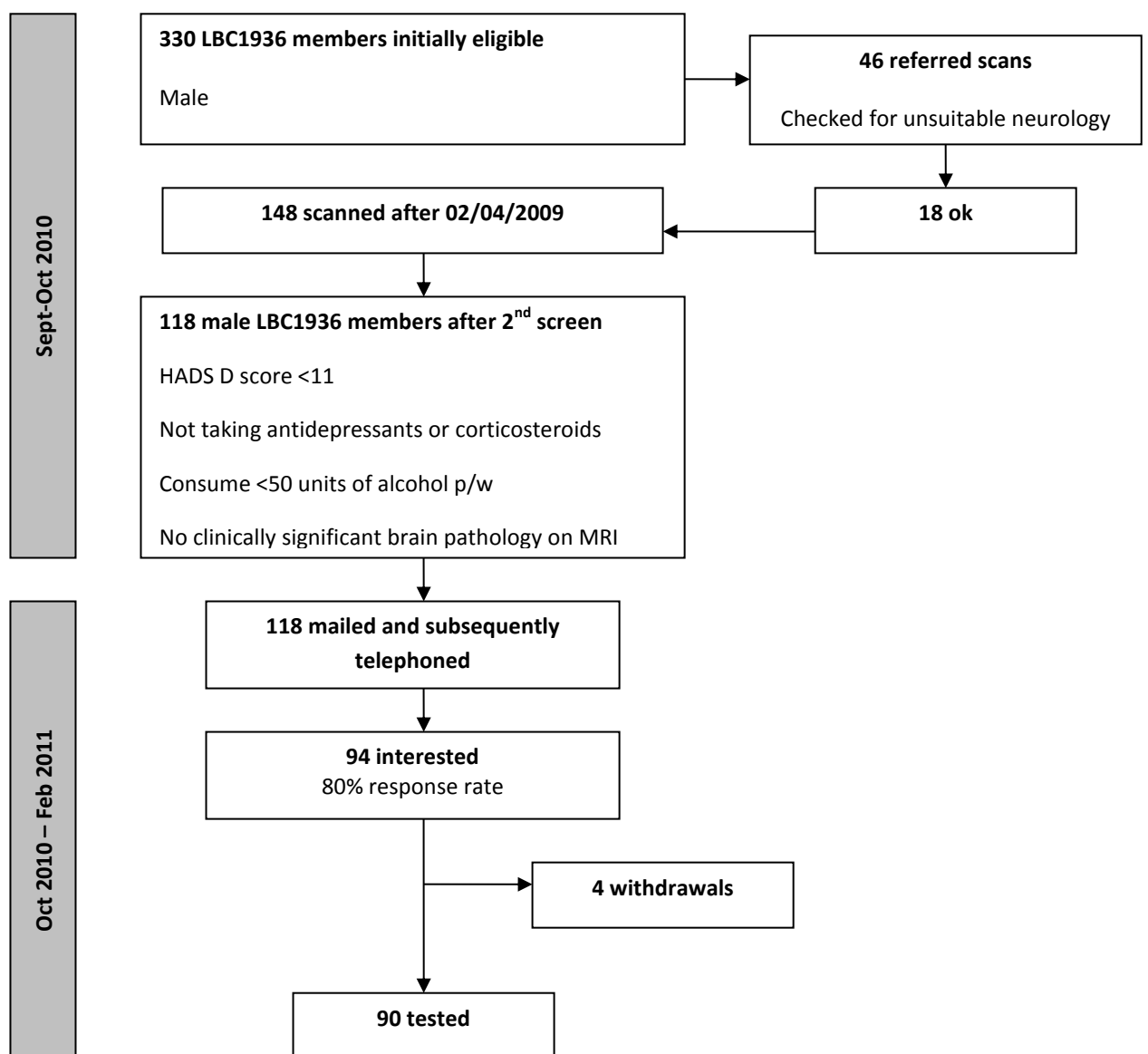


Figure 5.1. Recruitment flowchart for the LBC1936 in the current study.

## 5.2 Cognitive Testing

### 5.2.1 *Pre-existing Cognitive Measures*

A large number of pre-existing cognitive and background measures for the LBC1936 were collected and processed by staff of the Centre for Cognitive Ageing and Cognitive Epidemiology. Full details of the cognitive measures collected during wave 2 of LBC1936 testing are found in (Deary et al., 2007; Deary, Gow, Pattie & Starr, 2011). Cognitive measures relevant to the current study are described below:

#### 5.2.1.1 General Cognitive Factors

Three factors of cognitive ability had previously been derived from principal components analysis (PCA) of multiple tests undertaken by LBC1936 participants (details of PCA methods can be found in (Houlihan et al., 2010; Luciano et al., 2009) Table 5.1 describes the component tests from which a general fluid cognitive ability factor (*g*), a general factor of processing speed, and a general factor of memory were derived.



*Table 1.* Factors of cognitive ability created from regression scores of the first unrotated principal component of tests detailed in Deary et al., (2007).

<b>Cognitive Factor</b>	<b>Tests included in principal components analysis</b>
<i>g</i>	Backward digit span <sup>ab</sup> , letter-number sequencing <sup>ab</sup> , matrix reasoning <sup>a</sup> , block design <sup>a</sup> , digit-symbol <sup>a</sup> , symbol search <sup>a</sup> .
<i>speed</i>	Digit-symbol <sup>a</sup> , symbol search <sup>a</sup> , simple RT mean <sup>c</sup> , 4choice RT mean <sup>c</sup> , inspection time <sup>d</sup> .
<i>memory</i>	Logical memory <sup>b</sup> , verbal paired associates <sup>b</sup> , letter-number sequencing <sup>ab</sup> , spatial span <sup>b</sup> , backward digit span <sup>ab</sup> .

<sup>a</sup> Weschler Adult Intelligence Scale – III UK (Weschler, 1998a), <sup>b</sup> Weschler Memory Scale – III UK (Weschler, 1998b), <sup>c</sup> Cox, Hupprt & Whichelow (1993), <sup>d</sup> Deary et al. (2004).

#### 5.2.1.2 Moray House Test Number 12

Member of the LBC1936 sat this test at 11 years old, in the summer of 1947 as part of the Scottish Mental Survey (SCRE, 1949). It contained a variety of reasoning, arithmetic and language and spatial items, scored out of a maximum 76.

#### 5.2.1.3 NART (Nelson & Willison, 1991)

A measure that estimates peak cognitive ability, this test requires participants to read 50 irregular words out loud. The score is based on their ability to correctly pronounce each word, scoring a single point for each.

#### 5.2.1.4 Logical Memory

Participants are presented with two stories that both contain 25 elements. The first story is read aloud, and then scored based on the number of elements recalled immediately after reading. The second story repeats this pattern twice, and the participant is informed they will be tested again later. Following a delay, scores are based on the ability to recall as many items as possible from the two stories.

#### 5.2.1.5 Verbal Paired Associates

Eight pairs of unrelated words are read to participants; without a delay, they are then given the first of each pair and ask to recall the associated word. This is administered four times with no delay, and then a further trial following a delay. In the delayed trial, the word pairs are not read out first.

### *5.2.2 Neuropsychological Test Battery*

Testing took place in the University of Edinburgh Psychology Department between October 2010 and February 2011, and was conducted in accordance with Standard Operating Procedures (Appendix D), in compliance with departmental guidelines on participant testing and the Declaration of Helsinki. Ethical approval was gained from NHS Lothian Research Ethics Committee (NREC:07/MRE10/58) and the Philosophy, Psychology and Language Sciences Research Ethics Committee at the University of Edinburgh.

Written informed consent was obtained from each participant prior to testing. Information sheets delivered to participants with their invitation letter were also available to participants to read before commencement of testing at the University. Before consent was taken, it was ensured that participants understood the nature of the study, what testing would involve, and that they had the right to withdraw at any time without giving any reason. They were also informed that their data would be securely stored, fully anonymized in any published materials, and offered the chance to gain satisfactory responses to any questions about the study before giving their consent. Signed forms were stored securely with other study records.

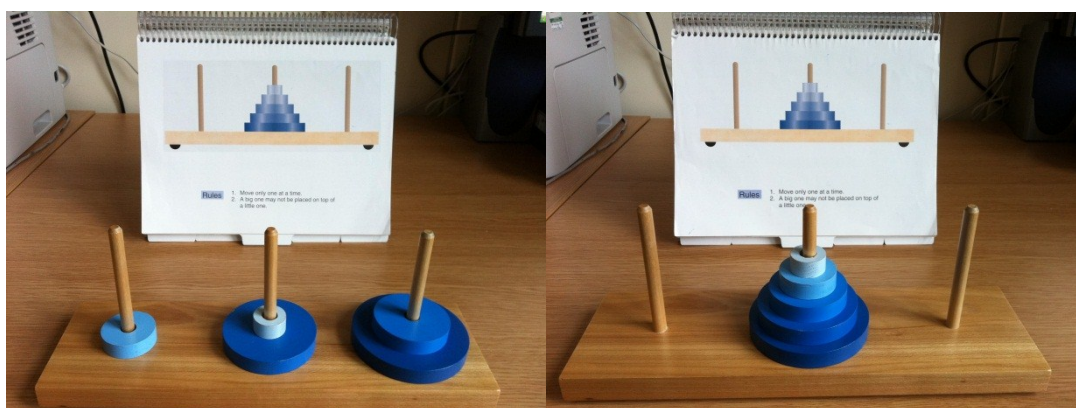
#### 5.2.2.1 D-KEFS Tower Test

The Tower of London test is taken from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan & Kramer, 2001) which comprises 9 standardised tests which measure various verbal and non-verbal executive functions. Successful completion of the Tower test taxes abilities such as planning, rule-learning, inhibition

and working memory (Swanson, 2005). As previously discussed in detail, convergent evidence from multiple domains suggests that the normal functioning of the DLPFC is necessary for competent performance in this task.

Each of the 9 problems begins with the wooden discs arranged in a particular configuration, with the object of moving the discs such that the wooden tower resembles a target picture in as few moves as possible. There are two rules to bear in mind, and these rules are always displayed at the bottom of the target stimuli (see Figure 5.2). The two rules are:

- 1) Participants must move only one disc at a time
- 2) A larger disc can never be placed on top of a smaller disc.



*Figure 5.2.* The D-KEFS Tower test from the examinee’s perspective. The figure shows problem 9 in its starting position (left) and completed (right). Participants can only move one disc at a time, and a large disc can never rest on top of a smaller disc.

The task begins with only two discs and requires a single move to complete. The number of discs and number of moves required increases until problem 9 which uses all 5 discs and requires a minimum of 26 moves. Each problem has a generous time limit which ranges from 30s for earlier problems to 4 minutes for the final towers. Therefore, the total time for administration cannot exceed 17½ minutes, although typically the test takes considerably less time. Each item is discontinued at the end of the time limit (and scored up to that point), and the entire test is stopped after three consecutive failures. Variables recorded on the score sheet are:

First move time

Total number of moves

Number of rule violations

Item completion time

Achievement score

Further scores that can be derived from the raw measures are:

Mean first move time (total 1<sup>st</sup> move time ÷ total # items administered)

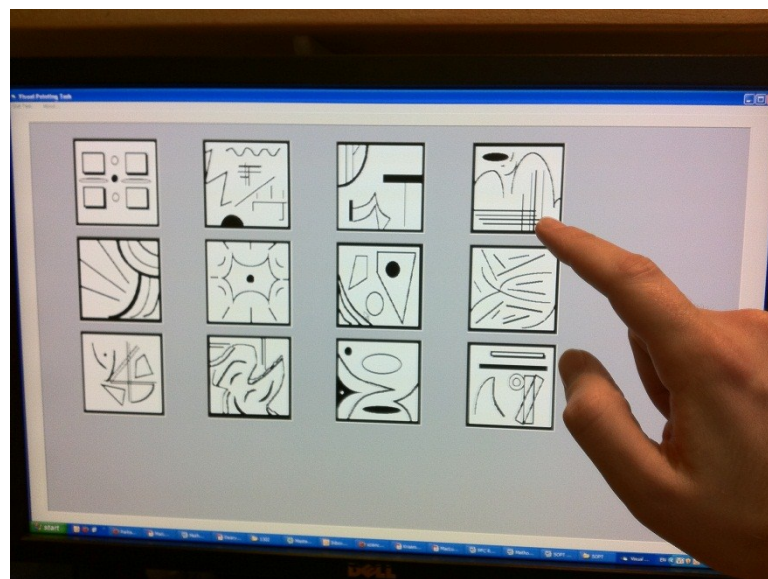
Time-Per-Move ratio (total item completion times ÷ total # moves)

Move Accuracy Ratio (total # moves ÷ total # minimum moves)

Rule-Violations-Per-Item Ratio (total rule violations ÷ total # items administered)

#### 5.2.2.2 The Self-Ordered Pointing Task (SOPT).

Commonly used as a test of working memory and monitoring (Petrides & Milner, 1982), this computerised version of the task presents a participant with a grid of 12 abstract designs (MacPherson et al., 2002). The examinee is required to select each item only once, choosing an item that they have not previously selected. Testing continues until 12 selections have been made. Following each choice, the order of some of the items in the grid is rearranged, to ensure participants remember the items previously chosen by their appearance, rather than by their location (see Figure 5.3). Participants were specifically asked not to adopt the strategy of returning to the same location each time. The test ends after three trials have been completed, and the trials are self-paced.



*Figure 5.3.* The SOPT administered on a touch screen. Participants are required to touch a design that they have not previously selected. Following each selection, the order of some of the designs is rearranged, preventing participants remembering the locations of previous choices.

The primary outcome measures are:

Number of times a previously-selected item is chosen.

Reaction time for each trial may also be accurately recorded for computerized versions, although the use of a mouse or mouse-pad on a laptop would have been inappropriate, given likely differences in older participants' familiarity with this device. As a result, the version selected for this study was presented on an iiyama ProLite T2250MTS 22'' touch screen device in 1920 x 1080 resolution, allowing the collection of accurate reaction time data and a user-friendly response format.

In this particular version of the test, a practice trial with 4 designs is given to participants following initial instructions. Then the main trial using the same 12 designs is repeated 3 times. Main outcome measures are the mean selection time, and the mean number of repetitions over all 3 trials, although raw scores for each trial are also kept.

#### 5.2.2.3 Reversal Learning Test

The participant is presented with two images and told that they must choose between them over a series of trials. After each selection, feedback will tell them if they have won or lost 25p of virtual money, and they will then see their running total. The goal is to gain as much money as possible by working out which of the pictures is the more profitable to choose. Although not made explicit in the instructions, one of the images will always give a win, and the other always a loss. Once the participant has clearly identified which of the two is the most profitable (defined in this study as 8

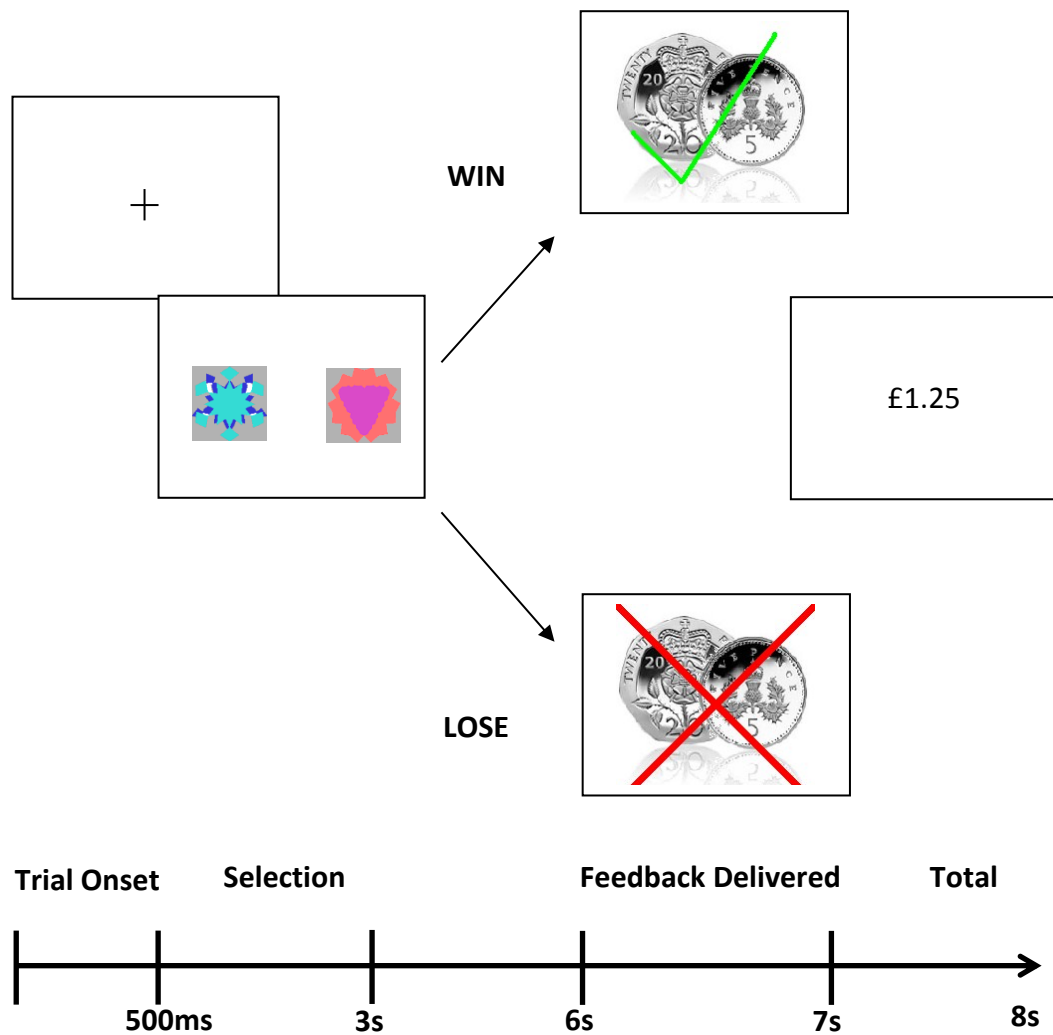
consecutive correct selections), the stimulus-reward contingency is reversed. In other words, the previously rewarding stimulus will now always yield a loss. This pattern continues for 50 trials, allowing a maximum of 5 reversals (after the initial contingency has been learned).

This task is a modified version of a previously reported neuroimaging paradigm (Hampton & O’Doherty, 2007). Modifications include removal of intermittent null event trials of 7s<sup>31</sup>, alteration of reward contingencies to deterministic from probabilistic (given the large amount of training typically required for deterministic studies), alteration of images from US cents to British pence, and clearer win/lose indication with green tick and red cross (Figure 5.4), in addition to the parameters mentioned in the preceding paragraph.

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<sup>31</sup> Used for fMRI state comparison – redundant in this setting.





*Figure 5.4.* A schematic of the Reversal Learning paradigm. A fixation point disappears after 500ms, followed by a window of 2.5 seconds in which the participant can choose between two abstract shapes. Three seconds later, feedback is displayed, followed by the running total for one second, before the trial finishes.

Main outcome variables are:

- Total number of errors

- Final running total (money)

- Total number of reversals

- Average moves to reversal

- Mean reaction time.

Participants are also asked several post-test questions in order to assess their understanding of the task (some participants with DLPFC lesions have been reported to perform poorly on the task due to confusion over task requirements; Rolls et al., 1996). Responses were recorded on the score sheet.

*How could you gain and lose points in the test?*

*What were you thinking at the start of the test?*

*What happened later?*

#### 5.2.2.4 Faux Pas Test.

Designed by Baron-Cohen, Jolliffe, Mortimore and Robertson (1997), this task requires the participant to identify a social faux pas in a series of short stories. A faux pas (from the French *false step*) refers to a situation where someone says something without realising that the listener may not want to hear it, or may have been hurt by what was said. The task includes 10 stories in which contain a faux pas, and 10 control stories. Participants are able to read each story at their own pace, and are instructed to let the experimenter know when they are finished each one. After each story, the participant is asked:

*i) Did anyone say something they shouldn't have said or something awkward?*

If the response is yes, these questions follow:

ii) *Who said something they shouldn't have said?*

iii) *Why shouldn't they have said it, or why was it awkward?*

iv) *Why did they say it?*

v) *Did X know that Y?*

vi) *How do you think X felt?*

All participants are then asked 2 control questions relating to factual information to ensure that they understood the story before moving on to the next story.

The raw scoring scheme is a single point for each correct response, but additional scores can be derived. The audio-taped responses were marked in accordance with the scoring guidelines on the day of testing, and both raw and composite scores input into the master spreadsheet.

Total - overall score - Faux pas and control stories combined

Faux Pas - the total score on the first five Faux Pas questions (/50)

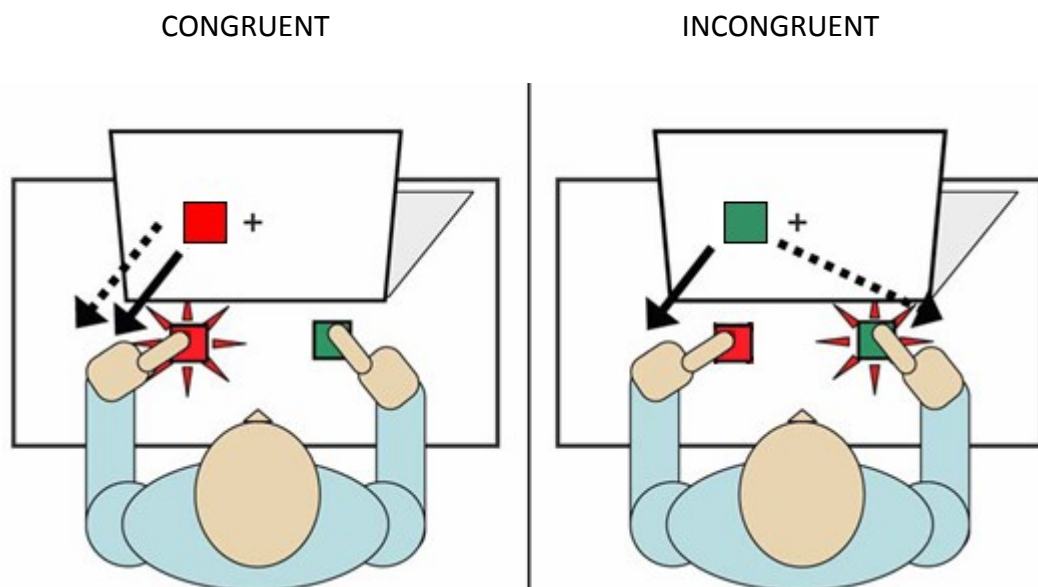
Controls - the number of control stories correctly identified (/10)

Comprehension – ability to correctly report factual information from all stories (/40)

Empathy - scores on question 6 from the Faux Pas stories, *“how do you think X felt?”*

### 5.2.2.5 The Simon Task

This task allows measurement of the difference in reaction times following congruent and incongruent stimulus-response trials. Participants are told that whenever they see a red square, they should press the red key, and likewise press the green key for a green square. Speed and accuracy are equally emphasised. A square appears either on the left or right of the screen, and the red and green keys are operated with the index finger of the left and right hand. Consequently, congruent trials are those where the square appears on the same side of the screen as the correct response key e.g. red square presented on left, red key on left, and incongruent trials are those where the square and the required key-press are on opposite sides e.g. red square on right, red key on left (see Figure 5.5). This version of the task is as reported in Pellegrino et al., (2007).



*Figure 5.5.* Congruent (left ) and incongruent (right) trials during the Simon Task. Adapted from Ridderinkhof et al. (2010).

Main outcome variables are:

Simon Effect: Similar to the Stroop effect, this contrasts reaction times during congruent and incongruent trials:

$$\frac{\text{Mean RT on incongruent trials}}{\text{Mean RT on congruent trials}}$$

Simon Effect by congruency: Over the course of the task, participants are exposed to consecutive trials that are both congruent, those that are both incongruent, and those where the contingency changes from one to another. Pellegrino et al (2007) reported that normal and non-vACC lesion groups showed a significant difference in RT dependent upon the direction in which the change was happening. Conversely, a group with ventral ACC lesions displayed little difference in RTs between the two directions of contingency change. Thus, this variable is calculated as follows:

$$\frac{\text{Mean RT on congruent} \rightarrow \text{incongruent trials}}{\text{Mean RT on incongruent} \rightarrow \text{congruent trials}}$$

Post-Error Slowing: Thought to represent a conscious compensatory adjustment of cognitive control, elicited when a participant is given feedback that they have just made an error (by selecting the inappropriate response). Whilst normal participants exhibit significant post-error slowing, Pellegrino and colleagues (2007) report that the dACC group do not.

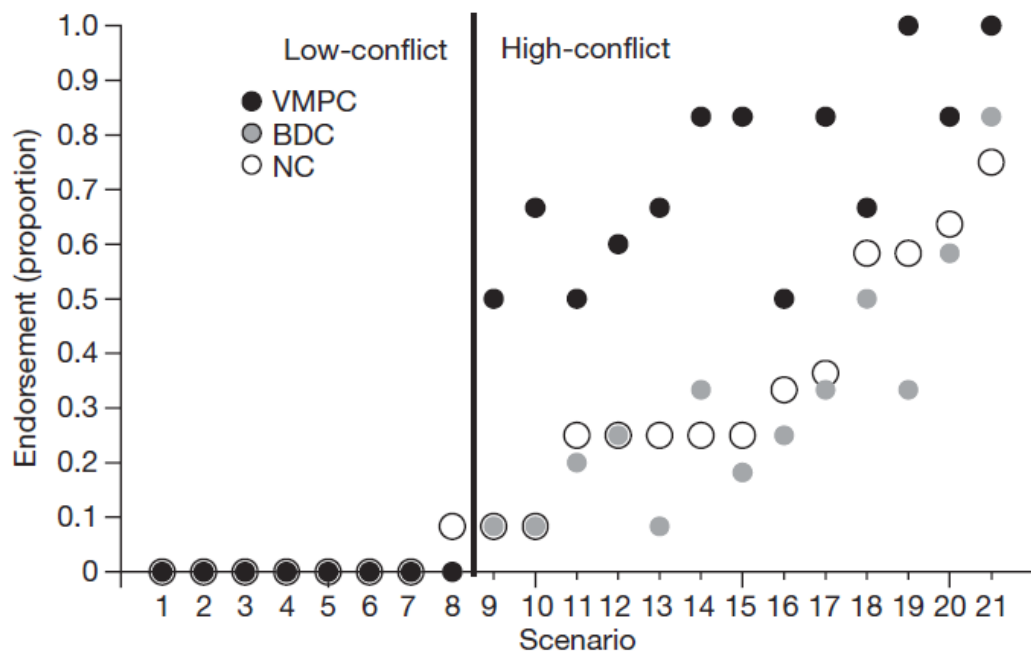
It is calculated as:

$$\frac{\text{Mean RT on trials following an error}}{\text{Mean RT on trials with no error}}$$

#### 5.2.2.6 The Dilemmas Task

This task presents participants with high and low conflict scenarios, each presented over 2 screens of text. The first sets the scene and the second develops the dilemma and introduces a potential course of action that could be taken to resolve it. A question follows each scenario that asks whether or not the respondent would take the suggested course of action, and they must respond by either pressing the y (yes) or n (no) key. Progress through the dilemmas is self-paced.

By manipulating conflict between the severity of the action required (*you must break the terrorist's son's arm*) and the moral value of the outcome (*thousands of lives will be saved*), healthy participants have been shown to vary in their tendency to endorse the suggested action, and the amount of time they take to make their decision (e.g. Greene et al 2001; 2004). On the other hand, VMPFC pathology results in a more utilitarian pattern of response (doing personal harm to others is more often endorsed) and a shorter amount of time is taken in order to reach this decision (Figure 5.6; Koenigs et al 2007; Ciaramelli et al 2007; Moretto et al 2009).



*Figure 5.6.* from Koenigs et al 2007. Levels of endorsement in low and high conflict trials amongst a group with lesions to the VMPFC, brain damaged controls (BDC) and normal controls (NC). Lesions outside the VMPFC do not produce a significantly different pattern of endorsement to both control groups.

The current test contains 10 high-conflict and 7 low-conflict trials. The scenarios were selected from those used by Koenigs and colleagues (2007) which initially came from a set of 60 developed by Greene et al (2001). Selection of the scenarios was made on the basis of overlapping categorisations of Koenigs et al., (2007) with those of Kahane & Shackel (2007), but a spread of high and low conflict dilemmas was maintained. Non-moral dilemmas were excluded altogether as 1) the literature suggests that only those containing moral content demonstrate sensitivity to frontal lobe insult and 2) many of these scenarios are not dilemmas at all (Kahane & Shackel, 2007). Therefore, the main outcome variables were mean decision time, and the percentage of actions endorsed in the high-conflict dilemmas.

### *5.2.2 Testing Schedule*

Participants were all tested over the course of a single weekday morning in the Department of Psychology. Start times were kept as close together as possible in an attempt to standardise the position of the reactive cortisol measures on the diurnal slope, although distance from the Department and issues of convenience for participants meant that precisely timing the start of the test battery from their wake time was not practicable. The testing interview took around 90 minutes to complete. Due to the length of testing and the age of participants, regular breaks were offered, and the running order of the battery was administered in reverse for half the participants in order to control for fatigue effects.

In order to minimise the time lag between each individual's MRI scan appointment and behavioural testing, CCACE's Human Testing Technician Jack Nissan tested 25 participants in accordance with the same SOP (Appendix D). Limited hardware and licenses for certain software further limited the times at which appointments could be made for testing, and therefore when two participants were tested on the same day, testing appointments were staggered.

### *5.2.3 Participant Confidentiality*

Each participant was assigned an identification number which was the only identifier on the master spreadsheet. This ensured that the testers remained blind to related (general cognitive and imaging) data until statistical analysis.



#### *5.2.4 Other Considerations*

Due to the age of participants, some found testing tiring. To minimize discomfort and fatigue, breaks and de-cafeinated refreshments were made available. In order to reduce travel issues associated with attending the department for testing, an honorarium was offered to cover taxi fare or parking and petrol costs.

#### *5.2.5 Data Handling and Record-Keeping*

Electronic data obtained from computer-based tasks during the test battery were backed up immediately after testing, and were entered, along with scores from paper score sheets, into a master file (Excel spreadsheet). All personal identifiers were removed except for ID numbers. This master file and all electronic data were stored in password-protected files, held on-site in the Psychology Department. Paper copies of the record sheets were stored in a secure filing cabinet in a locked office.

### 5.3 Magnetic Resonance Imaging

#### 5.3.1 Image Acquisition

The entire brain imaging protocol for the LBC1936 participants is detailed in Wardlaw et al. (2011). MRI data was gathered at the Brain Research Imaging Centre (BRIC), University of Edinburgh. Whole brain sequences with contiguous slice locations were acquired using a GE Signa Horizon 1.5T clinical scanner (General Electric, Wilwaukee, WI). T1 and T2\* weighted sequences, used for the volumetric measures reported herein (frontal sub-regions, hippocampal and intracranial) were acquired in the coronal plane at 1 x 1 x 1.3mm resolution, with the head oriented in the hippocampal axis. The diffusion tensor sequence protocol consisted of seven T2-weighted acquisitions and sets of diffusion-weighted ( $b=1000\text{s/mm}^2$ ) axial single-shot spin-echo echo-planar volumes acquired with diffusion gradients applied in 64 non-collinear directions (after Jones et al., 2002).

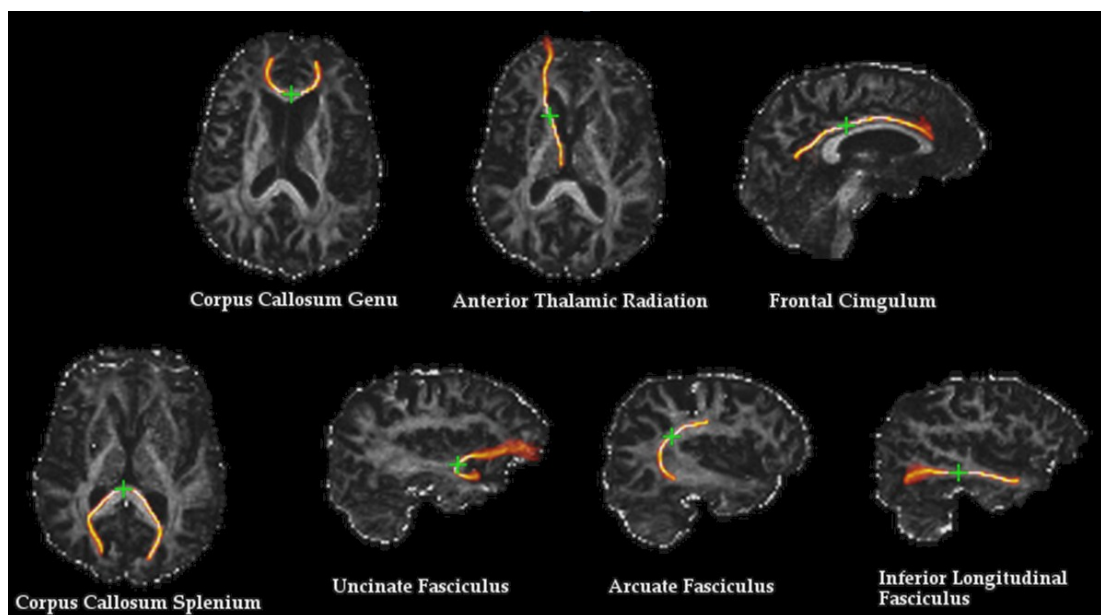
#### 5.3.2 DTI Tractography

Diffusion tensor imaging (DTI) allows the non-invasive quantification of random water molecule motion in each imaged voxel across the brain. In accordance with Brownian motion, water molecules move randomly due to thermal energy in unconstrained space, but when constrained by the presence of cellular structures, such as the boundaries of myelinated axonal fibre bundles, they move with greater directional coherence along the fibres than across them. Measures of the magnitude

of general water diffusion (mean diffusivity; MD) and its directional coherence (fractional anisotropy; FA) for each voxel can therefore allow an estimate of white matter microstructure. More tightly packed fibre bundles characteristically exhibit higher FA and lower MD, and comparison of DTI measures and post mortem histopathology suggests that diffusion parameters are generally reliable indices of reduced axonal integrity and demyelination and accumulation of intracellular fluid in fronto-temporal dementia (Larsson, Englund, Sjöbeck, Lätt, & Brockstedt, 2004), multiple sclerosis (Schmierer et al., 2007) and old age (Kochunov et al., 2007; Sullivan & Pfefferbaum, 2007).

Tractography is a method whereby the path of major axonal fibres can be estimated by using the directional information contained within water diffusion measurements. These allow tracts to be segmented voxel-by-voxel along their entire course and tract-averaged values of MD and FA obtained. In general, tracts recreated in this way provide generally good concordance with white matter fibres identified post mortem (Catani et al., 2012; Catani & Thiebaut de Schotten, 2008; Klein et al., 2010; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). The current method used probabilistic neighbourhood tractography (PNT) implemented in the TractoR package for fibre tracking and analysis (<https://github.com/jonclayden/tractor>) in order to segment 7 tracts of interest (genu and splenium of the corpus callosum, anterior thalamic radiation, uncinate fasciculus, cingulum, arcuate fasciculus and inferior longitudinal fasciculus; Bastin et al., 2010; Wardlaw et al., 2011; Figure 5.7). DTI data were initially pre-processed to extract the brain using FSL (Smith, 2002). A seed point is transferred from standard space, and then additional seed points are placed in the neighbourhood (7 x 7 x 7 voxels) of this

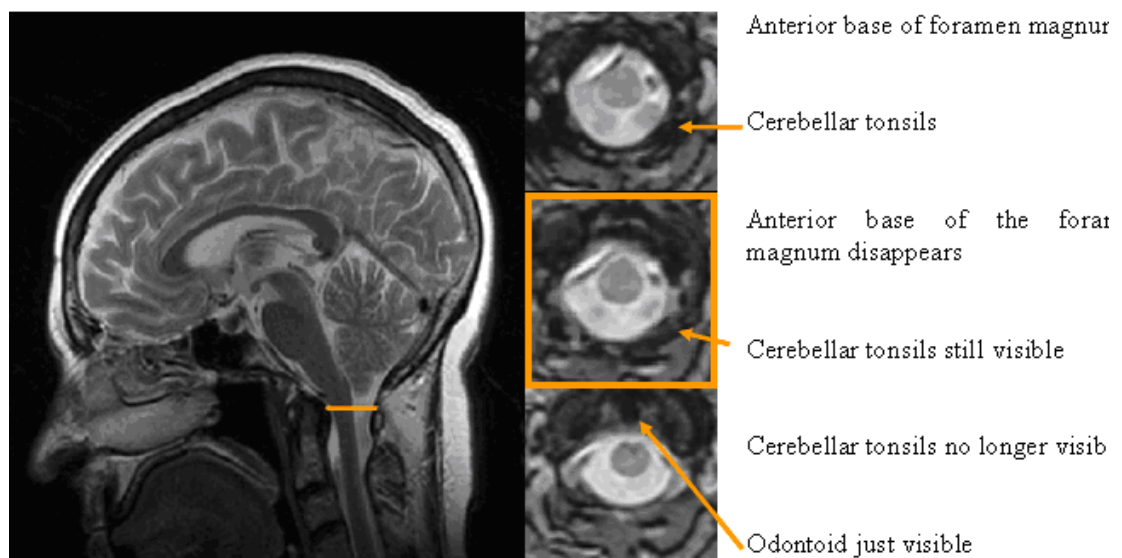
initial seed. The path of the tract of interest is then created based on the trajectory of the most similar tract from a library of candidates and the diffusion parameters in neighbouring voxels (Bastin et al., 2010; Clayden et al., 2007; 2009). All tractography was conducted by Drs Mark Bastin and Susana Munoz Maniega at the Brain Research Imaging Centre, Western General Hospital, University of Edinburgh.



*Figure 5.7.* Examples of segmented tracts using probabilistic neighbourhood tractography. CC: corpus callosum, ATR: anterior thalamic radiation, ILF: inferior longitudinal fasciculus. Image reproduced from Wardlaw et al. (2011).

### 5.3.3 Intracranial Volume (ICV)

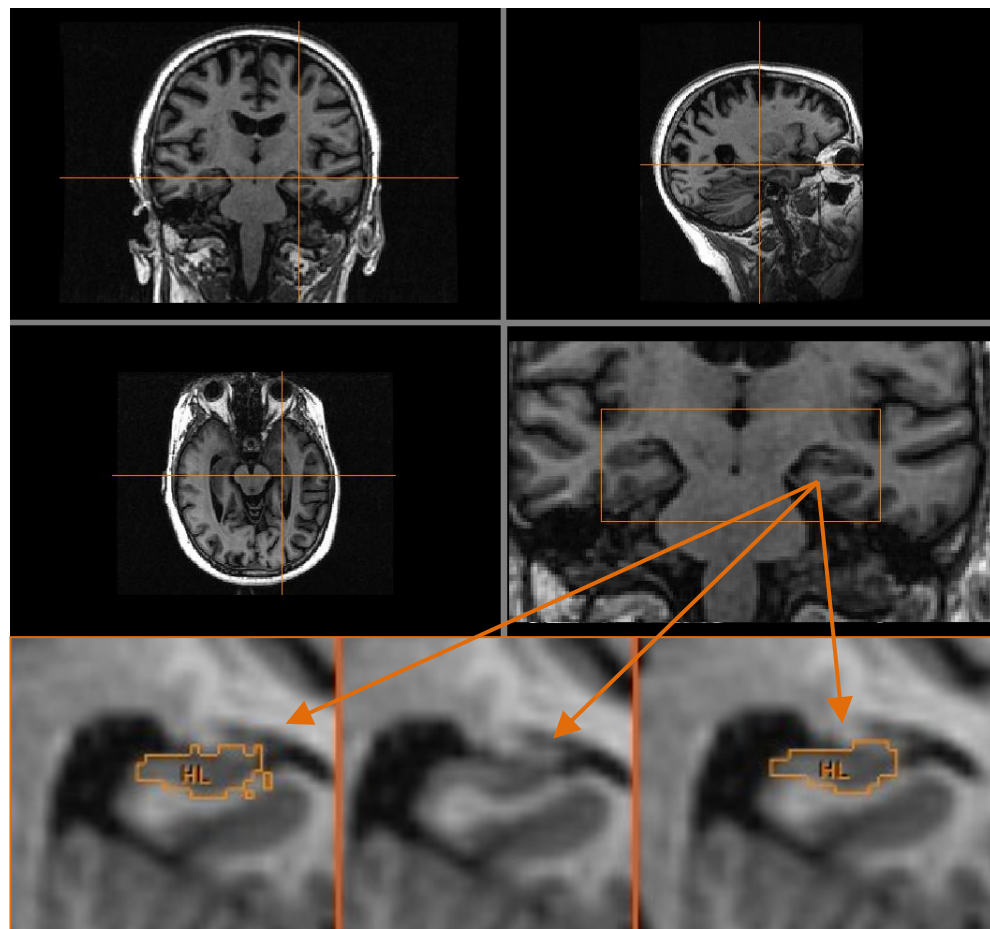
Measurements of ICV included the contents of the inner skull table and is used as an estimate of maximum brain size. ICV volume was initially obtained using the Object Extraction Tool in Analyze 9.0 (Mayo Clinic, Analyze 9.0. AnalyzeDirect, Inc. Mayo Clinic) using the T2\* weighted sequence. Then all matter beneath the inferior limit (the axial slice superior to the appearance of the odontoid peg at the foramen magnum and before the disappearance of the cerebellar tonsils; Figure 5.8) was manually removed by Ms. Natalie Royle.



*Figure 5.8.* Midsagittal slice from a T1W MRI sequence showing how the lower limit of the intracranial volume at the foramen magnum was defined by a slice at lower limit of tonsils prior to the odontoid peg. On the right-hand an axial view of the foramen magnum (orange), including the slices superior (top) and inferior (bottom) to the slice defining the lower limit of the ICV (middle). Image reproduced from the LBC1936 imaging data dictionary.

### 5.3.4 Hippocampal Segmentation

The hippocampus was initially segmented automatically and then each output was manually edited. Initial automatic segmentation was conducted using FSL FIRST, in which the T1 volume was registered to an age-appropriate template (Farrell et al., 2009) and then to an optimised sub-cortical mask. Visual assessment and manual editing of the object masks was then conducted by Ms. Natlie Royle (Figure 5.9).

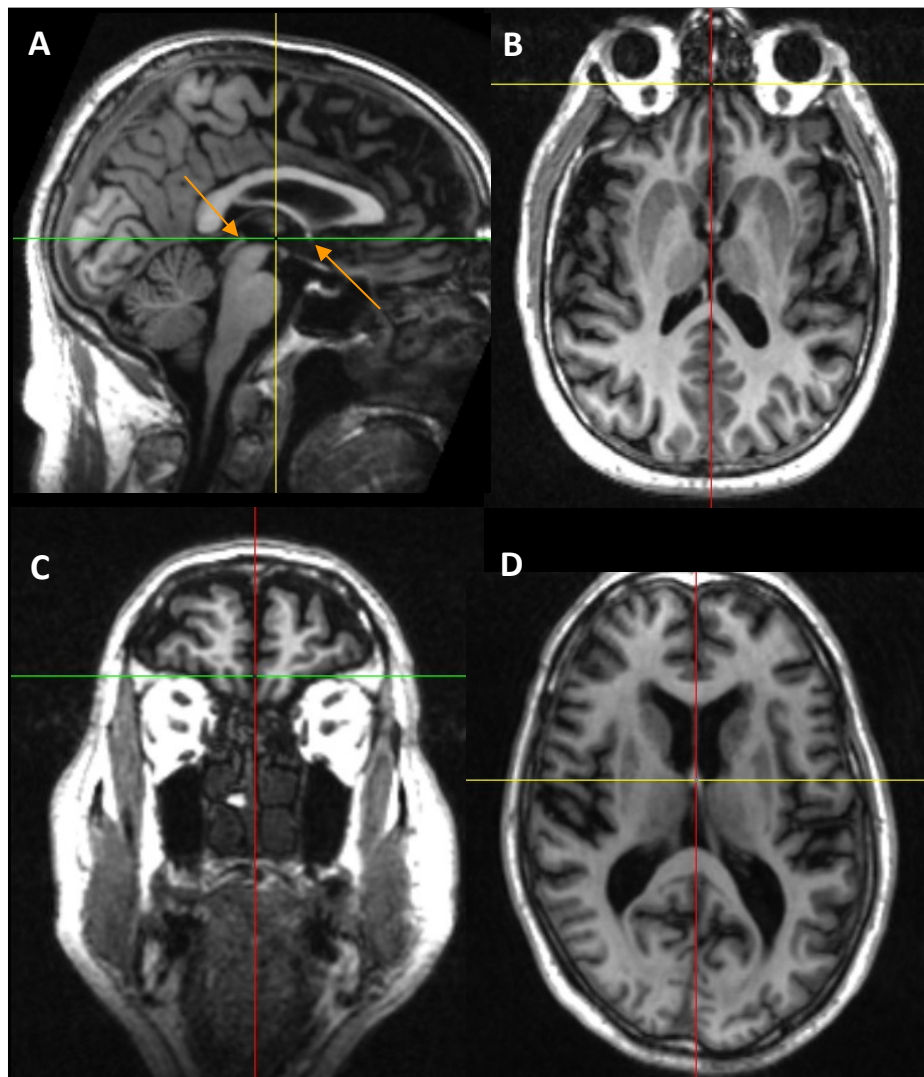


*Figure 5.9.* Location of the hippocampus in coronal (top left), sagittal (top right) and axial (middle left) orientations. Close-up of coronal view of hippocampus (middle right and bottom middle), FSL segmentation (bottom left) and edited segmentation (bottom right). Images adapted from the LBC1936 data dictionary.

### *5.3.5 Manual Parcellation of the Frontal Lobes*

#### 5.3.5.1 Image Alignment

The first processing step involves applying a rigid-body transform. This allows a cut-plane to be consistently applied across individuals. The transform is applied so that the line between Anterior and Posterior Commissure (AC-PC line) is horizontal in the sagittal plane (Figure 5.10a). The brain is also aligned along the central fissure in both coronal and axial views, using the orbits as a secondary guide (Figure 5.10 b & c). In cases where there is a distortion of the central fissure in the axial plane, the path of the central fissure in the frontal portion of the brain is used as a preferential guide (Figure 5.10d).



*Figure 5.10.* Alignment of T1 MRI in A) AC-PC line in sagittal orientation, B) & C) in the axial plane using the central fissure and orbits as a guide, and D) showing an inconsistent central fissure (see occipital lobe – bottom of the image).



#### 5.3.5.2 Thresholding

The transformed image is then thresholded using the mean value of sampled intensities of CSF and grey matter from 2 coronal slices posterior to the appearance of the temporal stem (a total of 4 sampling points, 3 x 3 voxels each; Ferguson & Wardlaw). The thresholded image is then saved as a separate file and used for the creation of ROI object maps.

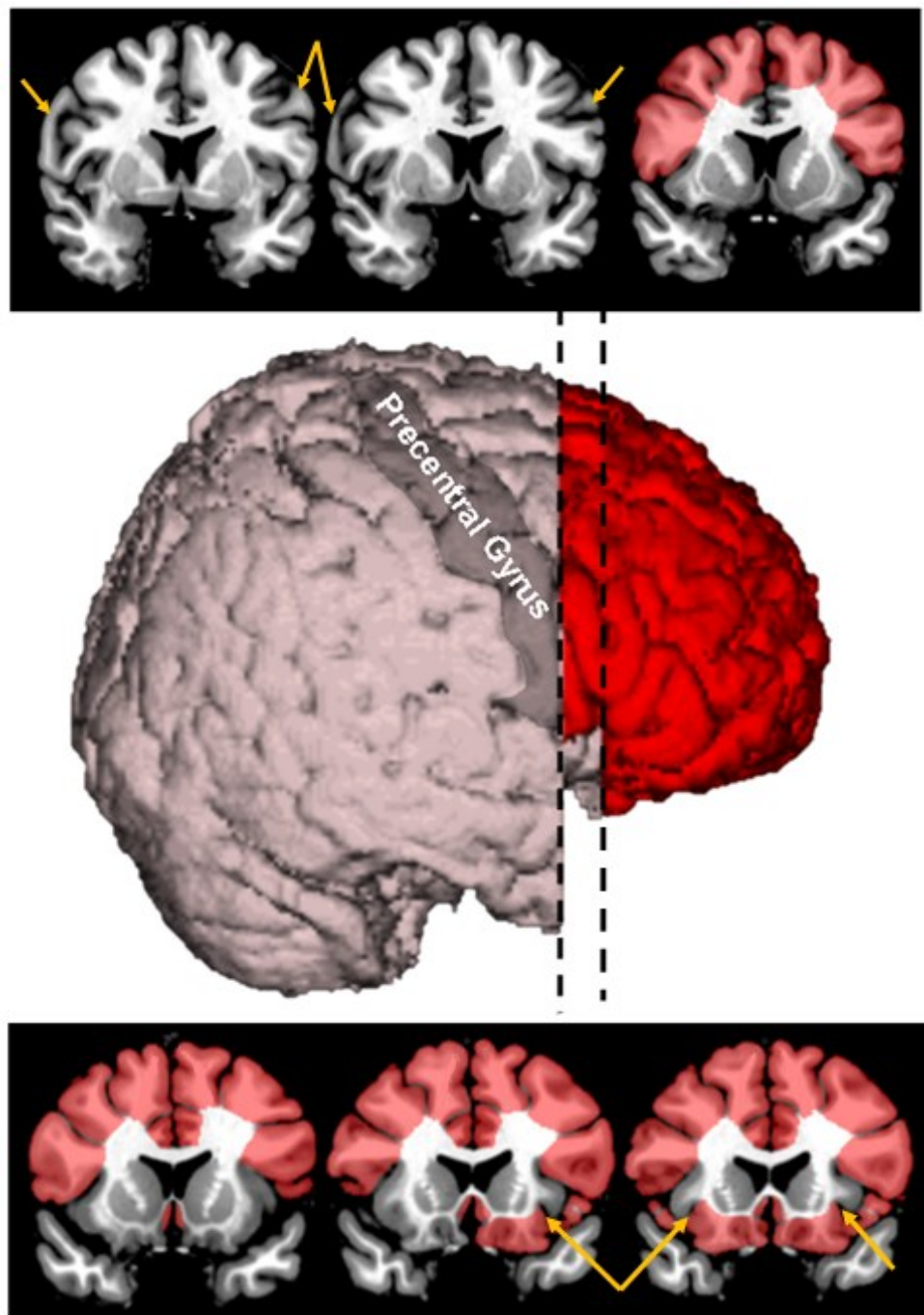
#### 5.3.5.3 Procedural Notes:

The delineation of sub-regions was done by first drawing boundaries into the depth of the relevant sulci. Next, the limit through white matter was established by connecting these sulcal boundaries with a straight line where possible. Where a straight line would pass through grey matter, it was necessary to deviate in order to include this in the ROI. Care was taken to exclude non-brain tissue from measurement, by drawing limits between meningeal and brain matter, and to avoid the inclusion of the putamen and other sub-cortical structures. The parcellated regions were then assigned their appropriate ROI using an automated flood-fill, which detected the grey matter - CSF boundary using as threshold (set at the same mean value of sampled intensities calculated during the thresholding procedure above). The ROIs in the following protocol were all traced in the coronal orientation, progressing from posterior to anterior using Analyze 9.0 (Mayo Clinic) and digitizing tablet. Viewing and marking of ROIs was also carried out in sagittal and axial planes in order to provide a set of guides during coronal tracing.

#### 5.3.5.4 Posterior PFC

The posterior boundary for the dorsal prefrontal cortex (superior, middle and inferior frontal gyri) can be identified as the coronal slice anterior to the appearance of the precentral gyrus (Figure 5.11). This has been selected as the boundary primarily to exclude motor and pre-motor regions whilst maintaining an easily-identifiable and reproducible cut-plane (Kates et al., 2002).

The posterior extent of the orbitofrontal cortex can be determined in the coronal plane as the most anterior slice in which the lateral orbital sulcus appears, allowing differentiation of orbital and insular cortices (Figure 5.11). At its most dorsal posterior extent, the cingulate gyrus conforms with the dorsal frontal boundary, and runs to its natural limits subgenually, as determined with the help of mid-sagittal views.

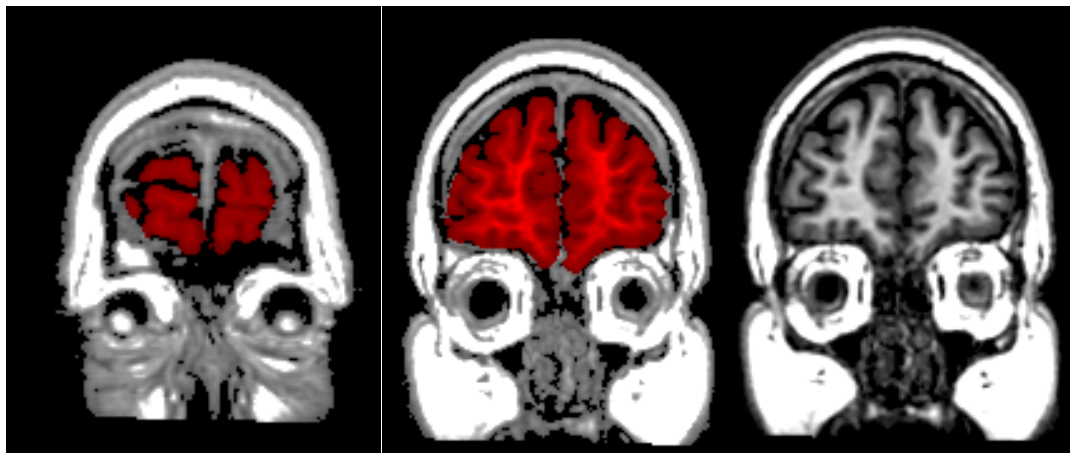


*Figure 5.11.* Manual definition of the ROI using coronal slices (left to right: posterior to anterior).. Top row shows the identification of the most posterior coronal slice before the appearance of the precentral gyrus (PrCG; after Kates et al., 2002; PrCG indicated with arrows). Bottom row shows identification of the most posterior appearance of the lateral orbital sulcus (LOS; indicated with arrows). Middle image shows a 3D rendering of the prefrontal ROI in red. Dotted line indicates the anterior-most extent of the PrCG (left) and the most posterior coronal appearance of the LOS (right).

#### 5.3.5.5 Frontal Pole

The initial method adopted to approximate BA10 was taken from John *et al.*, (2007). This should be the first area to be identified on the MR image, and can be done in the coronal view. Advancing from the front of the brain, the posterior boundary of the frontal pole is the slice before the olfactory sulcus can be clearly seen. It should be noted that the boundary may well differ between hemispheres within the same brain. In a small proportion of brains, the olfactory sulcus is unusually short, and would mean that the posterior boundary of the FP would extend far more posteriorly than the first (coronal) appearance of the ACC. In these instances, the posterior boundary of the frontal pole is taken as the anterior extent of the ACC. Once this boundary has been identified, the frontal pole extends forward to the very tip of the frontal lobes (Figure 5.12).

During the application of this method, it was noted that the ATOS was subject to wide individual differences, leading to a much higher variance than for any other frontal region (Appendix E). Use of method has not previously been reported for older individuals, and it is possible that age-related atrophic change may have differentially accentuated the depth of the olfactory sulcus. As a result, the frontal pole boundary was changed to use the coronal slice immediately anterior to the cingulate gyrus. This was established using a combination of sagittal and coronal views (Figure 5.13).



*Figure 5.12.* Coronal slices showing (from left to right) the anterior tip of the FP, mid-anterior FP, and the most anterior slice in which the ATOS is visible.

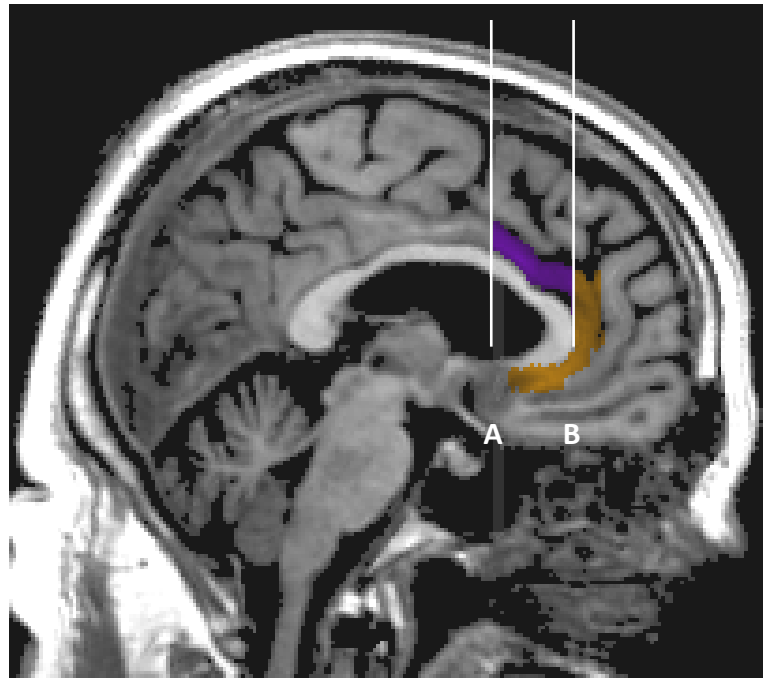


*Figure 5.13.* Use of the coronal plane at the antero-most extent of the anterior cingulate gyrus as the posterior frontal pole boundary. Plane A: cingulate still visible in the right hemisphere (orange arrows – top left). Plane B: cingulate absent (top right).

#### 5.3.5.6 Anterior Cingulate Cortex (ACC):

The tracing for this region corresponds to BAs 24, 25, 32 & 33 which can further be divided into dorsal and ventral portions, in keeping with the previously discussed functional data, recent connectivity studies and the selected behavioural tests for this study. The ACC should be outlined on a sagittal slice near the midline in the first instance. Where the PCG is present, this was included in the ACC region, thus making the paracingulate sulcus (PCS) the most superior boundary of the ‘ACC’ ROI. The tracing of this region should follow the path of the gyrus sub-genually to its clearest sub-callosal and posterior extent.

Moving to the coronal plane at the posterior boundary of the PFC and progressing toward the frontal pole, both dorsal (dACC) and ventral (vACC) regions can be traced, using the markings made from the sagittal slice for guidance. The dACC continues until posterior-most coronal slice in which the hemispheres are still connected by the corpus callosum, effectively creating Plane B (Figure 5.14). From this point forward, all cingulate regions are assigned to the vACC.



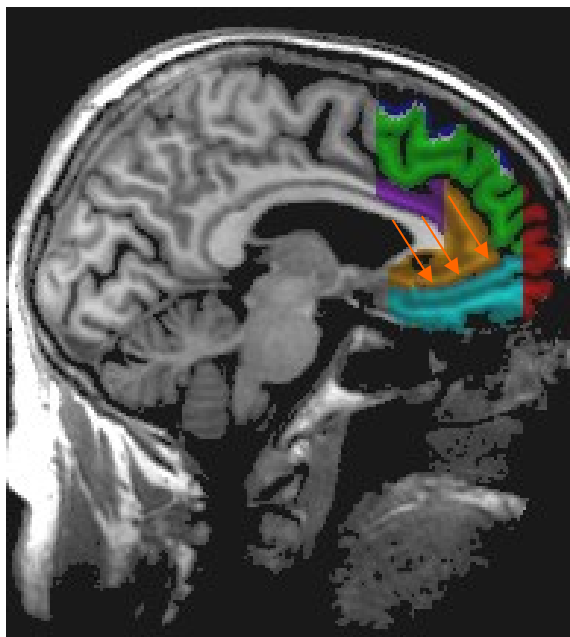
*Figure 5.14.* A sagittal slice near the midline showing the more posterior Plane A (denoting the posterior PFC limit) and the more anterior Plane B at the anterior tip of the corpus callosum which is used to differentiate ventral (orange) and dorsal (purple) regions of the anterior cingulate cortex.

#### 5.3.5.7 Superior Frontal Gyrus

The following outline is done to approximate BA9, BA46 and parts of BA8, with further parcellation of the superior frontal gyrus (SFG) into a lateral and medial portion. This distinction accords with neuropsychological evidence that suggests some functional distinctions between lateral and medial regions (see Shallice *et al.*, 2008a, 2008b for a review), but will also allow a more accurate measure of the DLPFC, as outlined by Rajowska & Goldman-Rakic (1995). Further, this distinction may also allow for some clarification regarding the consistent reference to the ‘medial prefrontal cortex’ in the neuroendocrine and neuropsychological literature. Both ACC and an element of the SFG can be found on the medial wall of the frontal

lobes, and therefore the ability to examine the medial SFG in isolation may afford an additional degree of clarity.

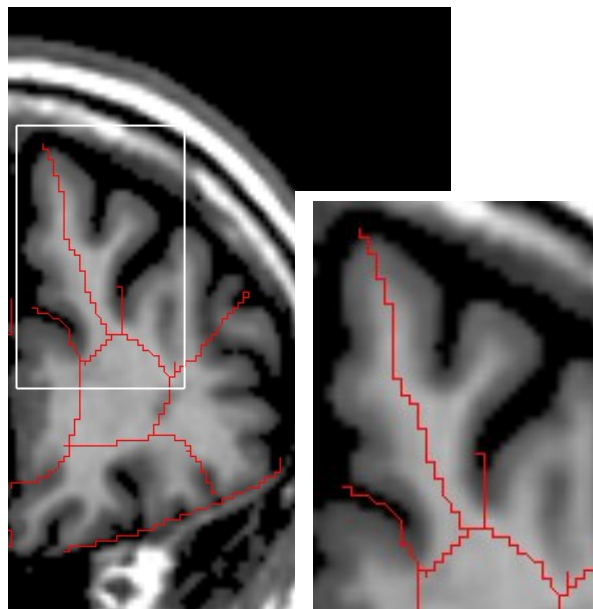
The SFG can be identified in both sagittal and axial planes before coronal tracing begins (although the medial/lateral differentiation can only be made accurately in the coronal orientation). On the sagittal plane, the SFG can be identified in a slice near the midline, and is limited by the frontal pole and the Anterior Cingulate Sulcus (ACS) or Paracingulate Sulcus (PCS) where present. When applying the initial frontal pole boundary, there were instances where the frontal pole did not end at the anterior genu of the cingulate gyrus on the medial wall. In such cases, the SFG and OFC were differentiated by the Superior Rostral Sulcus (SRS; Figure 5.15). Following the adoption of the replacement FP boundary, the use of the SRS became redundant.



*Figure 5.15.* The Superior Rostral Sulcus (SRS; orange arrows) was used to limit the OFC (purple) from the SFG (blue/green) where the SFG extends between the ACC (purple/orange) and Frontal Pole (red) in the superseded frontal pole procedure.



Returning to the coronal section and starting at the posterior PFC boundary, the SFG can now be traced from posterior-anterior until the appearance of the frontal poles. On the medial wall, the SFG is limited by the ACS or PCS, and is bound laterally by the SFS. This region can then be divided into lateral and medial portions by dropping a line through the crown of the most superior-medial gyrus of this area so that it bisects the roughly horizontal white-matter limit at the base of the gyrus into two equal portions. Often, a straight line may not be possible. In these cases, the line should follow the contours of the white matter branching until a straight line is feasible (Figure 5.16).



*Figure 5.16.* A coronal slice showing the boundary that divides the lateral and medial parts of the superior frontal gyrus.

#### 5.3.5.8 Middle Frontal Gyrus

As with the SFG, the parcellation of the MFG reflects the inferior extent of the DLPFC. Its dorsal and ventral boundaries are the SFS and IFS respectively, both of

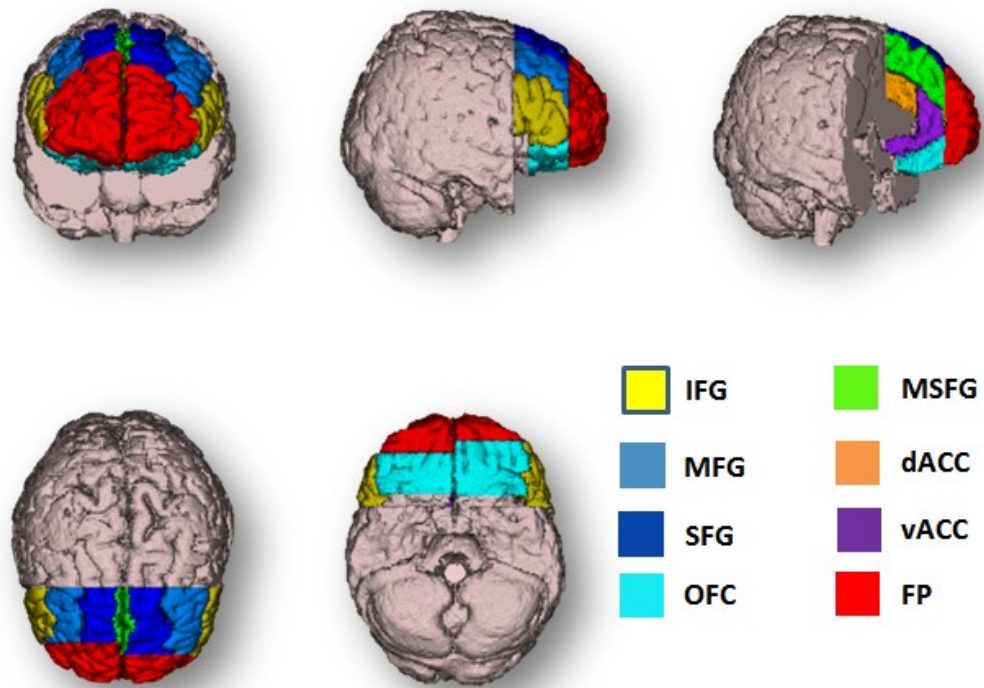
which can be clearly identified in more posterior coronal sections. As the tracing progresses into more anterior slices, it is important to ensure that the IFS and not the Intermediate Frontal Sulcus (IntFS) continues to be used as the ventral limit. This will often involve advancing several slices in order to guide the tracing of this limit.

#### 5.3.5.9 Inferior Frontal Gyrus

The IFG as defined by this protocol includes the opercular and triangular parts, representing BA44 and BA45, as well as dorsal parts of the pars orbitalis (BA47). The superior boundary is the IFS, and in more posterior coronal slices, the IFG is ventrally bound by the insula. With more anterior slices however, the insula cortex recedes, and the resultant Lateral Orbital Sulcus (LOS) becomes the new inferior boundary, differentiating the IFG from the OFC. Tracing continues until the frontal pole is reached, or until the LOS and IFS meet.

#### 5.3.5.10 Orbitofrontal Gyrus

The OFC is found on the ventral aspect of the frontal lobes, and in this approach comprises BAs 11, 12, 13, 14 and ventral 47. The OFC can first be identified in the most posterior coronal slice in which insula and OFC can be differentiated (Fig. 5.11). Care was taken to exclude subcortical structures and the olfactory bulb. On the medial wall, the OFC is consistently bound by the cingulate or paracingulate sulcus, and laterally this region is separated from the IFG by the LOS in more anterior slices until its termination at the frontal pole.



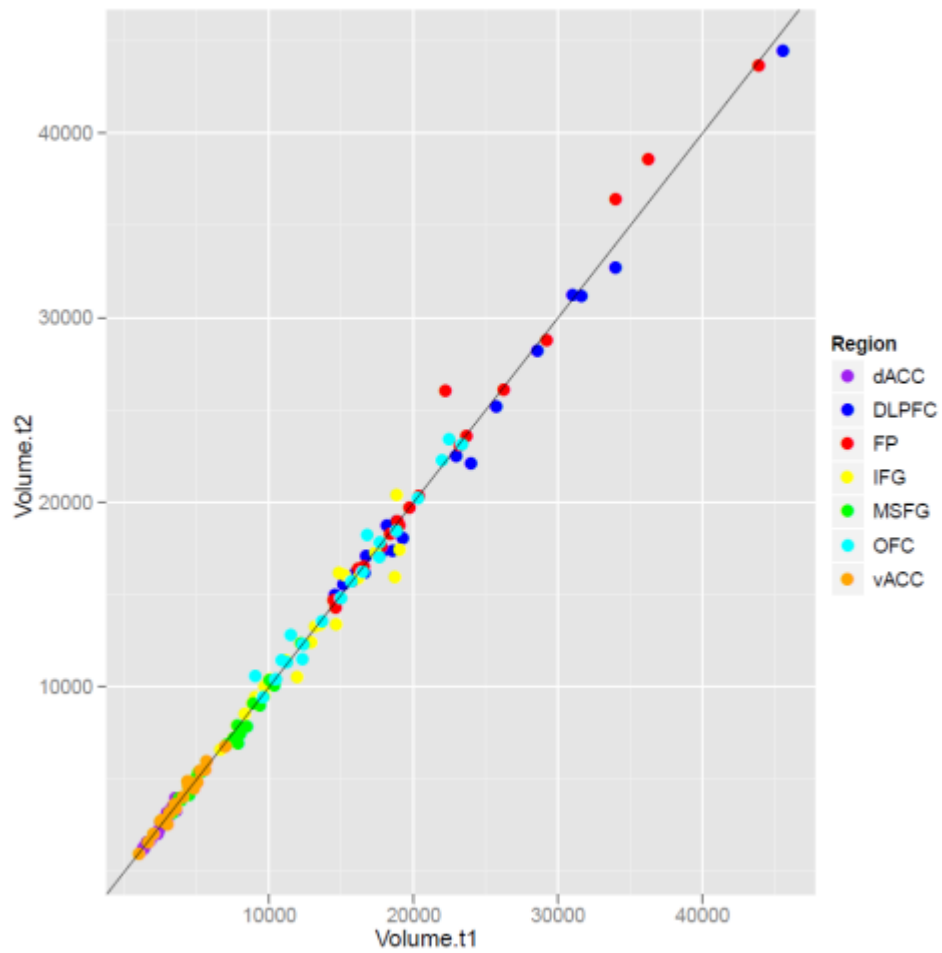
*Figure 5.17.* ROIs from the current protocol rendered onto a brain with the anterior temporal lobes removed for clarity. Top row: Anterior view, lateral view, medial view (right ROIs removed to show left medial wall. Bottom Row: dorsal view & ventral view. IFG: inferior frontal gyrus; MFG: middle frontal gyrus; SFG: superior frontal gyrus; OFC, orbitofrontal gyrus; MSFG: medial superior frontal gyrus; dACC: dorsal anterior cingulate cortex; vACC: ventral anterior cingulate cortex; FP: frontal pole.

#### 5.3.5.11 Intra-Rater Reliability

The protocol was then validated by measuring each region twice on two separate occasions, at least 2 weeks apart for a total of 20 measurements per region (10 brains). Volumetric comparisons between these two measurement occasions were examined using Intraclass Correlation Coefficients (ICCs) for agreement (Shrout & Fleiss, 1979) and Bland Altman analysis (Bland & Altman, 1986) to examine the percent mean difference between measurements (Figures 5.18 & 5.19, Table 5.2). The protocol has excellent reproducibility, with ICCs >0.95 for all regions and confidence intervals <15% mean difference. However, Bland Altman analysis showed that confidence intervals for the superior and middle frontal gyri were unusually wide. This is in part due to a single case in which the mean difference was 43.50% for the right SFG, and 24.08% for right middle frontal gyrus<sup>32</sup>. Visual examination showed that the intermediate frontal sulcus rather than superior frontal sulcus had been used as a boundary at one time point, but not the other. Differentiation of these two sulci is challenging using 2D views, particularly where there is a deep IntFS. Combining the SFG and MFG volumes into the DLPFC was shown to be very reliable, indicating that the majority of the variance was attributable to comparably inconsistent identification of the mutual border. This also more accurately aligns the regional volumes with the cognitive literature which refers to the DLPFC as combining BAs 9 and 46, thought to occupy both middle and superior frontal gyri (Rajowska & Goldman-Rakic, 1995).

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<sup>32</sup> In this same single case, the right DLPFC mean difference was 3.08%.

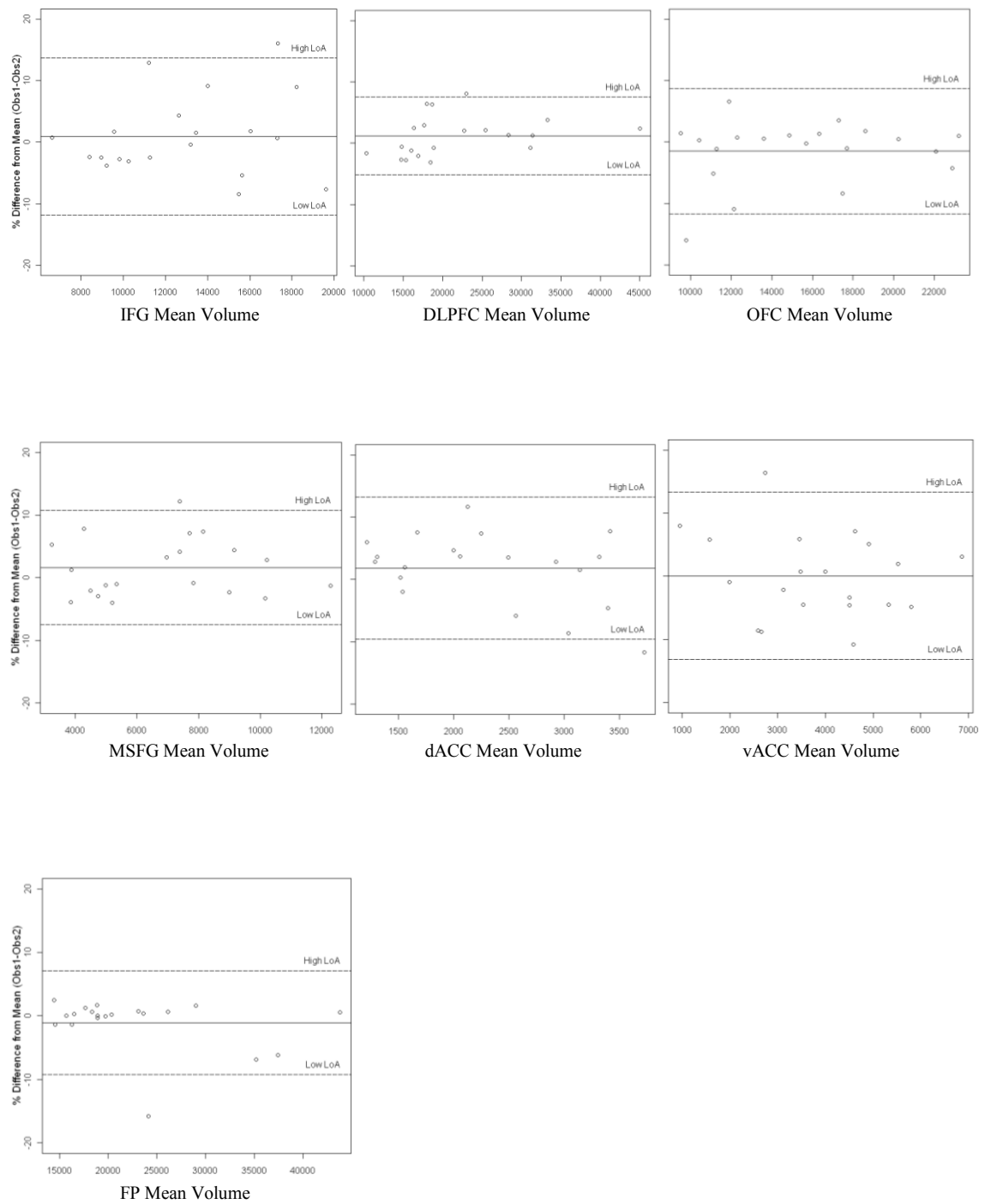


*Figure 5.18.* Comparisons of volume estimates for each ROI as measured on two separate occasions (t1 and t2), at least 2 weeks apart; 20 measurements for each sub-region.

Table 5.2. Indices of volumetric reliability for frontal ROIs.

ROI	ICC Agreement	Bland Altman	
		Mean	Confidence Interval
IFG	0.96	0.93	-11.81 to 13.67
MFG	0.98	3.20	-12.62 to 19.02
SFG	0.95	-0.76	-24.36 to 22.83
DLPFC	>0.99	1.19	-5.16 to 7.54
OFC	0.99	-1.48	-11.67 to 8.70
MSFG	0.99	1.64	-7.48 to 10.75
dACC	0.98	1.80	-9.60 to 13.21
vACC	0.99	0.08	-13.14 to 13.30
FP	0.99	-1.07	-9.25 to 7.11

ROI: region of interest, ICC: intra-class correlation coefficient, IFG: inferior frontal gyrus, MFG: middle frontal gyrus, SFG: superior frontal gyrus, DLPFC: dorsolateral prefrontal cortex, OFC: orbitofrontal cortex, MSFG: medial superior frontal gyrus, d/vACC: dorsal and ventral anterior cingulate gyrus, FP: frontal pole.



*Figure 5.19.* Bland Altman plots showing percent mean difference in volume between two measurements of the same region.

### *5.3.5 Data Handling & Record-Keeping*

In order to ensure that the image analysis was performed blind to the cognitive scores of participants, data pertaining to each was held in separate files with different identifier formats. Cognitive performance scores were written up and attached to a sequential participant number<sup>33</sup>, whereas the MRI analysis metrics were recorded alongside the participants' LBC1936 number. The two sets of data were only combined for analysis, after both sets of data had been completely collected.

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<sup>33</sup> Based on the order in which participants attended their cognitive testing appointment for the frontal battery.



## 5.4 Cortisol Sampling & Analysis

The decision to measure both diurnal and reactive cortisol profiles in participants was driven by two primary observations. Firstly, the relationship between HPA axis functioning and measures of cognition has been examined with a degree of inconsistency; as previously discussed, abnormalities in both types of profile have been independently associated with poorer cognitive ability and smaller volumes of certain brain regions. Secondly, no single study has yet examined the relationship between both types of profile in relation to cognitive variables and MRI measures in ageing. Therefore the precise relationship between diurnal and reactive measures, and whether both relate equally to brain structure and function in old age has not been fully elucidated. Thus, one set of samples would be required to determine the diurnal profile, and another set to give a measure of HPA-axis reactivity to a mild cognitive stressor (attending the testing session).

However, accurately measuring both types of profile imposes twice the sampling burden. The small pool of potential participants (118) at the outset, the level of imposition a sampling schedule may have was a driving factor in the study design. Saliva rather than blood samples were collected for each individual using Salivette devices (Sarstedt, Numbrecht, Germany) which involves chewing on a swab to saturation. Saliva samples have been shown to offer an equally accurate but far less invasive means of measuring cortisol levels, do not have to be administered by a healthcare professional, and are unaffected by individual differences in anticipatory stress response to blood sampling (Ahn, Lee, Choi, Kwon, & Chun-S-i, 2007; Nicolson, 2007).

#### *5.4.1 Diurnal Profile*

In response to the variability in sampling approaches reported in the literature to measure a representative diurnal profile, a recent study aimed to examine the test-retest and intra-assay correlation coefficients of cortisol samples taken at 5 time points throughout the day (Kraemer et al., 2006). The authors reported that samples taken on waking had superior test-retest reliability when compared to the waking+30 response. Also, the latter requires participants do not eat, drink or brush their teeth for 30 minutes and may also affect compliance (Kraemer et al., 2006), it was decided that the waking time point would provide the clearest and least burdensome anchor point for the diurnal profile.

Furthermore, the authors suggest that a morning/anchor and evening sample are sufficient to ascertain the diurnal pattern, providing a comparable estimate to a schedule of multiple samples over the course of the day (Kraemer et al., 2006). They observed that participants' self-report of the time they took the sample was as reliable as an automatic monitoring system fitted to the cap of each sample (Medication Event Monitoring System; MEMS Aardex Ltd.). Therefore, in advance of the appointment, a testing pack was sent out to participants with the confirmation letter. Participants were required to provide one sample on waking, one sample at 10pm, and to record the time and date on which they had been taken.

#### *5.4.2 Reactive Profile*

The reactive measurements were taken at the beginning and end of the testing session in order to assess HPA axis activity in response to a mild psychological stressor. The participant's wake time for the day of testing was recorded along with the length of the battery in order to better locate the sampling point along each individual's diurnal profile, and thus better harmonise this measure across subjects if necessary. As detailed below, the time of the testing appointment was subject to factors such as convenience for the participant, but care was taken to test all participants in the morning (Start time varied from 0930 – 1100).

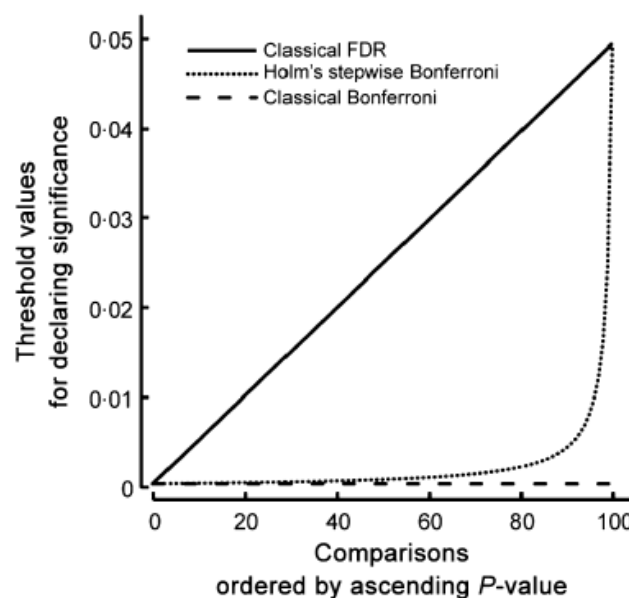
#### *5.4.3 Assay Handling & Analysis*

Following collection, Salivettes were stored at -80°C. Prior to dispatch for analysis, the samples were thawed in order to attach freeze-thaw resistant barcodes, in line with the requirements of the receiving lab. Samples were then re-frozen and shipped at -80°C via specialist courier. Assays were carried out by Dresden LabService GmbH in accordance with a Material Transfer Agreement. Intra-assay variation was <20% at the lower limit of quantitation and <15% above that. Correlation coefficients for regression lines were >0.99, consistent with typical international standards.

Assays were conducted following completion of behavioural testing and MR analysis. Therefore, results were merged into the master spreadsheet of data on receipt from Dresden.

#### 5.4.4 Statistical Analysis

All statistical analysis was carried out using R project versions 2.09 to 2.13, apart from principal components analysis and bootstrapping procedures for mediation analysis, which were conducted using SPSS version 19. Specific analyses are described in each chapter. Correction for multiple comparisons was conducted using classical one-stage False Discovery Rate (FDR; Benjamini & Hochberg, 1995) in order to control for type I errors while minimizing type II errors. This is a much less conservative method than traditional family-wise error correction, and is appropriate in situations where attempts can be made to meaningfully interpret a set of findings, even if one or more may have erroneously rejected the null hypothesis (Pike, 2011). It creates a monotonic linearly-increasing threshold, taking accounting of the number of comparisons and their significances (Figure 5.20).



*Figure 5.20.* Significance thresholds by number of comparisons using Bonferroni, Holm's (1979) step-wise method, and classical FDR (alpha .05). Image from Pike (2011).

## Chapter 6: Comparison of Manual and Automatic Atlas-Based Parcellation of the Frontal Lobe

Work presented in the following chapter is taken from the following published work:

Aribisala\*, B.S., Cox\*, S.R., Ferguson, K.J., MacPherson, S.E., MacLulich, A.M.J., Royle, N.A., Valdés Hernández, M.C., Bastin, M.E., Deary, I.J. & Wardlaw, J.M. (2013). Assessing the performance of atlas-based prefrontal brain parcellation in an ageing cohort. *Journal of Computer Assisted Tomography*, 37, 257-264.

\*Joint first authors.

There are a large number of available tools for quantifying cerebral characteristics from MRI. Relevant to the research questions of this thesis, deriving volumetric measurement of the brain's sub-regions can be performed using manual or automated procedures. Given that a relatively small volumetric change might be the result of lifecourse-accumulated insults from a variety of determinants (only one of which is studied here), selection and justification of the appropriate measurement protocol are worth addressing. This chapter demonstrates that even when the most promising automated protocol and non-linear registration (automated) tools are used, the test re-test reliability for the entire frontal lobe does not equate to a manual measure. Consequently, and in spite of the appeal of reduced person-hours, this automated technique is unlikely to deal accurately with the multiple boundaries required for

sub-regional frontal parcellation. However, in the wider context of methods development, this automated multi-atlas method holds promise for subsequent refinement, and could be attractive to researchers faced with analysing vastly larger numbers than the 90 participants herein, for whom accurate manual parcellation is feasible.

Author BSA wrote the code, developed and conducted the single- and multi-atlas segmentation and performed spatial similarity analyses. Author SRC contributed the initial library of manual lobar segmentations, contributed to the testing and development of the atlas similarity selection criteria, performed volumetric similarity measures and visually inspected automated outputs. The manuscript for publication (on which the current chapter is based) was contributed to equally by both authors.

## 6.1 Abstract

Inter-subject diversity in sulcal patterns represents a challenge for accurate anatomical boundary-matching in atlas-based parcellation of brain MRIs. Non-linear registration and multiple atlases improve the performance of atlas-based parcellation and reportedly produce accurate and consistent results. However, these reports are limited as they use only 1) volumetric comparison of performance, and 2) young healthy brains. It is unclear whether atlas-based parcellation is suitable in ageing cohorts because variability in age-related brain atrophy is a major confounding factor for automatic methods. We assessed the performance of atlas-based parcellation in an ageing population (90 non-demented healthy adults, aged  $72.7 \pm 0.7$  yrs) using measures of volumetric and spatial concordance, and visual assessment. Volumetric assessment showed that both single- and multi-atlas-based methods performed acceptably (Intraclass correlation coefficient, ICC: 0.74 to 0.76). Spatial overlap measurements showed that both single- (Jaccard Index, JI: 0.61 to 0.64, Dice Coefficient, DC: 0.75 to 0.78) and multi-atlas (JI: 0.73, DC: 0.84) approaches gave good agreement with the manual reference, but the multi-atlas approach offered an improvement of spatial overlap (JI: +0.10, DC: +0.06). Visual assessment also showed that multi-atlas out-performed single-atlas, and identified an additional post-processing step of CSF removal, enhancing concordance (ICC: 0.86, JI: 0.81, DC: 0.89). In conclusion, an atlas-based parcellation method performed reasonably well in the ageing population. Parcellation scheme performance should be assessed volumetrically, visually and by measures of spatial concordance in more varied subjects. Issues caused by brain shape variation, and particularly age-related atrophy

were partially overcome through targeted visual analysis and implementation of post-processing. This suggests that multi-atlas parcellation may be feasible in ageing cohorts.



## 6.2 Introduction

Image segmentation plays an important role in region-based analysis of structural MR neuroimaging data, and can be broadly categorised into two types of approach. The first method is manual delineation of a particular anatomical structure or the ‘region of interest’ (ROI) drawn on the image to be analyzed (Cabezas et al., 2011). This commonly-used approach is the reference standard, but it is time consuming because it requires ROIs to be drawn on every scan individually and it is also prone to user bias. The second approach is to use automatic parcellation methods based on image segmentation algorithms. This approach tends to require less user input, fewer person-hours, and is less susceptible to non-systematic bias. Automatic approaches can be summarised into four groups, namely atlas-based (Aljabar et al., 2009; Ashburner & Friston, 2005; Fischl et al., 2004; Heckemann et al., 2010), supervised learning techniques (Moghaddam & Soltanian-Zadeh, 2009), shape and appearance model approaches (Babalola, Cootes et al., 2008; Kelemen et al., 1999) and energy-based techniques (Leventon et al., 2000; Yushkevich et al., 2006). Of these, atlas-based methods have been shown to perform the best (Babalola et al., 2009; Babalola, Patenaude et al., 2008; Ginneken et al., 2007; Igual et al., 2011), and have been proposed as the standard paradigm for exploiting spatial prior knowledge in brain MR image segmentation (Cabezas et al., 2011).

The atlas-based segmentation technique uses a standard anatomical atlas (e.g. Talairach or MNI atlas) to define the ROI in the atlas space or individual subject’s native space, with the latter offering better accuracy due to reduction in partial volume effect errors (Aribisala et al., 2011). A significant step in atlas-based

methods is the registration of the atlas to each individual's native space which should potentially normalize variations in size and shape between the atlas and the individual's brain. Registration has most commonly used linear transformations (Jenkinson & Smith, 2001). However, both linear transformation and the use of a single atlas based on the brain of one individual do not adequately account for inter-subject variability in brain morphology. This results in relatively poor anatomical boundary matching. Non-linear registration has been demonstrated to improve boundary matching (Ardekani et al., 2005; Avants et al., 2011). Thus, a multi-atlas approach based on several brains rather than just one subject has been proposed (Heckemann et al., 2010). The multi-atlas approach appears to outperform the single-atlas approach (Aljabar et al., 2009; Cabezas et al., 2011; Heckemann et al., 2010; Rohlfing et al., 2004).

Segmentation of ageing brains presents a significant challenge to any automatic segmentation technique because age-related changes (Cabezas et al., 2011) such as brain atrophy (Appelman et al., 2009), skull thickening (Finby & Kraft, 1972; May et al., 2011), presence of white matter lesions (Debette & Markus, 2010) and infarcts (Appelman et al., 2010) increase inter-individual variability. Furthermore, the prefrontal lobe exhibits a particularly high degree of variation in sulcal folding patterns between subjects and is also highly susceptible to age-related atrophy and white matter lesions, both of which affect the performance of automated methods (Raz et al., 2005). Combined with the considerable research attention it has received due to its involvement in complex cognition and its association with psychiatric, behavioural and neurological disorders (Steele & Lawrie, 2004), the

prefrontal lobe is a highly relevant and challenging test-bed for shape-based automatic segmentation methods.

The performance of atlas-based techniques has been compared with manual methods in other studies (Desikan et al., 2006; Destrieux et al., 2010; Igual et al., 2011), but most of these have used small sample sizes, typically 10 to 40 subjects (Cabezas et al., 2011), and analyses have been restricted to data acquired from children (Igual et al., 2011) or young adults (Desikan et al., 2006; Destrieux et al., 2010; Igual et al., 2011) where age-related changes are not observable. In addition, measurements of comparison have tended to use either volumetric or spatial concordance, and rarely visual inspection. Although Desikan et al. (2006) compared atlas-based methods with manual segmentation in an ageing population, their sample of 10 older adults is unlikely to be representative of the full range of premorbid and age-related structural differences, thus limiting inferential power. In addition, their comparison measure was limited to ICC consistency. To the best of our knowledge, no study has investigated the performance of atlas-based image segmentation techniques on the frontal lobes in a large sample of well-characterised older adults, using rigorous and multi-faceted comparison measures.

Here we compared the performance of single- and multi-atlas-based parcellation methods with manual segmentation using brain MRI data acquired from healthy older adults with a narrow age range ( $72.7 \pm 0.7$  years). The comparative analysis combined visual assessment, volumetric agreement using Bland-Altman and intraclass correlation analysis with measures of spatial concordance. We also compared the choice of atlas selection for both single- and multi-atlas approaches. Selection of atlases is an important step in multi-atlas-based techniques as the final

outcome is significantly influenced by the choice of atlases, the number of atlases and the method for combining the atlases (Aljabar et al., 2009; Ginneken et al., 2007; Heckemann et al., 2010; Igual et al., 2011). These have been investigated (Aljabar et al., 2009; Heckemann et al., 2010) and the use of image similarity metrics (e.g. normalised mutual information or correlation ratio) has been proposed as the most reliable atlas selection method. In addition, an optimum number of atlases has been suggested and classifier fusion based on majority vote rule has been shown to be an accurate atlas-combination method (Aljabar et al., 2009). However, there have been no demonstrations of how these perform when applied to the ageing brain.

## **6.3 Methods**

### *6.3.1 Subjects*

Study data were selected from 700 members of the Lothian Birth Cohort 1936 (LBC1936; (Deary et al., 2012; Deary et al., 2007)). The LBC1936 are surviving participants of the Scottish Mental Survey of 1947 (Deary et al., 2007; Scottish Council for Research in Education, 1949) living in the Lothian (Edinburgh) area of Scotland. At mean age 70 years they undertook a battery of tests including detailed cognitive and medical assessments (Deary et al., 2012; Deary et al., 2007). Three years later, as many of these subjects as possible underwent repeat cognitive and medical tests, and brain MRI (Wardlaw et al., 2011). Written informed consent was obtained from all participants under protocols approved by the Lothian (REC 07/MRE00/58) and Scottish Multicentre (MREC/01/0/56) Research Ethics Committee. Ninety males were selected based on the following criteria: not taking corticosterone medication or anti-depressants, no pathological MRI findings as identified by a consultant neuroradiologist (JMW), no severe cognitive impairment (Mini Mental Score Examination score of 24 or above) and non-depressed (Hospital Anxiety and Depression Scale – Depression score below 11).

### *6.3.2 Brain MRI Acquisition*

Subjects were imaged with a GE Signa Horizon HDxt 1.5T clinical scanner (General Electric, Milwaukee, WI, USA) using a self-shielding gradient set with maximum gradient strength of 33 mT/m, and an 8-channel phased-array head coil. The imaging protocol included a coronal T<sub>1</sub>-weighted (resolution 1 x 1 x 1.3 mm thickness), axial

T<sub>2</sub>\*-weighted (1 x 1 x 2 mm thickness) and axial FLAIR (Fluid Attenuated Inversion Recovery, 1 x 1 x 4 mm thickness) whole brain scans; sequence details described in (Wardlaw et al., 2011).

### *6.3.3 Manual Image Processing*

Manual segmentation was performed using Analyze Software 8.1 (Mayo Clinic, Rochester, MN) (Mayo, 2008). T<sub>1</sub>-weighted volumes were transformed so that the AC-PC line was horizontal at the midline in sagittal orientation, and the central fissure was vertical in both coronal and axial planes. Thresholding was then applied in order to remove dark grey elements such as meningeal tissue and signal noise from the image (Ferguson & Wardlaw), which resulted in clearer grey matter-CSF boundaries.

The frontal lobe was then manually delineated on coronal slices of the transformed and thresholded image. This was achieved by first drawing a straight line between the depth of each adjacent major sulcus (superior and inferior frontal, lateral orbital, cingulate or paracingulate sulci) using a pen-driven cursor and tablet (Wacom Intuos 4, Wacom Co. Ltd., Saitama, Japan) to demarcate the internal extent of all major frontal gyri. An intensity-guided flood fill was then applied to enable automatic detection of the grey matter-CSF boundaries. The posterior boundary of the superior frontal lobe was identified as the slice immediately anterior to the appearance of the pre-central gyrus (Kates et al., 2002). The selection of this boundary allows the simple and reliable identification of the frontal areas excluding pre-motor cortex using a common landmark that is easy to identify. The orbital

aspect of the frontal lobe was identified using a coronal plane at the most posterior appearance of the lateral orbital sulcus, which allowed differentiation of the orbitofrontal cortex from insular cortex. Asymmetry of these boundaries between hemispheres of each individual was preserved. This process produced a library of 90 atlases with the anatomical scans.

#### *6.3.4 Automated Image Processing*

The brain was extracted from the surrounding tissue using a validated multispectral image processing tool, MCMxxxVI (Hernández et al., 2012; Hernandez et al., 2010). This semi-automatic segmentation tool fuses pairs of MRI sequences (e.g. T<sub>2</sub>\*-weighted and FLAIR) in the red-green colour space to enhance signal differences between tissues, hence improving computational differentiation of signal differences and increasing accuracy of extraction of specific anatomical structure or ROI. T<sub>2</sub>\*-weighted and FLAIR volumes were fused to extract the brain as they provide good differentiation between brain-CSF and the inner skull table. After image fusion, the object extractor tool of Analyze 8.1 software (Mayo, 2008) was used to extract the brain and the final result was visually inspected and manually edited to correct for any misclassification.

*Segmentation using a single template:* For single-atlas segmentation, we used atlases derived from four different representative brains in order to investigate how the choice of atlas selection affects performance. The first three were selected from the 90 subjects as the most representative in terms of intracranial volume, total brain tissue volume and frontal lobe volume. The fourth was a standard atlas developed

from a right handed male young adult, available in MRIcro (Rorden & Brett, 2000), included to compare the results of segmenting ageing brains using an atlas developed from a young adult with those achieved by applying an age-matched atlas.

Each of the four representative brains was transformed to individual subject's space using Automatic Registration Toolbox (ART; Ardekani et al., 2005)), which was selected as it has previously been demonstrated as one of the most robust nonlinear image registration algorithms (Klein et al., 2009). The registration process was in two stages. Firstly, the  $T_1$ -weighted volume from which the representative atlas was generated was registered to the  $T_1$ -weighted volume of each subject and the computed transformation matrix applied to the atlas using the nearest neighbour interpolation to preserve the binary nature of the atlas. Secondly, the atlas was applied to the  $T_1$ -weighted volume of each subject to extract the subject-specific prefrontal lobe.

*Segmentation using Multiple Atlases:* Multi-atlas segmentation consists of template selection, label propagation, label fusion and ROI definition (Leung et al., 2011). First we used FSL (FMRIB Software Library, University of Oxford, UK) image registration tool (FLIRT; Jenkinson & Smith, 2001)) to register all our library scans to each subject in a jack-knifing method (Efron & Tibshirani, 1993) and computed the similarity between the source and the target image. Using this approach, each of the 90 subjects in our library became the target image and the remaining 89 were the source images. We used two image similarity metrics: the normalised cross correlation (Collignon et al., 1995), and normalised mutual information (Studholme et al., 1999) in order to investigate their accuracy in ageing population parcellation. For each subject, the library atlases were ranked based on



the similarity metrics. The best-matched 20 atlases were selected as previously proposed (Aljabar et al., 2009), and were then registered to the target volume using ART (Ardekani et al., 2005), and combined using vote-rule-based decision fusion at every voxel (Aljabar et al., 2009). The resulting atlas was used to extract the participant's prefrontal region.

### 6.3.5 Comparative Analysis of Methods

The comparison between atlas-based and manual segmentation was conducted in three stages. Firstly, intra-class correlation coefficients (ICCs) (Shrout & Fleiss, 1979) and Bland-Altman metrics (Bland & Altman, 1986) were calculated to examine the volumetric agreement between approaches. Secondly, as volumetric agreement does not give information about spatial agreement, we assessed spatial concordance using the Jaccard Index (JI) (Gee et al., 1993; Jaccard, 1912) and Dice Coefficient (DC) (Zijdenbos et al., 1994). The JI is defined as the ratio of the intersection of two images to their union, while the DC is the ratio of the intersection of two images to their mean value, where A and M represent automatically and manually generated segmentations respectively.

$$DC = 2 \frac{|A \cap M|}{|A| + |M|} \dots\dots\dots 1$$

$$JI = \frac{|A \cap M|}{|A \cup M|} \dots\dots\dots 2$$

Both measures have values ranging from 0 to 1 representing complete disjoint and complete overlap respectively. Paired t-tests were used to compare the spatial agreement between methods.

Finally, results were visually assessed by inspecting consecutive sections displayed together on the same screen and three-dimensional rendering. Volumes which exhibited particularly high or low measures of spatial concordance were specially inspected in order to identify reasons for extreme values. Visual inspection typically showed that initial single- and multi-atlas outputs misclassified CSF voxels as brain matter, and that the output masks did not map well onto the gyral patterning of the target brain. In order to rectify this, the dark grey elements such as meningeal tissue and signal noise were removed from the  $T_1$ -weighted volumes using the threshold value identified during manual segmentation. The masks generated from this process were then applied to the results from single- and multi-atlas parcellation to produce CSF free prefrontal lobes.

## 6.4 Results

Table 6.1 presents the descriptive statistics for the study participants. Two subjects were excluded from the analysis because of registration failure, resulting in a sample of  $n=88$  for analysis using the multi-atlas method. For the single atlas-based method, the agreement metrics for each of the study-based representative brains were excluded from the analysis, reducing the sample size to 87. Further registration failure after applying the young adult single-atlas method resulted in a cohort of  $n=77$  for analysis using this approach.

*Table 6.1* Descriptive Statistics

	Mean	SD	Range
Age at MRI (yrs)	73.30	0.37	72.41-74.22
MMSE	28.54	1.52	24-30
HADS-A	3.97	2.71	0-10
HADS-D	2.74	2.33	0-10

MMSE = Mini Mental State Exam (max=30), HADS-A = Hospital Anxiety and Depression Scale – Anxiety Subscale (max=21), HADS-D = Hospital Anxiety and Depression Scale – Depression Subscale (max=21).

#### *6.4.1 Reproducibility of Manual Segmentation*

In order to measure intra-rater reliability, 10 of the study cohort were randomly selected and segmented two weeks apart by the same rater (SRC). The resultant similarity measures (ICC = 0.99, Bland-Altman mean = -0.07 %, 95% limits from 2.59 to -2.72 %; JI = 0.81, DC = 0.87) suggest that the manual method is highly reproducible.

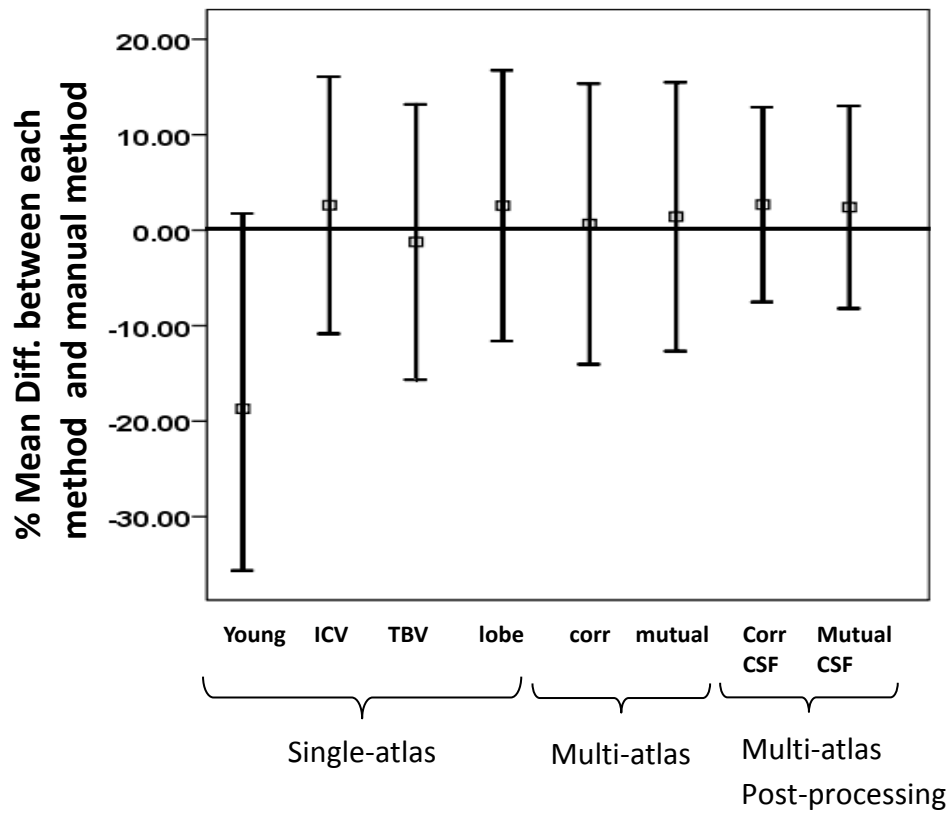
#### *6.4.2 Single-Atlas*

All four representative single-atlases had comparably good spatial agreement with the manual method (range: JI = 0.61 to 0.64, DC = 0.75 to 0.78), but there was significant divergence with respect to volumetric measures (Table 6.2, Figure 6.1). The three atlases selected from the target cohort gave acceptable volumetric agreement (ICCs > 0.74) with comparably wide Bland-Altman 95% confidence intervals (26.92 to 28.83 %, Table 2, Figure 2) and no apparent over- or under-estimation. However, where the young adult brain was used, it resulted in a very low ICC (0.31), systematic overestimation of frontal lobe volume (Bland-Altman mean = -18.70 %) and the widest Bland-Altman confidence interval spans of all approaches (34 %).

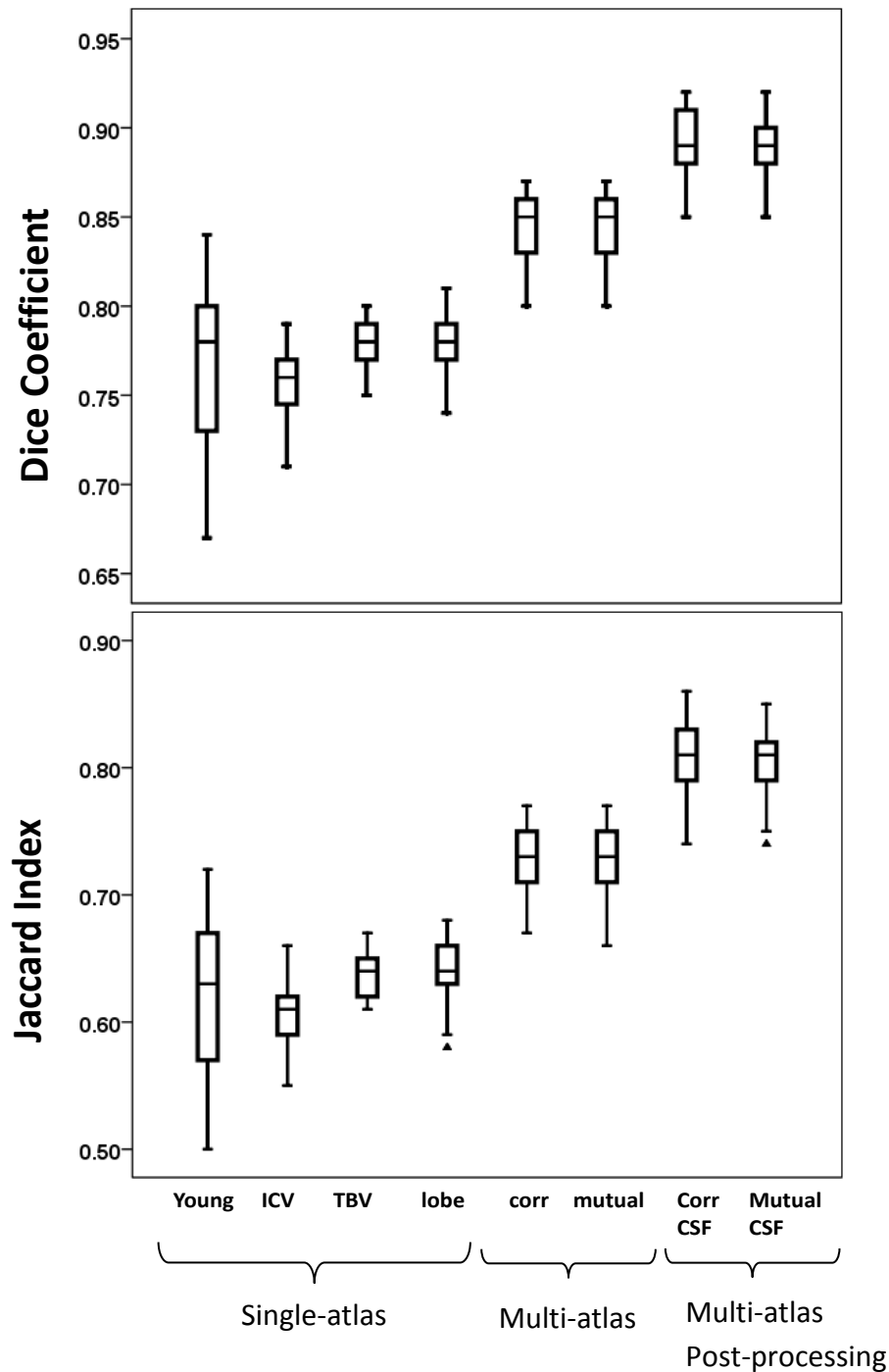
#### *5.4.3 Multi-Atlas*

Both multi-atlas methods (atlases selected using normalised mutual information and normalised correlation coefficients) initially gave highly similar volumetric (ICCs =

0.76) and spatial agreement ( $J\text{I} = 0.73 \pm 0.02$ ,  $\text{DC} = 0.84 \pm 0.02$ ) with the manual segmentation (Table 6.2, Figure 6.3). Although the volumetric agreement did not appear to improve with the use of multi- compared to single-atlases, the spatial agreement was significantly better, with  $J\text{I}$  improving by 0.09 and  $\text{DC}$  by 0.06; differences computed using atlases selected based on total brain tissue volume and normalised mutual information (paired t-test,  $p < 0.001$ ). Removal of misclassified CSF voxels in a post-processing step identified via visual assessment further improved the performance of both multi-atlas methods (Figures 6.1 & 6.2, Table 6.3). Specifically, ICC agreement improved by 0.11, and there was a reduction in Bland-Altman confidence intervals of 6.94 (normalised correlation) and 8.97 % (mutual information). Furthermore, spatial overlap was significantly improved for both the  $J\text{I}$  (0.08) and  $\text{DC}$  (0.05) (paired t-test,  $p < 0.001$ ). The distribution of both measures (Figure 3) also showed the multi-atlas based method performed better than the single-atlas method.



*Figure 6.1* Bland-Altman analysis showing the variation of % mean difference against mean values between automated single-atlas and manual segmentation. Tails denote upper and lower confidence limits. *Single-Atlas*: Young, ICV, TBV and lobe denote the representative brains selected based on young adult brain, ICV, total brain tissue volume and frontal lobe volume respectively. *Multi-atlas*: corr, mutual, corr CSF and mutual CSF denote selections of atlases using normalised correlation coefficient, normalised mutual information, normalised correlation coefficient followed by CSF removal and normalised mutual information followed by CSF removal respectively.



*Figure 6.2* Agreements between manual and automatic atlas-based segmentation methods. Single-Atlas: Young, ICV, TBV and lobe denote the representative brains selected based on young adult brain, ICV, total brain tissue volume and frontal lobe volume respectively. Multi-atlas: corr, mutual, corr CSF and mutual CSF denote selections of atlases using normalised correlation coefficient, normalised mutual information, normalised correlation coefficient followed by CSF removal and normalised mutual information followed by CSF removal respectively.

Table 6.2 Volumetric and spatial agreement measures between manual and automatic parcellation.

Volumetric Comparison				
		ICC	Bland-Altman	
			Mean (%)	Confidence Limits (%)
Manual	Reference Standard	0.99	0.07	2.59 to -2.72
Single-atlas	Atlas selected based on ICV (N=87)	0.76	2.61	16.07 to -10.85
	Atlas selected based on TBV (N=87)	0.76	-1.23	13.17 to -15.66
	Atlas selected based on frontal lobe volume (N=87)	0.74	2.56	16.73 to -11.62
	Standard Atlas (N=77)	0.31	-18.70	1.74 to -35.65
Multi-atlas	Atlases selected based on correlation coefficient (N=88)	0.75	0.65	15.34 to -14.04
	Atlases selected based on mutual information (N=88)	0.75	1.41	15.49 to -12.67
Spatial Comparison				
		Frontal lobe Volume	Jaccard Index	Dice Coefficient
Manual	Reference Standard	193888 ± 23250	0.81±0.24	0.87±0.22
Single-atlas	Atlas selected based on ICV (N=87)	188330 ± 17361	0.61 ± 0.02	0.75 ± 0.02
	Atlas selected based on TBV (N=87)	195680 ± 18208	0.64 ± 0.02	0.78 ± 0.02
	Atlas selected based on frontal lobe volume (N=87)	188388 ± 17147	0.64 ± 0.02	0.78 ± 0.01
	Young Adult Standard Atlas (N=77)	235242 ± 27553	0.62 ± 0.06	0.76 ± 0.05
Multi-atlas	Atlases selected based on correlation coefficient (N=88)	211559 ± 19335	0.73 ± 0.03	0.84 ± 0.02
	Atlases selected based on mutual information (N=88)	209965 ± 18596	0.73 ± 0.03	0.84 ± 0.02

ICC: Intra-class correlation coefficient, ICV: Intracranial volume, TBV: total brain volume.



Table 6.3: Change in volumetric and spatial agreement measures for multi-atlas methods before and after CSF post-processing.

Volumetric Comparison				
		ICC	Bland-Altman	
		ICC	Mean (%)	Confidence Limits (%)
Initial	Atlases selected based on correlation coefficient (N=88)	0.75	0.65	15.34 to -14.04
	Atlases selected based on mutual information (N=88)	0.75	1.41	15.49 to -12.67
CSF Removed	Atlases selected based on correlation coefficient (N=88)	0.86	2.68	12.88 to -7.53
	Atlases selected based on mutual information (N=88)	0.86	2.40	13.01 to -8.21
Spatial Comparison				
		Volume	Jaccard Index	Dice Coefficient
Initial	Atlases selected based on correlation coefficient (N=88)	211559 ± 19335	0.73 ± 0.03	0.84 ± 0.02
	Atlases selected based on mutual information (N=88)	209965 ± 18596	0.73 ± 0.03	0.84 ± 0.02
CSF Removed	Atlases selected based on correlation coefficient (N=88)	189010 ± 19846	0.81 ± 0.03	0.89 ± 0.02
	Atlases selected based on mutual information (N=88)	188129 ± 19334	0.81 ± 0.03	0.89 ± 0.02

CSF: Cerebrospinal fluid, ICC: Intra-class correlation coefficient.

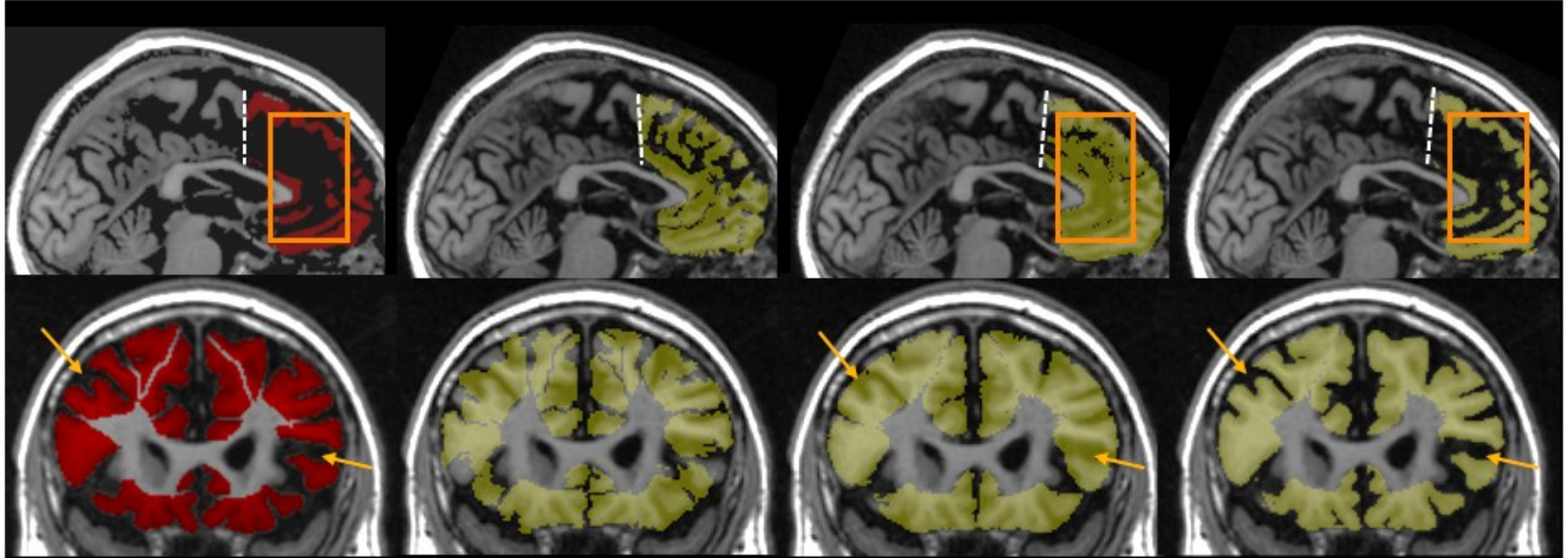


Figure 6.3: Sagittal (top row) and coronal (bottom row) planes for comparison of parcellation method on a representative brain from the cohort. From left to right, manual, single atlas, multi-atlas, multi-atlas after post-processing to remove CSF. For single atlas, local patterns of gyrification were not well-matched. For multi-atlas, prior to CSF removal, voxels in lateral (orange arrows) and medial aspects (orange box) were classified as brain tissue. Broken white lines indicate posterior boundary. Single-atlas method shown was when representative brain was selected based on the total brain tissue volume. Multi-atlas method shown was when normalised correlation coefficient was used to select atlases.

#### 6.4.4 *Visual Assessment*

Preliminary visual assessment confirmed that boundary matching and grey matter-CSF boundaries were more accurately represented using the multi-atlas approach (the manual, single- and multi-atlas mask comparison is illustrated in Figure 6.3). The output masks from the single-atlas method did not map well onto the gyral patterning of the target brain. For the multi-atlas method, prior to the removal of CSF, estimation errors were primarily at medial and dorsolateral extents, and the posterior lobar boundary was often imprecise. This was particularly apparent amongst individuals who exhibited a higher degree of atrophy, although brain shape that deviates significantly from the atlas may also be a confounding factor for non-linear registration. However, introducing the post-processing step of CSF removal showed a marked improvement in the concordance between multi-atlas and manual methods. Following this step, variability between automated mask and reference was mainly confined to the posterior boundary, with medial and dorsal over-estimation showing improvement (Figure 6.3).

## 6.5 Discussion

We have presented an investigation of the performance of atlas-based brain parcellation techniques in an ageing population. As an exemplar, we parcellated the prefrontal lobe using both single- and multi-atlas-based approaches and compared their performance with that of manual parcellation. We also investigated the choice of atlas selection and their effects on parcellation accuracy. We found that, whereas single-atlas measures were inconsistent in terms of volumetric and spatial indices of comparison with the reference standard, both methods of multi-atlas parcellation gave consistently good results. Multi-atlas performed better than single-atlas on the majority of similarity measures, particularly those that consider spatial concordance. We also found that the additional post-processing step of CSF removal improved the performance of the atlas-based methods. The spatial agreement measures show that the performance of multi-atlas methods in this ageing population compare very well with the implementation in young adults (Aljabar et al., 2009; Heckemann et al., 2010) and with the state-of-the-art segmentation techniques (e.g. Fischl et al., 2004) applied to young adults; therefore the current approach shows promise.

Our investigation on the choice of atlas selection revealed that the targeted selection of a study-based atlas for single-atlas methods of segmentation is of methodological importance. Using the atlas of a young healthy male resulted in much poorer performance than did the use of a study-based, older adult atlas. This supports an earlier finding (Aljabar et al., 2009) that application of an age-based atlas improves

accuracy. Basing the single-atlas selection on average intracranial volume, brain tissue volume or frontal lobe size all seem to confer similar improvements on overall output but the selection based on the total brain tissue volume and frontal lobe volume gave the best performance. Both the multi-atlas methods showed an improvement in the spatial measures of similarity with the reference manual segmentation compared to the single-atlas approach. The multi-atlas method should now be tested in a much larger and more varied population. The current participants were comparatively healthy and cannot fully represent the extent of normal or pathological variation seen with advancing age. Any such approach should be used with caution until wider knowledge of the limitations is available.

On a further methodological note, we emphasise the importance of rigorous comparisons between automated and reference outputs. It is clear from the inconsistencies across measurement modalities that agreements in volume do not necessarily equate to accuracy; here the spatial improvement conferred by multi-atlas methods, as identified by both computational and visual assessment, is not reflected in the volumetric comparison. Furthermore, visual assessment is a crucial tool in the identification of errors and potential improvements; the potential to make significant improvements to the most promising methods by removing misclassified CSF voxels was only identified through visual comparison of the outputs. This implies that the performance of any automatic parcellation technique should not only be measured using ICC but also with spatial concordance and visual assessment by a trained rater.

Nevertheless, even when we used robust criteria for atlas selection, chose the best registration method and a large ROI, variance in brain morphology and particularly the effects of age-related atrophy continue to present challenges to purely automated methods. The implementation of post-processing largely rectified these discrepancies, although issues with posterior boundary positioning remained. An alternative approach is to combine automated methods with manual editing to correct discrepancies. This hybrid approach might confer advantages over automated methods in terms of accuracy, and at the same time reduce the amount of researcher-hours that are required for a purely manual method. Hence, future use of automatic parcellation methods could usefully be followed by visual assessment, cogent post-processing strategies and manual editing.

In addition to our robust assessments of performance, this study benefits from a large sample and narrow age range, making this the largest study to have investigated atlas-based parcellation performance in an ageing population. We also used a state-of-the-art non-linear registration tool and a well-validated semi-automatic tool for brain extraction. The present study is limited in that only healthy older male participants were used. We therefore do not offer an assessment of performance for healthy ageing female brains, or age-related degenerative disorders. There is increased skull-thickening in post-menopausal women, and this could affect the performance of the atlas-based method. Likewise, significantly higher degrees of atrophy in pathological ageing are likely to present increased, and possibly novel, challenges to the present method. Further work could usefully test the effects of skull-thickening on automated parcellation and amongst subjects with significantly more brain atrophy than healthy cohorts, such as dementia.

Moreover, this method has only been applied to a large cortical region that is predominantly bound by CSF. Future studies will assess performance on other brain regions, particularly sub-cortical areas that may not benefit from the post-processing step used here.

In conclusion, atlas-based parcellation methods performed reasonably well in our generally healthy ageing population, with the multi-atlas method performed better than the single-atlas, although this was only apparent using visual inspection and measures of spatial concordance. The performance of any parcellation scheme should be assessed by a robust and multi-faceted series of measures. However, brain shape and particularly the effects of age-related atrophy still challenge the performance of this, and other, computational methods. Visual assessment also allowed a targeted post-processing method to be identified and implemented, further augmenting the agreement of multi-atlas parcellation across all measures. We suggest that a high degree of volumetric and spatial concordance can be achieved when this method is combined with minimal manual editing, and may be a promising method for lobar parcellation in large ageing cohorts.

Nevertheless, significant further development would be necessary to implement this to an acceptable standard of accuracy. Given the lack of control that even the present multi-atlas method confers on boundary positioning, and the fact that sub-regional frontal lobe parcellation would likely require manual editing of a large number of boundaries on a large number of contiguous slices, it is clear that – for now at least - manual parcellation is a preferred method of MRI analysis for the current study.

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## **Chapter 7: A Comparison of Cognitive Measures from Differential Psychology and Neuropsychology**

### **7.1 Introduction**

The brain's frontal lobes support a range of complex cognitive processes and comprise several densely interconnected, but structurally heterogeneous sub-regions. They are a key focus of interest in both neuropsychology and differential psychology. The former discipline attempts to understand how the structure of the brain directly relates to cognitive processes and behaviour. To this end, a large body of cognitive tests have been developed that elicit specific brain activation patterns (from functional imaging) or have sensitivity to behavioural profiles caused by focal brain lesions. Differential psychology is driven by the desire to understand the nature and causes of individual differences in psychological traits and states, including cognitive abilities. Normal healthy individuals who perform well in one cognitive domain (such as processing speed, memory and reasoning) also tend to perform well in another. The aim has therefore been to reliably and validly to enumerate and measure the domains of cognitive performance and understand their correlations and causes (environmental and genetic).

Both neuropsychology and differential psychology have developed tests that are thought to be relevant to frontal lobe function. The former aims to understand the individual contributions that the frontal lobe and its sub-regions might make to complex cognition, and the latter is interested in the general and specific cognitive domains subserved by a large-scale brain network, of which the frontal lobes form a part. The

mutual interest that these two fields share in the frontal lobes of the brain might lead one to ask how much tests from these two areas of psychology share, yet comparisons of tests thought to tap a specific sub-regional function versus measures of general cognitive ability (or *g*) and the major domains of cognitive differences are scarce. Moreover, increasing age is accompanied by a decline in some frontal tests (Kemp et al., 2012; Lamar & Resnick, 2004; MacPherson et al., 2002) and also *g* and other cognitive domains (Deary et al., 2009; Salthouse, 2004). A comparative examination of relationships between tests from neuropsychology and differential psychology can inform two key points. Firstly, it is unclear how cognitive measures devised by differential psychologists such as general intelligence, speed of processing and memory ability are associated with tests of function for frontal sub-regions. Secondly, models of the neural correlates of general intelligence differences suggest a primary role for dorsolateral (DLPFC) and anterior cingulate (ACC), but not orbital (OFC) frontal regions (Duncan et al., 2010, Jung & Haier, 2007) though more recent evidence does not clearly replicate this (Glascher et al., 2010; Narr et al., 2007). Thus an attempt to reconcile these two types of cognitive measure may prove to be mutually informative, and the current study aims to do so by examining the associations between scores on six tests thought to be preferentially sensitive to the functioning of three key frontal sub-regions (DLPFC, OFC and ACC) and measures of general intelligence (*g*), and the cognitive domains of memory and processing speed.

### *7.1.1 The Frontal Lobes in Neuropsychology*

The emergent picture from neuropsychology, based on lesion studies and neuroimaging, indicates modularity for frontal lobe structure-function mapping whereby distinct regions, whilst densely interconnected, each make discrete contributions to ‘higher’ cognitive processes. This has led to the identification of a broad segregation of function between dorsolateral and ventromedial frontal regions (MacPherson, Phillips & Della Sala, 2002; Phillips & Della Sala, 1998; Sarazin et al., 1998; Steele & Lawrie, 2004; Stuss, Shallice, Alexander & Picton, 1995; Stuss & Levine, 2002). The DLPFC typically comprises Brodmann’s Areas (BAs) 9/46, whilst the ventromedial portion comprises both the ACC, and OFC, each of which are likely to support different, but complementary processes.

The DLPFC has been extensively linked to working memory and problem-solving. As discussed in Chapter 2, damage to this region impairs performance on tasks that require remembering and avoiding previous choices, such as the Self-Ordered Pointing Task (Petrides & Milner, 1982), or that require planning several steps ahead, such as the Tower task, in contrast to unimpaired performance following other frontal and some non-frontal brain lesions. Likewise, functional imaging studies report DLPFC activity during both the Tower and SOPT.

In contrast, evidence suggests that the OFC allows the extensive integration of visceral information to guide future behaviour (Kringelbach, 2005). Lesions to this part of the frontal lobe lead to alterations in personality, social behaviour and emotional

processing (e.g. Eslinger & Damasio, 1985; Rolls, Hornak, Wade & McGrath, 1994). Tests such as the Reversal Learning paradigm and the Faux Pas task are sensitive to orbital lesions, and it is thought that both tests require an ability to judge the potential value and punishment of actions (Rolls et al., 1996; Baron-Cohen et al., 1997).

The ACC has been consistently implicated in normal performance of stimulus-response conflict (SRC) tasks (Botvinick, Cohen, & Carter, 2004; Mansouri, Tanaka, & Buckley, 2009; van Veen, Cohen, Botvinick, Stenger, & Carter, 2001). Such processing is thought to be indexed by differences in reaction times between congruent and incongruent response requirements and post-error slowing (PES; increased reaction times following an error) in tasks such as the Stroop (Stroop, 1992), Simon (Simon & Berbaum, 1990) and Flanker (Eriksen & Eriksen, 1974) tests. It is also thought that the ACC can be fractionated into a dorsal and ventral region, based on differential connectivity with DLPFC and OFC respectively (Beckmann, Johansen-Berg, & Rushworth, 2009; Devinsky, Morrell & Vogt, 1995) and the activation patterns elicited in functional neuroimaging paradigms (Bush, Luu, & Posner, 2000; Stuss & Levine, 2002).

Strong double dissociations in terms of function across all sub-regions remain comparatively rare, but some widely-used cognitive tests have accrued convergent evidence that suggests normal performance is more sensitive to the adequate functioning of one sub-region over another within the frontal lobes. Behavioural tasks comprise many components and it is important to be able to identify the proportion of variance in a given score that can be accounted for by a hypothesised source. The fact that different

task elements may tap different frontal regions introduces complications, but examination of the way in which task performance is affected by lesion locations has aided methodological adaptations in some tasks to account for this. For example, patients with dorsolateral pathology can be impaired on some ventromedial tasks due to an inability to attend to crucial stimuli. However, this can be identified through post-test questionnaires in the Reversal Learning Task; (Hornak et al., 2004; Rolls, Hornak, Wade, & McGrath, 1994) or control questions to ensure a factual understanding of the story content in the Faux Pas test (Stone, Baron-Cohen, & Knight, 1998).

### *7.1.2 The Frontal Lobes in Differential Psychology*

General intelligence, or ‘g’ robustly accounts for c.40% of the total variance amongst test batteries containing a large variety of cognitive tests (Deary, Penke & Johnson, 2010) and individual differences in general intelligence as measured by psychometric tests show moderate to high stability from childhood to old age (Deary, Whalley, Lemmon, Crawford, & Starr, 2000; Deary, Whiteman, Starr, Whalley & Fox, 2004; Gow, Johnson, Pattie, Brett, Roberts, Starr & Deary, 2011). Higher intelligence measured in early life predicts that an individual is more likely to have better health and live longer than contemporaries with lower g (Batty, Deary, & Gottfredson, 2007; Batty *et al.*, 2009; Calvin et al., 2010) and has real-life implications for socioeconomic mobility (Gottfredson, 1997; Johnson *et al.*, 2010a, 2010b). The frontal lobes also figure in attempts to characterise the biological basis of general intelligence, and their

complexity is reflected in two prominent accounts. Similarities between the Multiple Demand Network (MDN; Duncan, 2010) and the Parieto-frontal integration theory (P-FIT; Jung & Haier, 2007) can be seen in Figure 7.1. The P-FIT model arose from a review of functional and structural brain imaging evidence and describes an extensive distributed network including the lateral convexity of the frontal lobe comprising Brodmann Areas (BA) 6,9,45,46,47, anterior cingulate cortex (ACC; BA 24 & 32) and the frontal pole (FP; BA 10), whereas orbitofrontal areas (BA 11, 12 & 47) are notable by their absence<sup>34</sup> (Jung & Haier, 2007). The MDN is described as defining and controlling structured mental programs to cope with complex task demands (Duncan, 2010). With the exception of the frontal pole and arcuate fasciculus, it implicates similar regions to the P-FIT. Although it is debated whether *g* represents a single ability on which numerous parts of cognition might draw, or a multitude of cognitive abilities required for the various tasks from which it is derived (Glascher et al., 2010), both schemas suggest that dorsolateral and cingulate, but not orbital frontal regions play an important role in fluid intelligence.

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<sup>34</sup> Partly, as mentioned, this is due to reports that OFC lesions do not result in a decline in IQ (e.g. Stuss et al 1983).

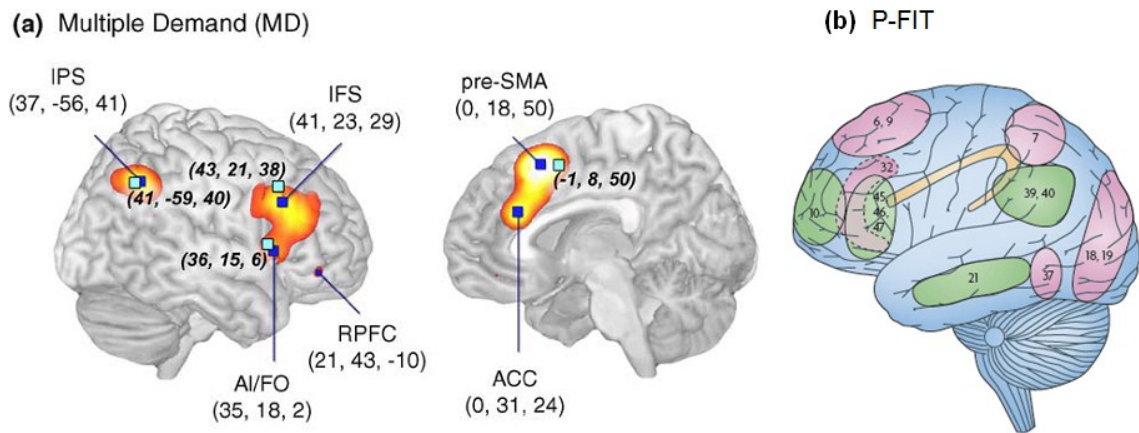


Figure 7.1. a) Multiple Demand Network from Duncan et al. (2010), and b) P-FIT model (Jung & Haier 2007) taken from Deary et al (2010).

This concept is not without its detractors; one criticism of the P-FIT model is that the ‘convergence of evidence’ cited by Jung & Haier to implicate the majority of brain regions is not particularly convergent. Less than half of the reviewed papers tended to support the inclusion of most brain areas, and there was little overlap between papers using functional and structural methods (Colom 2007). In further opposition, other studies report evidence of orbitofrontal contributions to *g* using voxel-based morphometry (Colom et al., 2009; Narr et al., 2007) and lesion-based mapping (Barbey et al., 2012; Gläscher et al., 2010). The former two studies reported a significant relationship between IQ and the thickness of the cortex at BA 10/11 and 47<sup>35</sup>. The two latter papers mapped focal lesion location in patients, and found that lesions located in

<sup>35</sup> Although the degree to which these clusters encroach into the OFC is unclear. As discussed in the introduction to this thesis, the morphology of this brain area is highly variable between participants – combined with the lack of clarity regarding where OFC cytoarchitecture begins, it could equally be argued that the relevant clusters are frontal pole and ventral IFG rather than OFC.

orbital regions (in addition to regions previously linked to g) were significantly associated with general intelligence – both showed a predominantly left-lateralised network of regions. Whether or not the lack of convergence is caused by registration artefacts, correction strategies or other reasons (Narr et al., 2007), data from a novel perspective may usefully contribute to the current picture.

### *7.1.3 Previous Comparative Studies of Neuropsychological and Psychometric Tests*

Comparisons of neuropsychological and psychometric tests are not without precedent. Two studies have examined tests of executive functioning in relation to domains of cognitive ability in large cohort with a wide age range (Crawford et al., 2000; Salthouse, 2005). Although they did not specifically address the underlying biology of the cognitive tests, both the Stroop and Tower of Hanoi were examined as tests of inhibition and planning respectively. Both tests showed high loadings on factors of general cognition (Full-scale IQ: Crawford et al., 2000; speed for the Stroop, and memory + vocabulary for the Tower: Salthouse, 2005). Moreover, Salthouse reported that the age effects that were present for the Stroop and Tower were entirely explained by the relationship between age and related cognitive domain. Given the implication of DLPFC and dorsal anterior cingulate (dACC) functioning in general cognitive ability and both Tower and Stroop, this finding is unsurprising. However, neither study included tests associated with OFC function. A more recent paper focussed on patients with various focal brain lesions, and found that deficits on ‘frontal’ tasks can be mainly explained by a loss of



general intelligence, although this was not the case for the Faux Pas test (Roca et al., 2010). Faux Pas scores were not entirely explained by g, and scores showed the expected association with inferior frontal lesions.

#### *7.1.4 Summary and Aims*

In summary, the frontal lobes are centrally implicated in both general cognitive ability and discrete cognitive processes. There is a lack of clarity in the ageing literature regarding (1) the underlying neural contributions within the frontal lobes to general intelligence, and (2) whether (and to what degree) measures of general cognitive ability and major cognitive domains overlap with behavioural performance on all neuropsychological tests. Both areas may benefit from detailed comparison of psychometric and neuropsychological tests. Based on the general schema outlined above, we expect the following pattern:

Firstly, the frontal tests themselves should exhibit internal consistency, and there should also be notably stronger associations between tests of functions within frontal sub-regions. That is, if two tests preferentially measure the functioning of one frontal region, they should correlate more strongly with each other than with tests for other sub-regions, provided that the neuropsychological tests are sufficiently sensitive to the functioning of one specific frontal sub-region over others in old age. The following relationship between neural substrate and function would be reflected in significant relationships between tasks sensitive to dysfunction within same region:

Dorsolateral	-	Tower Test, Self-Ordered Pointing Task (SOPT)
Orbitofrontal	-	Reversal Learning, Faux Pas Test
Anterior Cingulate Cortex	-	Simon Task, Dilemmas Task

ACC tasks were selected to explore the fractionation of the cingulate into a dorsal (dACC) and ventral (vACC) portion, which preferentially connect to the lateral and ventral frontal cortex respectively, with dACC relating to the Simon Task, and vACC relating to the Dilemmas Task.

Secondly, tests related to DLPFC and dACC functioning should correlate with *g* more strongly than OFC and vACC tasks, because *g* theoretically has little bearing on ventromedial task performance, based on the outlined theories of the neural substrates of intelligence, and effects on *g* following ventromedial damage.

Thirdly, methodological considerations for each frontal test should have minimised reliance on general memory and processing speed abilities (apart from the speeded Simon Task), and therefore the unique contributions that general memory and speed of processing make should be explained by *g*.

## 7.2 Methods

Details of the participants, cognitive testing and scoring are described in the Methods section and Appendix D.

### 7.2.1 *Outliers and normality*

In advance of statistical analysis, all variables were screened for outlying data points ( $\pm 3 SD$ ). Outliers were examined and winsorized unless there were robust reasons for exclusion. For example, a single Post-Error Slowing data point was removed as it was based on a single reaction time (this does not change the significance of relationship with any variable). One participant who made errors on 50 of the 51 Reversal Learning trials was also excluded based on post-test interview. Next, variables were examined to ascertain normality of distribution using visualization of histograms, QQ plots, and Shapiro-Wilks statistic as a guide. The majority of variables were found to exhibit normal distributions, with the exception of scores on the Faux Pas, Reversal Learning and mean reaction times taken to respond during the Dilemmas task. Log and square root transformations did little to alter this for both Faux Pas and Reversal Learning, although a log transform did result in more normal conformity for Dilemmas reaction times.

### 7.2.2 Internal Consistency

The internal consistency of the frontal tests was also examined. Within-test items were compared using Cronbach's Alpha for the SOPT. Intraclass Correlation Coefficients (Shrout & Fleiss, 1979) were used for the remaining tests, apart from the Tower test which was reported in the Delis-Kaplan Executive Function System (D-KEFS) Technical Manual (Delis, Kaplan & Kramer, 2001), for which normative scores have already been produced using 125 participants, aged 70-79. Coefficients were derived using an odd-even methodology and corrected using the Spearman-Brown formula.

For the Self-Ordered Pointing Task, Cronbach's Alpha was calculated between the numbers of repetitions made on each of the three trials. For the Faux Pas test, scores for odd and even stories containing a Faux Pas were summed and compared<sup>36</sup> and split halves of the number of errors during Reversal Learning were created for each participant and compared.

The measure for Post-Error Slowing (PES) in the Simon Task used in the analysis is calculated as the mean reaction time (RT) for trials following an error divided by the mean RT of trials following correct responses. Therefore, consistency was calculated by comparing the mean of odd and even occurrences of PES RTs divided by the mean RT of trials following correct responses for every participant who made more than one error (n=78). In order to ascertain the consistency of the Simon, and directional Simon Effect, a similar procedure to that described for PES was conducted. For the

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<sup>36</sup> *excluding both the empathy question and the 2 control questions at the end of each story, as described in the methods section.*

Simon Effect, the mean was of the ratio of RTs on a) incongruent and b) congruent trials. Means for a) were then divided by b). For the directional Simon Effect, this was where the change in contingency went a) from congruent to incongruent and b) from incongruent to congruent. Means for a) were then divided by b) in order to replicate the format used in the analysis, and the internal consistency was calculated by correlating odd and even instances of a/b.

Finally, in the Dilemmas task, both percentage of actions endorsed and the reaction time data for high conflict scenarios were split into two halves of comparable mean emotionality rating (5.70 versus 5.86; ratings reported in Koenigs et al 2007). Spearman-Brown correction (Brown, 1910; Spearman, 1910) was applied to all tests of reliability except the SOPT and Tower.

### *7.2.3 Fatigue Effects*

The test battery took on average 1.5 hours to complete, and the running order of the test battery was reversed for 45 participants in order to test for any effects that factors such as fatigue might have on task performance. Two-tailed t-tests or 2-sample Wilcoxon Rank-Sum tests<sup>37</sup> between the two participant groups were performed to examine possible effects of fatigue.

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<sup>37</sup> Not to be confused with the Wilcoxon Signed-Rank Test for used with matched pairs it is appropriate for independent samples, equivalent to the Mann-Whitney U-Test.

#### *7.2.4 Test Score Correlations*

Pearson's product-moment correlation tests were performed to examine relationships between test scores for parametric variables. Spearman's rank order correlation tests were used for those that were non-parametric. Next, relationships between frontal tests and general cognitive ability and factors of memory and processing speed were performed. Tests for significant differences between correlations (Crawford et al., 1996) were used to test predictions that DLPFC and ACC tasks would correlate more strongly with *g* than OFC tasks.

Partial correlations were then conducted between frontal test scores for the same region, partialling out any shared variance with scores for other frontal regions. Further analyses tested intercorrelations between frontal tests after partialling out *g*, to identify unique shared variance between frontal test scores that is not common with *g*.

#### *7.2.5 Principal Components Analysis*

The correlational structure of cognitive performance was further examined using three principal components analyses (PCA) of neuropsychological frontal tests, first without, then with the inclusion of *g* factor scores, and finally using the 6 Weschler subtests used to derive the *g* factor itself: digit-symbol substitution, digit backwards, block design, letter-number sequencing, matrix reasoning and symbol search (described in Chapter 5), using SPSS 19.

### 7.3 Results

Summary statistics for the cognitive scores, including measures of internal consistency for the frontal tests appear in Table 7.1. Scores were not significantly different between participants who took the tests in forward and reverse order, suggesting that fatigue did not have a systematic effect on performance. In general the variables also exhibited acceptable internal consistency (ICCs  $>.75$ ), including the SOPT, which was the test with the lowest value (Cronbach's  $\alpha = .67$ ).

Although no participants obtained a perfect score on any task, one participant made no errors on the Simon Task, and there was a markedly skewed distribution for the Faux Pas test, indicative of a ceiling effect. The Simon Effect and directional Simon Effect means indicated that response times were longer for incongruent than congruent trials, and for contingency switches from congruent-incongruent than incongruent-congruent.

Participants' mean scores for  $g$ ,  $gspeed$  and  $gmemory$  were close to 0, indicating that this sample has general cognitive abilities that are representative of the cohort from which they were drawn (as these scores were calculated for the whole sample; Deary et al., 2007).

Table 7.1. Descriptive Statistics of Frontal Lobe Measures

	<i>n</i>	Mean	SD	Min	Max	Cons.	Number of Trials	Order ( <i>t</i> / <i>W</i> )
<b>Tower</b>	90	17.60	3.95	9	29	.78 <sup>a</sup>	9	-.69
<b>SOPT</b>	88	2.56	0.94	0.67	4.67	.67	3	1.76
<b>Faux Pas</b> ◇	90	39.40	7.35	16.09	49	.86 <sup>b</sup>	10	787.5
<b>RL Errors</b> ◇	87	12.90	7.17	5	28	.89 <sup>b</sup>	51	1112.5
<b>PE Slow</b>	88	1.28	0.17	0.91	1.78	.86 <sup>b</sup>	<i>variable</i> <sup>c</sup>	0.16
<b>Simon Effect</b>	89	1.08	0.06	0.94	1.24	.75 <sup>b</sup>	120	0.75
<b>SE Direction</b>	89	1.05	0.07	0.89	1.20	.81 <sup>b</sup>	<i>variable</i> <sup>d</sup>	-0.66
<b>Dilemmas MRT (sec)</b> ◇	86	8.60	4.45	2.75	2.32	.82 <sup>b</sup>	9	699
<b>Dilemmas % Endorsement</b>	86	58.14	23.05	0	100	.91 <sup>b</sup>	9	-0.65
<b>g</b>	90	0.03	1.14	-2.47	3.17			
<b>g speed</b>	90	-0.10	1.03	-2.82	2.15			
<b>g memory</b>	89	-0.09	1.21	-2.97	2.46			

Winsorized descriptive statistics are reported, prior to log transformation, ◇ non-parametric variable (Wilcoxon method used). Cons: consistency, SOPT: Mean number of repetitions made on the Self-Ordered Pointing Task, RL Errors: total errors on the Reversal Learning Task, PE Slow: Post-Error Slowing, MRT: mean reaction time, <sup>a</sup>: based on a separate sample of 125 participants, 70-79 years, reported in the D-KEFS technical manual, <sup>b</sup>: Spearman-Brown corrected <sup>c</sup>: Mean number of errors = 6.87, sd = 7.12, <sup>d</sup>: Of the total 250 trials, participants encountered a mean of 116 variable-relevant trials, SD = 16.07.



### 7.3.1 Frontal Lobe Test Correlations

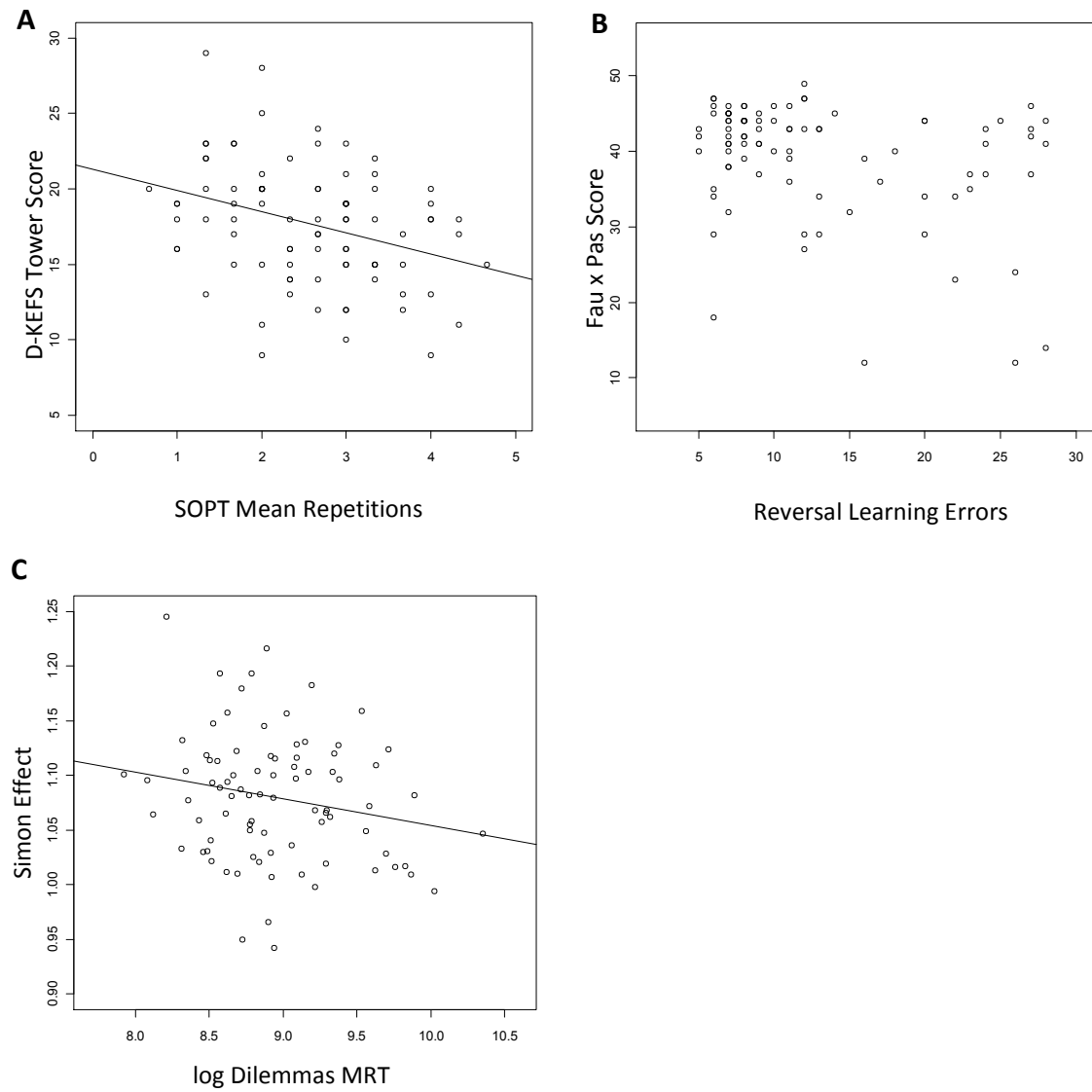
Intercorrelations between frontal lobe tests are presented in Table 7.2 and Figure 7.2.

For tasks thought to be sensitive to dorsolateral functioning, more repetitions on the SOPT were significantly associated with a poorer score on the Tower Test ( $r(86)=-.33$ ,  $p=.001$ ). For orbitofrontal tasks, participants' success at correctly identifying a story in which a Faux Pas had been committed was negatively correlated with the total number of errors commissioned during the Reversal Learning task ( $\rho(85)=-.24$ ,  $p=.023$ ). Finally, the Simon Effect tended to correlate with the mean time taken to respond during the Dilemmas task ( $r(83)=-.20$ ,  $p=.068$ ).

In addition, there were significant correlations between tasks tapping different frontal sub-regions in some cases. Mean response time on the Dilemmas task (ACC) was significantly related to the Faux Pas score (OFC;  $\rho(84)=-.27$ ,  $p=.013$ ). Total score on the Tower Test which relates to the DLPFC correlated significantly with both orbitofrontal tasks: the Faux Pas score ( $\rho(88)=.31$ ,  $p=.003$ ) and the total errors during Reversal Learning ( $\rho(85)=-.37$ ,  $p<.001$ ). The mean number of repetitions on the SOPT also correlated significantly with the score on the Faux Pas test ( $\rho(86)=-.36$ ,  $p<.001$ ) and a trend with total errors on Reversal Learning ( $\rho(83)=.20$ ,  $p=.070$ ). Furthermore, better performance on the Faux Pas task was associated with quicker mean decision time during the Dilemmas task ( $\rho(84)=-.27$ ,  $p=.013$ ).

Partial correlations revealed that the relationship between the OFC tasks (Faux Pas tests and Reversal Learning) still showed a trend towards significance when shared

variance with SOPT performance was partialled out ( $\rho(85)=-.20, p=.067$ ). However, it was not significant when partialling out the Tower score ( $\rho(87)=-.15, p=.170$ ). In contrast, the relationship between the DL tasks (Tower and SOPT) remained significant when accounting for the relationship with either OFC task (Reversal Learning:  $\rho(85)=-.29, p=.006$ ; Faux Pas:  $\rho(88)=-.25, p=.019$ ). These findings indicate that there is significant shared variance both between scores for the same sub-region, but that there are also some tests that share similar amounts of variance with tests thought to tap other regions.



*Figure 7.2.* Relationships between tests of DLPFC (A), OFC (B) and ACC (C). SOPT: Self-ordered pointing task, MRT: Mean reaction time.

Table 7.2. Correlations Between Frontal Test Measures

DLPFC			OFC		ACC				
	Tower Score	SOPT Repetitions	Faux Pas <sup>◇</sup>	RL Errors <sup>◇</sup>	Post-Error Slowing	Simon Effect	SE Direction	Dilemmas Mean RT	Dilemmas % Endorsement
Tower Score	-----	-.33**	.31**	-.37***	.10	-.22*	.10	-.16	-.05
SOPT Reps.		-----	-.36**	.20 <sup>†</sup>	-.05	-.07	-.07	.16	.01
Faux Pas <sup>◇</sup>			-----	-.24*	.04	.05	.07	-.27*	-.15
RL Errors <sup>◇</sup>				-----	-.20 <sup>†</sup>	.23*	-.14	.08	.08
PE Slow					-----	-.26*	-.04	-.02	.07
Simon Effect						-----	.95**	-.21 <sup>†</sup>	.14
SE Direction							-----	-.06	-.13
Dilemmas MRT								-----	-.03
Dilemmas % Endorsement									-----

<sup>◇</sup> non-parametric variable (Spearman method used), \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ , <sup>†</sup> trend ( $.08 < p < .05$ )

### *7.3.2 Frontal Lobe Test Correlations with g, gspeed and gmemory*

#### 7.3.2.1 General Intelligence

Current neurobiological models of general intelligence posit that dorsolateral and dorsal cingulate but not ventromedial prefrontal regions comprise part of the ‘g network’ (Jung & Haier 2007; Duncan et al 2010). Therefore, it was hypothesised that dorsal cingulate (i.e. Simon Task) and DL tasks will correlate with general intelligence factor more strongly than OFC and ventral cingulate (i.e. Dilemmas) tasks. The results are reported in Table 7.3 and Figure 7.3

*g* correlated significantly with both OFC and DL tasks with medium and large effect sizes (0.29-0.53; Cohen 1998), with a small effect size with two measures from ACC tasks (Dilemmas mean RT and PES in the Simon Task). As shown in Figure 7.4, there was a general trend for the magnitude of these correlations to be higher for DLPFC than for OFC tasks, and lowest for ACC tasks (although these differences were not significant in every case).

#### 7.3.2.2 General Speed of Processing

During selection of the test battery, attempts were made to ensure that, where appropriate, outcomes could not be confounded by individual differences in processing speed. A generous time limit was allotted for each Tower problem, or trial for the Reversal Learning task, and the Faux Pas and Dilemmas tasks were self-paced. However, the speed and accuracy were equally emphasised during the Simon Task and

SOPT. It was predicted that there would be no correlations between gspeed and the main outcome variables, apart from the Simon Task and SOPT, beyond that explained by *g* itself.

Individual differences in speed of processing ability significantly correlated with all outcome variables except the Simon effect and the percentage of high-conflict actions endorsed in the Dilemmas task (Table 7.3). However, because *g*, gspeed and gmemory are not orthogonal (there is some overlap in the cognitive test scores used to establish each latent variable, and both gspeed and gmemory are correlated with *g*), residuals for gspeed and gmemory were created from respective linear regressions with *g*. In this way, it was possible to examine the unique relationships between the frontal tests, speed and memory independent of their contributions to general intelligence. An examination of Table 3 shows that the speed component of gspeed did not significantly correlate with any of the frontal tests apart from post-error slowing in the Simon Task. This suggests that the element of gspeed that is shared with *g* can predominantly account for score variation.

#### 7.3.2.3 General Memory

As with speed of processing, it was anticipated that the selected tests would avoid confounding effects of memory ability over and above the shared variance between memory and *g*. For example, the written scenarios for the Faux Pas and Dilemmas tasks were available for reference at all times in order to minimise any possible memory load.

Likewise, the rules for the Tower task were displayed clearly in front of participants for the duration of each trial, along with the target stimuli. As a result, no significant correlations were expected between the residualised memory score and FL task performance. Memory correlated significantly with all variables except both Simon task measures and the percentage endorsement in the Dilemmas task. This appears to directly contradict our hypothesis, although correlations with residuals of a linear regression between *g* and *gmemory* show that the only task on which memory uniquely predicts performance beyond *g* is on the Faux Pas stories (Table 7.3).

Table 7.3. Correlations Between Frontal Test Measures and General Cognitive Ability

	Tower Score	SOPT Repetitions	Faux Pas $\diamond$	RL Errors $\diamond$	Post-Error Slowing	Simon Effect	SE Dir.	Dilemmas Mean RT <sup>a</sup>	Dilemmas % Endorsement	g	gspeed	gmemory
<b>g</b>	<b>.51***</b>	<b>-.53***</b>	<b>.43***</b>	<b>-.32**</b>	<b>.21<sup>†</sup></b>	-.11	.01	<b>-.24*</b>	-.02	*****		
<b>g speed</b>	<b>.45***</b>	<b>-.44***</b>	<b>.29**</b>	<b>-.28**</b>	<b>.32**</b>	-.10	.10	<b>-.23*</b>	.00	<b>.78***</b>	*****	
<b>g memory</b>	<b>.49***</b>	<b>-.51***</b>	<b>.51**</b>	<b>-.35***</b>	<b>.25*</b>	-.11	.07	<b>-.28**</b>	-.08	<b>.83***</b>	<b>.66***</b>	*****
<b>speed</b>	.08	-.05	-.10	-.13	<b>.25*</b>	-.02	.15	-.06	.11	.00	<b>.62***</b>	.02
<b>memory</b>	.12	-.14	<b>.38***</b>	-.15	.15	-.02	.07	-.13	-.08	-.00	.04	<b>.56***</b>

Speed: unstandardized residuals from the correlation between gspeed and g. Memory: unstandardized residuals from the correlation between gmemory and g. <sup>a</sup> log transformed,  $\diamond$  non-parametric variable (spearman method used), \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ , <sup>†</sup> trend ( $.08 < p < .05$ ).



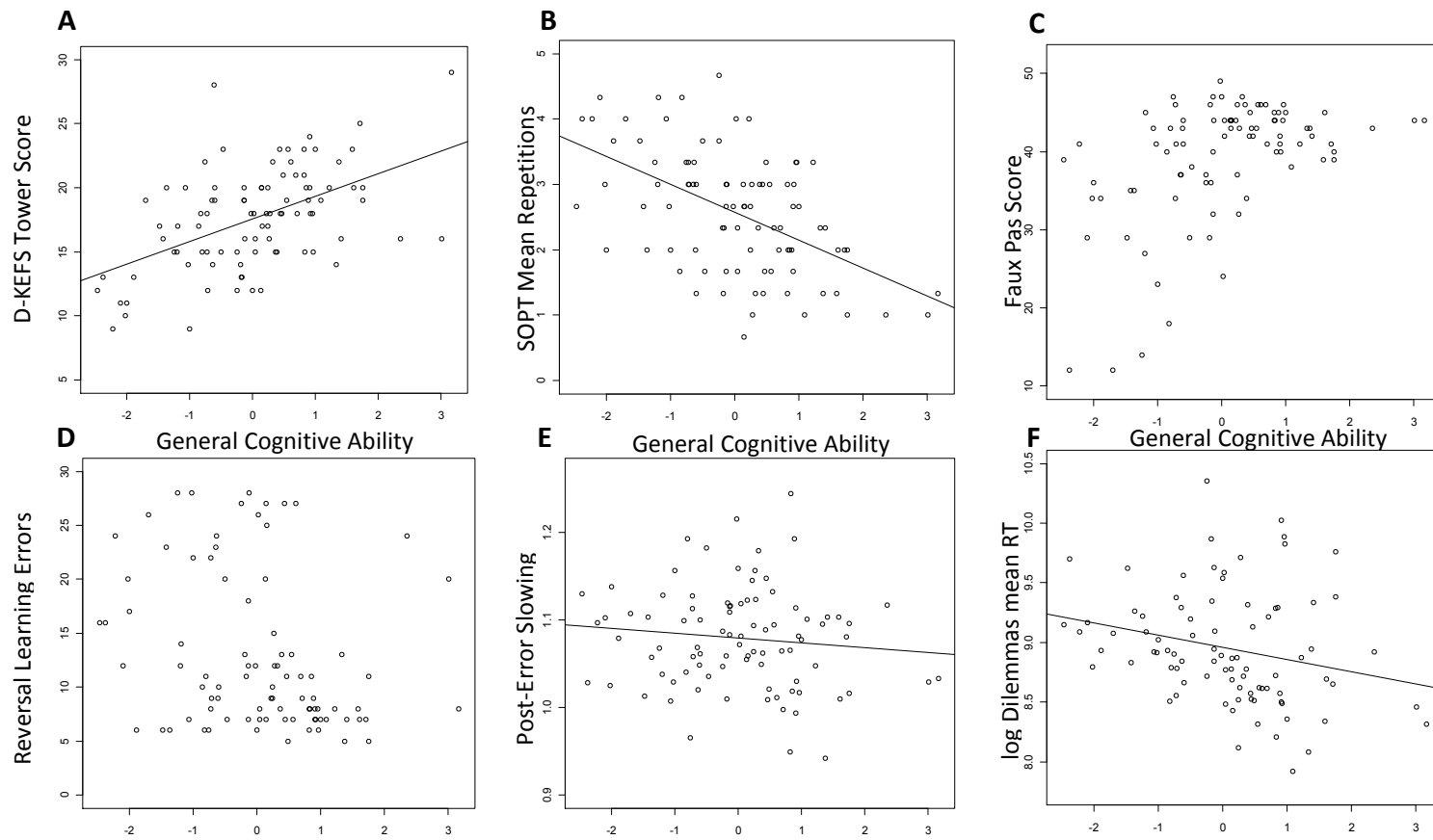
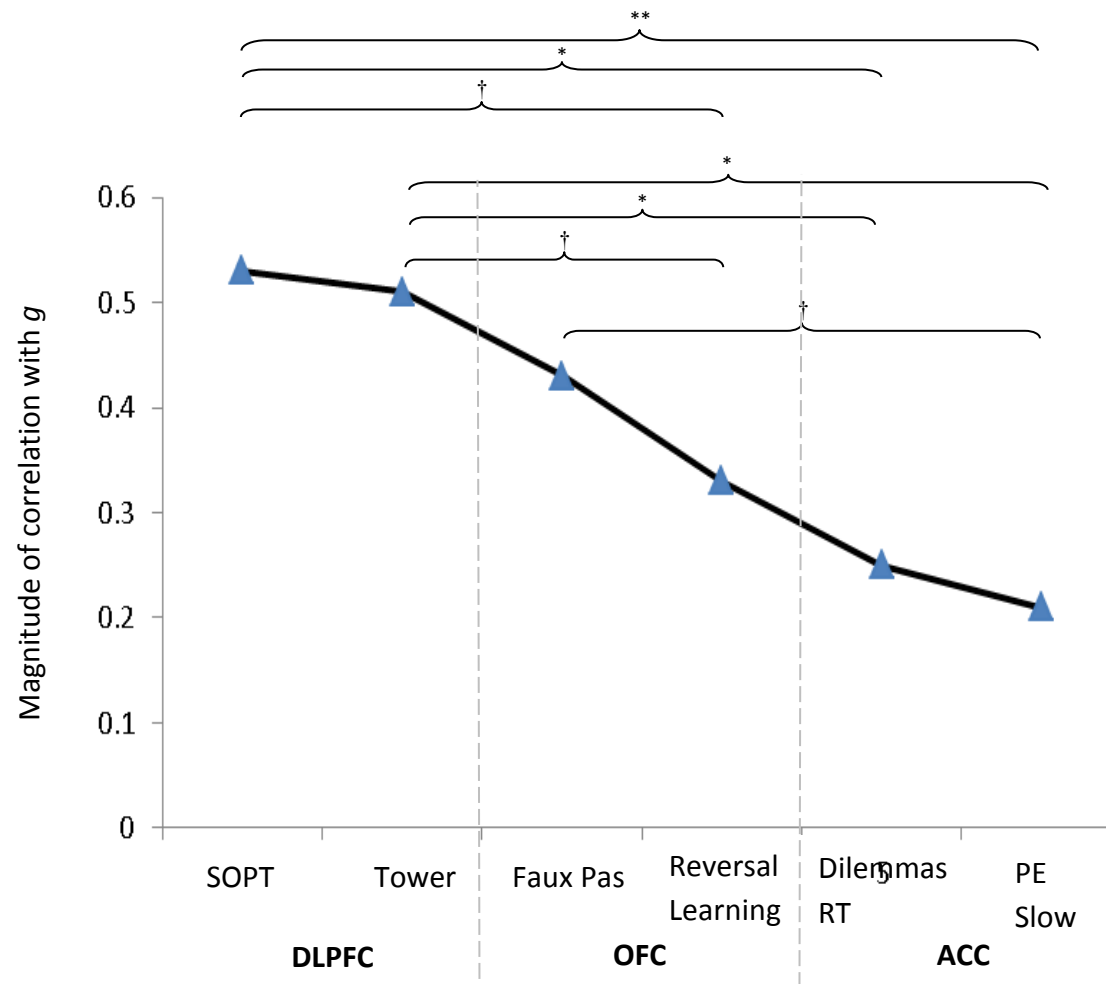


Figure 7.3. Correlations between g and neuropsychological tests, as reported in Table 3.



*Figure 7.4.* Magnitude of correlations between frontal tests and *g*. Braces denote significant or trend differences between correlation magnitudes; \* $p < .05$ , \*\* $p < .01$ , † trend ( $.08 < p < .05$ ). DLPFC: Tests thought to tap the dorsolateral prefrontal cortex, OFC: tests thought to tap the orbitofrontal cortex, ACC: tests thought to tap the anterior cingulate cortex.

### 7.3.3 Partial Correlations Between Frontal Test Measures controlling for *g*

In light of the consistent relationship between frontal test scores and *g*, correlations between frontal tests were conducted that partialled out the variance accounted for by *g* (Table 7.4). Only the relationship between the Tower score and total errors during Reversal Learning remained significant, indicating significant shared variance beyond their mutual relationship with *g*. The remaining correlations between all other associated tests that both shared variance with *g* were non-significant.

As illustrated by Figure 7.5, the relationship between the Reversal Learning score and *g* became non-significant when controlling for Tower score ( $\rho(87)=-.18$ ,  $p=.09$ ) but the relationship between Tower score and *g* remained significant when controlling for the total errors during Reversal Learning ( $\rho(87)=.42$ ,  $p<.001$ ).

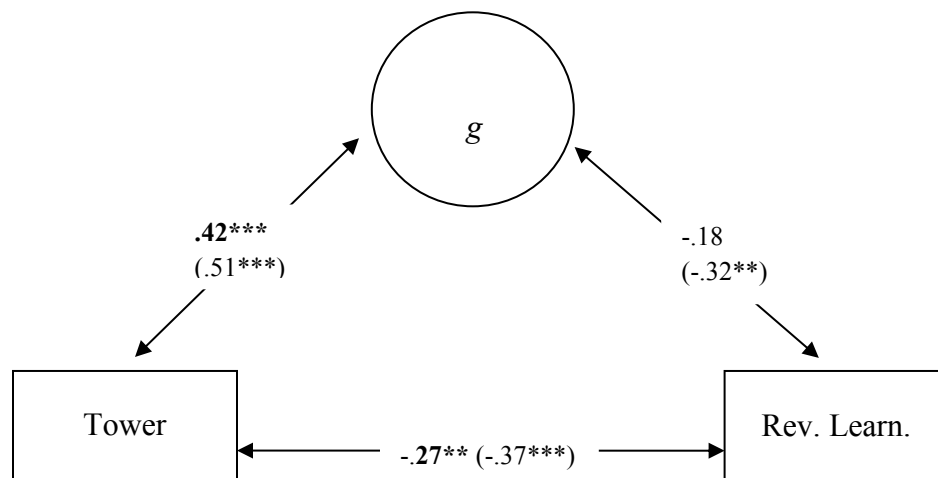


Figure 7.5. Correlations between total score on the Tower test, total errors during Reversal Learning, and *g*. \* $p<.05$ , \*\*\* $p<.001$ . Value in brackets indicates relationship prior to partialling out the secondary test score.

Table 7.4. Partial Correlations Between Frontal Test Measures controlling for g

DLPFC			OFC		ACC				
	Tower Score	SOPT Repetitions	Faux Pas◇	RL Errors◇	Post-Error Slowing	Simon Effect	Simon Effect Direction	Dilemmas Mean RT	Dilemmas % Endorsement
Tower Score	*****	-.08 (-.33)	.13 (.31)	-.27**(-.37)					
SOPT Reps.		*****	-.19 (-.36)	.06 (.20)					
Faux Pas ◇			*****	-.13 (-.24)					-.18 (-.27)
RL Errors ◇				*****	-.16 (-.20)				
PE Slow					*****				
Simon Effect						*****			
Simon Effect Direction							*****		
Dilemmas MRT								*****	
Dilemmas % Endorsement									*****

† non-parametric variable (spearman method used), \* $p < .05$ , \*\* $p < .01$ , † trend ( $.08 < p < .05$ ). Cells in grey are those in which g did not correlate with both frontal tasks, or in which the two frontal variables do not correlate.

#### *7.3.4 Principal Components Analysis*

The first unrotated principal component using only frontal test scores was described by both DLPFC and both OFC tests, post-error slowing and the mean decision time during the Dilemmas task. It accounted for 24% of the data's variance (Table 7.5). The scree plot shown in Figure 7.6 indicated the extraction of 3 factors (cumulatively explaining 53% of the variance), which were extracted using varimax rotation and are also shown in Table 7.5. The first component of this three-factor solution is described by decision-time on the Dilemmas task, both DLPFC and both OFC tasks, accounting for 24% of the variance. The second component accounted for a further 16%, loading primarily on the ACC scores (PES, Simon Effect and Dilemmas MRT). Component 3 accounted for a further 13% of the variance, and comprised only the Dilemmas %endorsement and directional Simon Effect; variables which do not correlate with other cognitive scores.

Introducing *g* into the PCA provides information about the correlational structure of the frontal lobe tests and *g*. The first unrotated component has loadings from *g* and the same tests as before (Table 7.6). It accounted for 27% of the total test variance. The resultant scree plot (Figure 7.7) suggested the extraction of 3 factors, whose loadings are shown in Table 7.6. The pattern and magnitude of the loadings across the three extracted components were similar to those described without *g*; *g*'s loading was strongest on rotated factor 1, which also had high loadings from the Tower, SOPT, Faux Pas, Reversal Learning and Dilemmas response time. Factor 2 showed a low *g* loading, accounting for 14% of total test variance. It had high loadings from post-error slowing, the Simon Effect, Dilemmas response time, but Tower score

(.23) and Reversal Learning (-.26) errors also showed some additional loading.

Factor 3 was similar to before, and also had a low loading from *g*.

Though this chapter focusses on the correlational structure of the frontal lobe tests and their relationship to general cognitive ability, considering the correlational structure by including the subtests from which *g* is derived (in place of the factor score) could offer an alternative perspective. Examination of the scree plot indicated a single factor dominated the PCA. However, three factors were extracted for the sake of comparison with the previous PCA analyses, though the introduction of additional tests thought to load heavily on *g* meant there were now 10 of the 15 tasks with hypothesised *g* loadings. This potentially swamped the relevance of the shared non-*g* variance which is of particular interest, given that the reversal learning, tower score, post-error slowing and Simon effect (now a minority) appear to have additional non-*g* components. As expected, using tests that comprise *g* in place of participants' *g* factor score proportionally increased the amount of variance that the principal component accounted for (31.14%), compared with the rotated second (10.31%) and third components (9.41%; Table 7.7). However, it did little to alter the factor structure in terms of loadings when compared to the previous two PCAs. The first component had a high loading ( $>.65$ ) for all the scores comprising *g* (digit-symbol substitution, digit span backward, block design, letter-number sequencing, matrix reasoning and symbol search) and also loadings of Tower, SOPT, Faux Pas, Reversal Learning and Dilemmas reaction time (.34-.65; Figure 7.8) as seen in the previous two PCAs. Also as before, the second rotated component also showed modest loadings for the Tower (.27) and Reversal Learning scores (-.29; indicative of their shared variance above *g*) and larger loadings for Post error slowing, Simon

effect and Dilemmas reaction time. The only notable change in factor structure elicited by this variant of the PCA was the composition of the third component. The largest loadings were on the percent of endorsed dilemmas (.72), matrix reasoning (-.55) and modest loadings on the Dilemmas reaction time, Faux Pas, Reversal Learning and post error slowing (magnitude range .29 to .32).

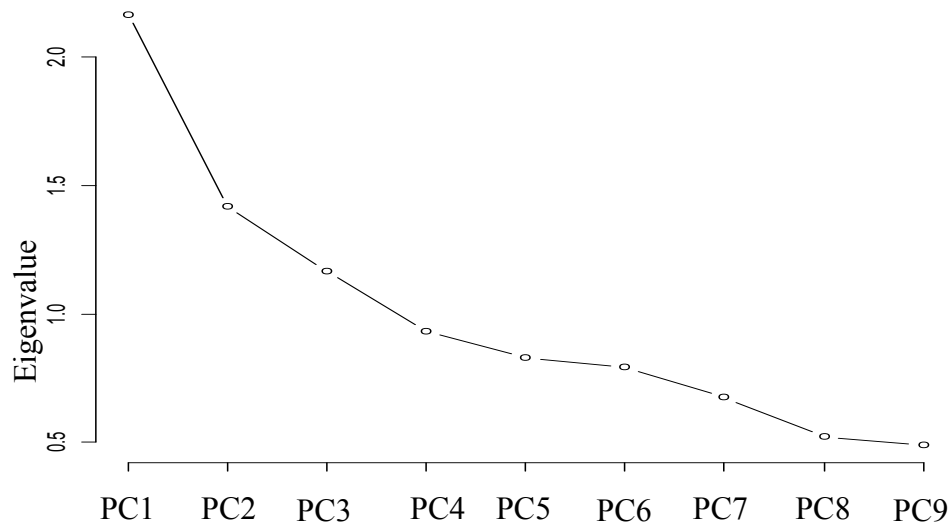


Figure 7.6. Scree plot from principal components analysis of frontal tasks only.

Table 7.5. Principal Components Analysis loadings without g

	1 <sup>st</sup> unrotated	Rotated Components		
		PC1	PC2	PC3
<b>Tower Score</b>	<b>-.69</b>	<b>-.64</b>	.25	-.15
<b>SOPT</b>	<b>.69</b>	<b>.73</b>	.15	.01
<b>Faux Pas</b>	<b>-.71</b>	<b>-.74</b>	-.06	.00
<b>RL Errors</b>	<b>.65</b>	<b>.60</b>	-.29	.10
<b>PE Slowing</b>	<b>-.30</b>	-.25	<b>.60</b>	<b>.36</b>
<b>Simon Effect</b>	.17	-.01	<b>-.83</b>	.15
<b>SE Direction</b>	-.16	-.10	-.07	<b>-.66</b>
<b>Dilemmas MRT (msec)</b>	<b>.37</b>	<b>.47</b>	<b>.44</b>	-.08
<b>Dilemmas % Endorsed</b>	.15	.03	-.13	<b>.75</b>
<b>Eigenvalue</b>	2.20	2.12	1.45	1.18
<b>Explained Variance (%)</b>	24	24	16	13
<b>Cumulative Proportion</b>	-	24	40	53

Loadings  $>.3$  s are shown in bold. SOPT: Self-ordered pointing task, RL: Reversal Learning, PE: post-error, SE: Simon Effect, MRT: mean reaction time.



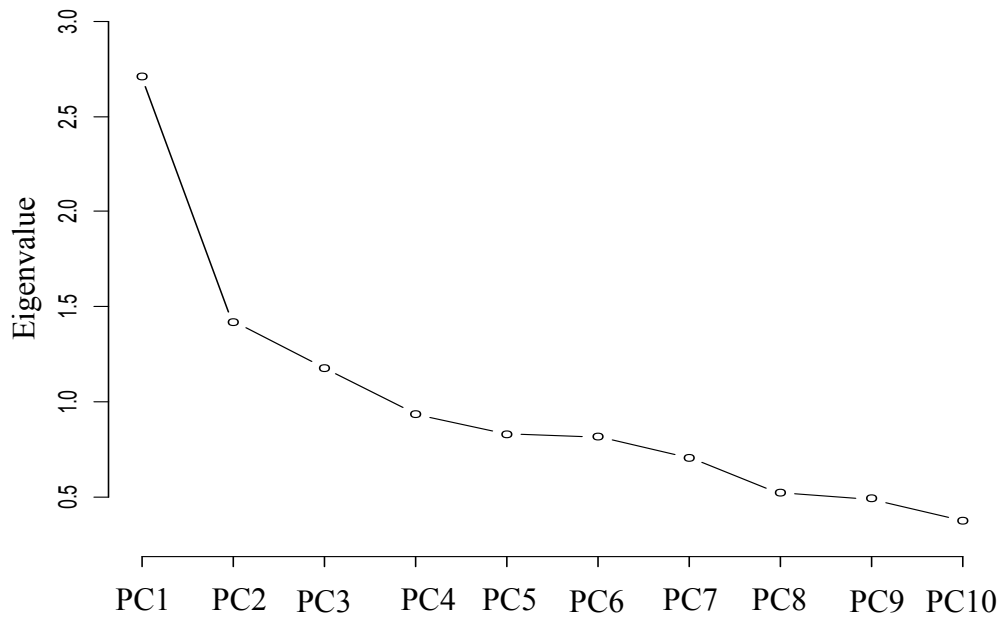


Figure 7.7. Scree plot from principal components analysis of frontal tasks with *g*.

Table 7.6. Principal Components Analysis loadings with *g*

	1 <sup>st</sup> unrotated	Rotated Components		
		PC1	PC2	PC3
<b><i>g</i></b>	<b>.81</b>	<b>.81</b>	.09	.07
<b>Tower Score</b>	<b>.69</b>	<b>.66</b>	.23	-.14
<b>SOPT</b>	<b>-.70</b>	<b>-.73</b>	.18	.01
<b>Faux Pas</b>	<b>.70</b>	<b>.72</b>	-.09	-.01
<b>RL Errors</b>	<b>-.57</b>	<b>-.53</b>	-.26	.15
<b>PE Slowing</b>	<b>.30</b>	.25	<b>.59</b>	<b>.34</b>
<b>Simon Effect</b>	-.16	-.04	<b>-.83</b>	.14
<b>SE Direction</b>	.11	.08	-.08	<b>-.68</b>
<b>Dilemmas MRT (msec)</b>	<b>-.37</b>	<b>-.43</b>	<b>.46</b>	-.06
<b>Dilemmas % Endorsed</b>	-.10	-.04	-.12	<b>.74</b>
<b>Eigenvalue</b>	2.71	2.68	1.43	1.19
<b>Explained Variance (%)</b>	27	27	14	12
<b>Cumulative Proportion</b>	-	27	41	53

Loadings >.3 are shown in bold. SOPT: Self-ordered pointing task, RL: Reversal Learning, PE: post-error, SE: Simon Effect, MRT: mean reaction time.

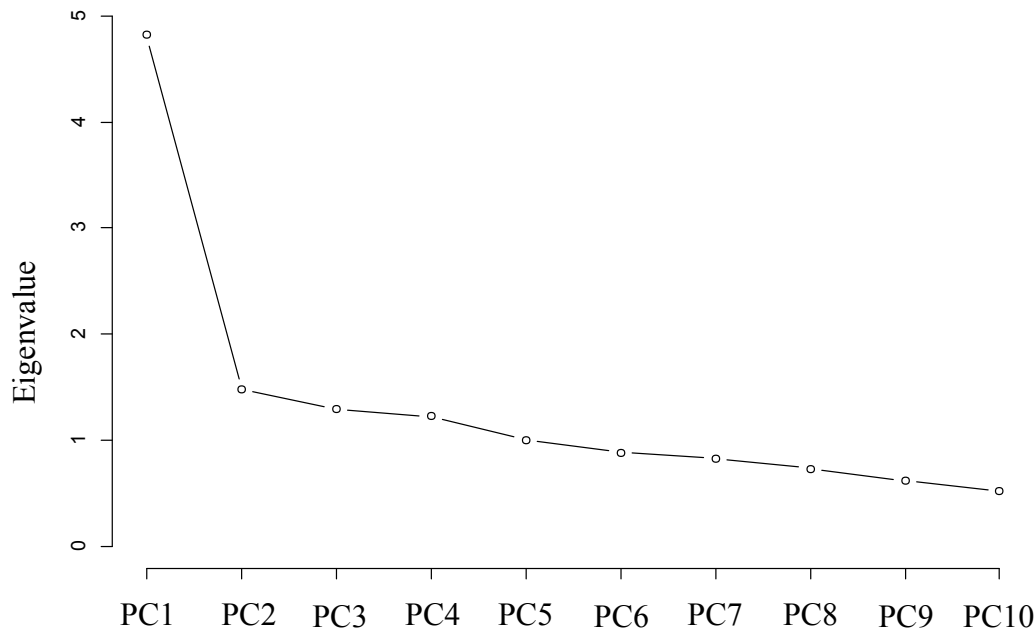


Figure 7.8. Scree plot from principal components analysis of frontal tasks with g.

Table 7.7. Principal Components Analysis loadings with tests comprising g

	1 <sup>st</sup> unrotated	Rotated Components		
		PC1	PC2	PC3
Digit Symbol	<b>.76</b>	<b>.76</b>	.17	.07
Digit Span Backwards	<b>.80</b>	<b>.81</b>	.17	.09
Block Design	<b>.65</b>	<b>.65</b>	-.07	-.19
Letter-Number Seq.	<b>.79</b>	<b>.79</b>	.28	.14
Matrix Reasoning	<b>.68</b>	<b>.60</b>	.14	<b>-.55</b>
Symbol Search	<b>.73</b>	<b>.77</b>	-.06	.06
Tower Score	<b>.63</b>	<b>.57</b>	.27	-.20
SOPT	<b>-.64</b>	<b>-.65</b>	.17	.22
Faux Pas	<b>.62</b>	<b>.59</b>	-.05	<b>-.32</b>
RL Errors	<b>-.52</b>	<b>-.34</b>	-.29	<b>.30</b>
PE Slowing	.27	.21	<b>.65</b>	<b>.32</b>
Simon Effect	-.15	.02	<b>-.80</b>	.23
SE Direction	.06	.06	.03	.01
Dilemmas MRT (msec)	<b>-.32</b>	<b>-.43</b>	<b>.36</b>	-.29
Dilemmas % Endorsed	-.04	.06	.00	<b>.72</b>
Eigenvalue	4.84	4.67	1.55	1.41
Explained Variance (%)	32.26	31.14	10.31	9.41
Cumulative Proportion		31.14	41.46	50.86

Loadings >.3 are shown in bold. SOPT: Self-ordered pointing task, RL: Reversal Learning, PE: post-error, SE: Simon Effect, MRT: mean reaction time.

## 7.4 Discussion

### *Frontal Lobe Test Correlations*

This study aimed to determine how much variance in cognitive performance on tests thought to tap specific regions of the frontal lobe can also be accounted for by the latent measures of cognitive ability. Measures of performance on the frontal tests each exhibit acceptable internal consistency, and the performance of participants was not systematically affected by the order in which tests were presented. As predicted, both DLPFC tasks correlated with each other, as did both OFC tasks; this is partially consistent with the hypothesis that they are sensitive to the functioning of the same frontal sub-regions. Likewise, there was a trend-level relationship between the congruency effect of the Simon Task and the mean RT for the Dilemmas task. However, there was also a significant proportion of shared variance between tasks for different regions. Given the dense interconnectivity between frontal sub-regions, and the fact that performance on any single task is not contingent upon one brain region alone, this is not entirely unexpected. For example, shared variance between the Dilemmas and FP task is unsurprising, as there is dense reciprocal connectivity between OFC and vACC (Beckmann et al., 2009). By the same token, the correlation between the Simon Effect and Tower score was predicted, given that Beckmann and colleagues also showed preferential connectivity between dACC and lateral frontal cortex. The authors also identify connections between the dACC and OFC (albeit far weaker than the dACC-DLPFC and vACC-OFC links), which could partially explain correlations between two putative dACC measures (PES and the Simon Effect) with an OFC task (total Reversal Learning errors). Nevertheless, the fact that correlations

between tests of different regions were of similar or greater magnitude than those relationships within regions does not readily fit with the position that these tasks exhibit the same sub-regional sensitivity in ageing as they might amongst lesion patients or young participants during fMRI.

Our analysis also aimed to parse these contributions apart and examine whether our sub-regional tests share unique variance (above that accounted for by relations with tests of other regions) that might reflect the functioning of the target ROI. The OFC tasks still appeared to share some common variance (albeit a trend towards significance) when SOPT score was controlled for, but this was not the case when Tower score was the covariate. The DLPFC tasks still shared a significant relationship when controlling for either OFC task. The two covarying ACC measures (the Simon Effect and the Dilemmas MRT) did not share associations with any other frontal test. Therefore, it appears that whilst OFC and DLPFC test scores share a common core (also evidenced in their high loadings on the principal component), some variance in the frontal tests may also be attributable to the functioning of a specific ROI or mutual network. This is in line with neuropsychological evidence, but further work could ideally test this with integrity measures of sub-regional cortical and connective integrity, with functional neuroimaging.

#### *7.4.1 Neuropsychological Test Scores and g*

The general factor of cognitive ability shared a common core with the majority of frontal tests. We had predicted that DLPFC and the dACC task would show the strongest correlations with *g*, given their hypothesised overlap with the *g* network.

As predicted, DLPFC tasks correlated highly with *g*, consistent with the implication of this ROI in both types of performance. Equally, the OFC tasks and mean reaction time for the Dilemmas task tended to show smaller correlations with *g* than DLPFC tasks, also consistent with the study's hypotheses. However, the correlation between *g* and post-error slowing on the Simon Task was of a significantly smaller magnitude than those between *g* and DLPFC test scores.

Although *g* correlated with the mean decision-making time in the Dilemmas task, and there was a trend towards significance with PES on the Simon Task, relationships between *g* and the other three ACC measures were absent. Given the consistent nature of the manifold effect reported in previous literature, it was unexpected to find tests that show no significant loading on *g*. It is possible that they quantify robustly unique cognitive abilities, and a recently-published study corroborates the finding that PES does not load heavily on general cognitive ability (WASI verbal IQ  $r=.08$ , *ns*; performance IQ  $r=.08$ , *ns*; full scale IQ  $r=.08$ , *ns*; Fjell et al., 2012). Yet, for the congruency effect of the Simon task, previous literature suggests that variables derived from SRC-type tasks do show associations with *g*. For example, the effects of age on the Stroop effect<sup>38</sup> correlated with reasoning and processing speed in a large sample size ( $n=681$ ; Salthouse, 2005) and full-scale IQ (Crawford et al., 2000). In the present study, the comparable congruency effect (Simon Effect) shows no such correlations, and both the directional Simon Effect and percentage of Dilemma endorsements show very low loadings on both of the first rotated principal components, with or without *g*. It is possible that cross-study comparison is partially confounded by differences in the tests used to derive

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<sup>38</sup> The difference between response times on incongruent versus congruent trial types.

cognitive domain scores. Haier and colleagues (2009) observe that VBM-determined gray matter clusters related to one measure of general intelligence show little overlap with general intelligence as measured using a different test battery. Furthermore, the use of the directional Simon Effect in the current study (reaction times on trials where the contingency changed from incongruent-congruent divided by congruent-incongruent – see methods) was selected due to its reported sensitivity to ACC lesion (Pellegrino et al., 2007). Whilst the congruency effect correlates with two other measures from different tasks, the complete absence of any covariance with any other test for both the directional Simon Effect and the Dilemmas percentage endorsement suggests that these variables should be treated with caution. Comparisons with brain regions and tracts may well offer an additional perspective on this matter, and will be examined in the next chapter.

#### *7.4.2 Neuropsychological Test Scores with Speed and Memory*

The majority of frontal test measures also showed highly significant correlations with the speed and memory components of *g*. By examining correlations between the orthogonal residuals of speed and memory with the frontal test scores revealed that the majority of these associations were due to the variance that speed and memory shared with *g*, with two exceptions:

Firstly, the association of memory with the Faux Pas score maintained a significant association after the removal of *g*, contradicting our assumption that, by making the stories available to participants throughout the test, we would be reducing the memory load. In spite of this, Faux Pas score and memory performance still share

some unique variance, although an examination of precisely which cognitive process or underlying brain regions are common to both is beyond the scope of this chapter. Given that the OFC is not directly implicated in memory processes does suggest that memory ability is an appropriate covariate if OFC-specific contributions to the Faux Pas test are of particular interest to researchers.

Secondly, speed of processing uniquely contributed to the percentage of endorsements in the Dilemmas task – this is difficult to explain, given the total absence of correlations between *g*, and the orthogonal *g*memory or *g*speed. Higher reaction times (measured during the LBC1936 test battery) predict a lower percentage endorsement of the suggested action in the Dilemmas task, and this is not accounted for by *g*, memory, or the amount of time taken to respond during the Dilemmas task itself. Processing speed and moral reasoning intuitively represent opposite ends of the spectrum of consciously-accessible cognition<sup>39</sup>. Thus, not only is such a relationship unexpected, but it is not apparent what this shared variance might reflect. It is possible that it reflects the speed with which multiple representations are able to be integrated – for processing speed: visual cues with motor responses of varying complexity based on task demands, and for Dilemmas: combining personal and public moral incentives for comparison and eventual selection. The mean reaction time for the Dilemmas task itself could be driven by additional factors such as the decision-making process or reflecting on relevant personal experience, once task requirements and relevant information have been integrated, though it unclear why this does not apply to *g*. On the other hand, the fact that (1) this relationship is only a trend, (2) occurred in the context of several other

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<sup>39</sup> Where responses to motor reaction-time tests are rapid and sometimes reflexive, moral reasoning is deliberative and introspective.

simultaneous comparisons, (3) does not show correlations with any other cognitive variable and (4) only loads on the third rotated component of the PCA (with another test with which it does not correlate, and which does not correlate with any other test) may suggest that this association is due to chance.

#### *7.4.3 Unique Frontal Test Performance*

In accord with the previous psychometric literature, *g* accounts for a large proportion of the variance in most of the frontal test variables, reflected in the pattern of loadings on the first rotated component with both frontal tests and *g*. Although some of the remaining variance can be ascribed to measurement error and noise, there is a substantial amount of performance that is still unexplained by general cognitive ability. Whilst the loadings on the second rotated components were predominantly ACC tasks, there were still substantial loadings from Reversal Learning and Tower scores, which is expected given the unique variance these tests share after partialling out *g*. Therefore, although the second component defies categorisation to putative tests of a single frontal sub-region, it explains 14% of the data's variance above *g*.

The underlying assumption in selecting the tests for the frontal lobe battery was that performance is differentially reliant, to some degree, on the functioning of frontal lobe sub-regions. Once the variance common to *g* was partialled out, the relationship between DLPFC tests was no longer significant, in accord with the DLPFC/*g* link. However, this also attenuated the relationship between the two OFC tasks. Although it is tempting to conclude that *g* also relies on the functioning of the



OFC (thus controlling for  $g$  also removes the common variance contributed by this region), there are other possible interpretations of this finding:

- 1)  $g$  does not rely on the OFC, but nor do the OFC tasks.
- 2)  $g$  relies on the OFC, but the OFC tasks do not.
- 3) Variation in the functioning of other regions involved both  $g$  and OFC task performance account for most of the variance in performance, leaving only a small amount of OFC-unique variance ( $\rho = -.13, p = .24$ ) that this study does not have the power to detect.

Options 1&2 may appear redundant, yet the assumption that all tests selected for the current frontal battery are sensitive to age-related alterations in frontal sub-regions deserves further examination. Ageing is generally thought to confer a relatively global decline in brain integrity, in comparison to the immediate and focal aetiologies found amongst frontal lobe patients. It could be that the age-related decline of the brain experienced by our relatively high-functioning, healthy, self-selecting cohort is not sufficiently severe (and sub-regionally focal) to elicit the relatively distinct patterns of behaviour seen in lesion patients. Similarly, individual differences in susceptibility and exposure to risk factors over the life course confer decrements to different (non-frontal) foci which are also involved in task performance. It is also possible that there are age-related changes to the organization and composition of functional networks used for a cognitive task when compared to younger participants (e.g. Park & Reuter-Lorenz, 2009). As a result it is conceivable that individual differences in cognitive scores are driven by age-related changes to other (non-frontal) parts of functionally relevant networks, or age-related re-organisation of those networks. Moreover, tests of complex cognition could also

reflect multiple cognitive processes related to various frontal regions which are differentially affected by age (for example, the dorsolateral prefrontal theory of ageing; MacPherson et al., 2002). This could explain the apparent tension between the findings of Roca et al., (2010), who found that Faux Pas scores in lesion patients (aged 27-69) were not entirely explained by *g*, and the results of the current study.

The only relationship amongst the frontal tests to remain significant after controlling for *g* was between one DLPFC test (Tower) and one OFC test (Reversal Learning). Although not consistent with the hypothesis that tests within regions should show stronger internal correlations than with tests of other ROIs, the cooperation of both regions to successful decision-making has been emphasised (see introductory chapter). This is also reflected in the sensitivity of some complex decision-making tasks to lesions in both DLPFC and OFC. For example, the Iowa Gambling Task (Bechara, Damasio, Damasio & Anderson, 1994) involves integrating rules and planning to override the desire for immediate rewards in place of longer-term profit, and it has been demonstrated that lesions to both DLPFC and OFC can impair performance on this task (Fellows & Farah, 2005; MacPherson et al., 2009; Manes et al., 2002). The intralobar connectivity between these regions is well-studied both post-mortem (Catani & Stuss, 2012; Jacob translated in Theodoridou & Triarhou, 2012; Meynert, 1885) and more recently *in vivo* using DTI (Catani et al., 2012). However, no study has yet examined the integrity of frontal lobe interconnectivity in the context of such frontal lobe tests. It is possible that the shared unique variance between the Tower and Reversal Learning tests, over and above that accounted for by *g* represents such an integrative capacity. Further work is planned to examine this, by using the manually-traced frontal lobe maps created

during this thesis to guide tract-based measurement of sub-regional interconnectivity. In the meantime, the neural correlates of the derived principal component scores will be examined in the following chapter by correlating them with frontal lobe sub-regions.

## Chapter 8: The Neural Correlates of Cognitive Performance in Old Age

### 8.1 Introduction

The previous results chapter discussed the relevance of the brain's frontal lobes in both differential psychology and cognitive neuropsychology. The network hypothesised to underlie general intelligence (*g*) comprises dorsolateral and dorsomedial/cingulate areas of the frontal lobe (e.g. Duncan et al., 2010), as well as the arcuate fasciculus (Jung & Haier, 2007). Functional neuroimaging studies suggest that these cortical regions are involved in reasoning, planning and monitoring behaviours. Moreover, lesions to these brain areas affect performance on tasks thought to tap these cognitive functions - such as the Tower, Self-Ordered Pointing or Simon task - when compared to control participants, or individuals with lesions to other areas of the frontal lobe (discussed in Chapter 2). Orbital and ventral cingulate parts of the frontal lobe are not thought to make major contributions to *g*, but are heavily implicated in cognitive abilities that involve the processing of reward and emotional information by functional imaging and lesion studies, suggesting that the Faux Pas and Reversal Learning and Dilemmas tasks appear sensitive to the functioning of these brain areas.

The findings from the previous chapter suggest that individual differences in performance on tasks aimed at tapping dorsolateral prefrontal (DLPFC) and orbitofrontal cortex (OFC) function shared significant overlap with general intelligence (*g*), but not with putative dorsal or ventral cingulate measures. This led

to a re-evaluation of assumptions about the underlying neural correlates of these tasks in old age. Though the selected cognitive tests show some sensitivity to lesions to frontal lobe sub-regions, or elicit particular patterns of activity amongst (predominantly young) healthy participants during functional imaging, it is unclear how individual differences in performance relate to structural differences in old age. Lesions represent a very different mechanism of cerebral change to that experienced with advancing years, and neuroimaging participants in whom BOLD activity patterns are reported tend to be many decades younger than those in the current study. Thus, inferences regarding the overlapping neural bases of these tests using cognitive scores alone, should be made cautiously. This chapter will therefore investigate the relationship between cognitive scores and structural brain measures in this cohort.

#### *8.1.1 Brain Volumes and Cognitive Functioning*

Testing the relationships between structure and function is also of key importance to the overarching hypothesis of this thesis: associations between cortisol levels and cognitive performance will be partially explained by the relationship between cortisol and structure. Such a finding would be consistent with the glucocorticoid hypothesis of ageing (Landfield et al., 2007), and it is therefore necessary to identify how individual differences in cognition relate to variance in brain structure. The putative fronto-cortical correlates of our selected tests have been discussed in previous chapters (Chapters 2 and 7). Consistent with this literature, it is hypothesised that the strongest relationships between structure and function will exist between the following tests and structures:

Dorsolateral	-	Tower Test, Self-Ordered Pointing Task (SOPT), <i>g</i>
Orbitofrontal	-	Reversal Learning, Faux Pas Test
ACC	-	Simon Task & <i>g</i> (dorsal), Dilemmas Task (ventral)
Frontal Pole	-	<i>g</i>

In addition to the cognitive tests introduced thus far, memory performance is of considerable interest in the study of GC effects on cognition with age, and there have been some findings in the human ageing literature that increased diurnal cortisol output and a flatter diurnal rhythm tend to relate to poorer memory function amongst older individuals (e.g. Comijs et al., 2010; Evans et al., 2011; Lee et al., 2007) although most studies report no relationship between higher GCs and reduced hippocampal volume in the healthy elderly (e.g. Gold et al., 2005; Kremen et al., 2010a; MacLulich et al., 2005, 2012). The hippocampus is a structure heavily implicated in memory functioning (van Petten, 2004), though it is important to note that this region is only one part of a large-scale brain network that is thought to facilitate learning and recall. Specifically, lesion studies and neuroimaging have implicated the bilateral hippocampus, supramarginal gyrus, middle temporal gyrus and left lateral prefrontal cortex in memory encoding and retrieval (Allen, Tranel, Bruss, & Damasio, 2006; Buchsbaum, Padmanabhan, & Berman, 2011; Cabeza & Nyberg, 2000; Cabeza, Dolcos, Graham, & Nyberg, 2002; Morcom, Good, Frackowiak, & Rugg, 2003; Scoville & Milner, 1957; Squire, 2009; Vallar & Baddeley, 1984; Warrington & Shallice, 1969). It is possible that GCs may affect memory performance via effects on other parts of this network.

Distinctions are made in the literature between the neural substrates for immediate recall or working memory (WM) and those for long-term memory (LTM) ability. For example, whereas hippocampal fMRI activation is present during both WM<sup>40</sup> and LTM tasks, left dorsolateral areas appear more active during WM than LTM, and left ACC regions show more activation during LTM than WM (Cabeza et al., 2002). Some human lesion cases exhibit intact WM but impaired LTM (Corkin, 2002), or the converse (Vallar & Baddeley, 1984; Warrington & Shallice, 1969). This distinction may also be reflected in the GC literature, as delayed and immediate verbal memory recall sometimes show contrasting associations for different cortisol measures (Li et al., 2006; Lupien et al., 1994; 1997; 1998; Seeman et al., 1997) but not in all cases (Coluccia et al., 2008; Comijs et al., 2010; Gerritsen et al., 2009; Kuningas et al., 2007; Lee et al., 2007).

Measures of immediate and delayed memory recall are also used here to identify neural correlates for prospective mediation analysis in line with the overall research question of this thesis. Based on the data reviewed above, it is hypothesised that both immediate and delayed recall will positively correlate with bilateral hippocampal volumes, and left lateral (DLPFC and IFG) volumes. In addition, delayed verbal recall ability is expected correlate positively with the volume of the anterior cingulate cortex.

Finally, the three rotated components derived from principal components analysis in the previous chapter (Table 7.6 and Figure 7.7) were extracted and their

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<sup>40</sup> That is, WM tasks where the interval is relatively long (e.g. 12 seconds in the task used by Cabeza & Nyberg, 2002). Shorter interval (a few seconds) WM tasks appear to show no discernible impairment following hippocampal lesion (e.g. Cave & Squire, 1992) or fMRI activity (Cabeza & Nyberg, 2000). The longer interval pattern is more similar to the immediate recall condition for both logical memory and verbal paired associates and so it is possible that the hippocampus is involved in both LTM and longer-delay WM tasks.

correlations with brain structure examined. As discussed in the previous chapter, and also observed by Rabbitt (2011), our inferences about the functional relatedness of cognitive measures should not be based purely on associations between behavioural measures and their bases in cognitive theory. Rather, investigating their biological basis may offer an additional framework to inform our understanding of their statistically obtained components of covariance in old age.

### *8.1.2 White Matter and Cognitive Functioning – General White Matter*

#### *Characteristics*

Our understanding of how white matter connectivity relates to function (and therefore the cognitive implications of age-related connective decline) is limited. Diffusion tensor imaging (DTI) has allowed the quantification of markers that are thought to represent tract integrity, allowing the study of tracts *in vivo*. Individual differences in tract integrity (and change over time) have therefore been adopted as a useful method for understanding possible functional roles of white matter tracts. The normal ageing process is accompanied by a pattern of anterior>posterior decrease in white matter integrity, based on DTI parameters (Head et al., 2004; Sullivan & Pfefferbaum, 2006; Zahr, Rohlfsing, Pfefferbaum, & Sullivan, 2009). A general slowing of processing speed with increasing age is a well-documented phenomenon, and is thought to represent the general degradation of white matter fibres which allow efficient integration and processing amongst distributed neural networks (Deary, Penke, & Johnson, 2010; Neubauer & Fink, 2009; Penke et al., 2012; Salthouse, 1996). Furthermore, specific tracts connecting to frontal areas such as the cingulum, uncinate, arcuate fasciculi, anterior thalamic radiation and inferior



longitudinal fasciculus show age-related increases in diffusivity and declines in anisotropy (Westlye et al., 2010). Corpus callosum integrity declines with age, as measured using DTI (Head et al., 2004;(Head et al., 2004; Madden et al., 2009; Sullivan, Adalsteinsson & Pfefferbaum, 2006) .

However, studies examining the possible functional implications of such changes remain relatively rare. With respect to domains of cognitive ability, Grieve and colleagues (2007) compared white matter FA at the lobar level with performance on tasks such as the ‘Executive Maze’ (a path-finding test) and four-choice reaction time in 87 participants (aged 20-73 years). They showed that statistically significant associations between scores on the two tasks and frontal lobe FA were partially attenuated by controlling for age<sup>41</sup>. Individual differences in general tract integrity appear to facilitate general intelligence via fast, efficient information integration in 420 members of the LBC1936 (Penke et al., 2012), but tract-specific roles in age-related cognitive decline are still relatively under-explored.

### *8.1.3 White Matter and Cognitive Functioning – Tract-Specific Characteristics*

Though diffusion measures of different tracts tend to be highly correlated (Penke et al., 2012), their distinct connectivity profiles mean that different tracts are likely to preferentially support some cognitive processes over others. Connective pathways between frontal and posterior brain regions such as the arcuate fasciculus have been assumed to play a central role in processes related to general intelligence (Jung &

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<sup>41</sup> A voxel-wise analysis revealed white matter clusters predominantly in the dorsal white matter of the frontal lobes, although given that the analysis took place in standard space, their power to detect the significance of gyral white matter (where individual differences in morphology provide difficulties for accurate registration) is diminished.

Haier, 2007), but arcuate integrity showed no correlations with intelligence in a subsample of the LBC1936 (Penke et al., 2010). Rather, better integrity of callosal tracts (which facilitate inter-hemispheric transfer) correlate with higher *g* (Penke et al., 2010) and faster processing speed (Madden et al., 2004) in old age. Moreover, memory recall in ageing brains is also related to the corpus callosum (de Chastelaine, Wang, Minton, Muftuler, & Rugg, 2011), and the fornix<sup>42</sup> (Metzler-Baddeley, Jones, Belaroussi, Aggleton & Sullivan, 2011), which connects the hippocampus to the prefrontal cortex (Catani & Thiebaut de Schotten, 2008; Poletti & Creswell, 1977).

With respect to tract-specific involvement on frontal-type tasks, the data are also scarce. Examining the fornix, uncinate fasciculus and posterior cingulum bundle, Metzler-Baddeley et al. (2011) found no associations between these tracts and performance on the D-KEFS Tower or Stroop tests. This finding is unsurprising given that the uncinate and posterior cingulum are not primarily linked to the brain regions thought to be responsible for task performance. This is corroborated by the finding that a measure of executive functioning (a latent variable comprising Stroop and Go-NoGo performance) correlated with the integrity of the clusters in the arcuate fasciculus (Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2012). Zahr and colleagues (2009) reported that, alongside callosal and fornix integrity, the uncinate and inferior longitudinal fasciculi correlated with PCA factors for working memory and problem solving. However, they did not include a measure of the arcuate fasciculus.

Although there is little evidence to link white matter fibres with congruency effects such as those elicited by tasks such as the Stroop and Simon tasks, there is

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<sup>42</sup> For which there is no measure in the LBC1936.

comparatively strong evidence for a white-matter basis for post-error slowing. Event-related negativity<sup>43</sup> has been related to the integrity of the posterior cingulum (Westlye, Walhovd, Bjørnerud, Due-Tønnessen, & Fjell, 2009). More recently, post-error slowing (PES) during the Ericksen Flanker test was negatively correlated with diffusivity in the arcuate and inferior fronto-occipital fasciculi<sup>44</sup>, corpus callosum and the anterior thalamic radiation (ATR), though not the cingulum bundle in young healthy participants ( $n=255$ ; Fjell, Westlye, Amlie, & Walhovd, 2012). The absence of a relationship between PES and the cingulum bundle is unexpected as the ACC is strongly implicated in this cognitive ability, and is a key facilitator of rapid communication between the cingulate and other brain regions (Fjell et al., 2012). The motoric stimulus-response conflicts during the Simon task are likely to require rapid inter-hemispheric communication in order to identify the relevant behavioural response and then initiate either left or right pre-motor and motor activity – thus the corpus callosum is also a reasonable candidate tract. This is in contrast to the Dilemmas task; the conflict is not motoric or speeded, and therefore it is unlikely that callosal integrity will play a major part in either the deliberation time or the percentage of endorsements themselves.

The ATR is the medial part of the anterior limb of the internal capsule, which carries fibres from the mediodorsal thalamic nuclei to the frontal cortex (Klein et al., 2010, Ray & Price, 1993); the anterior thalamic nucleus receives efferents from the hippocampus (Mitchell, Dairymple, Alford & Christie, 2002). Better integrity of the ATR is associated with better scores in the domains of memory, executive functioning and crystallised intelligence (Mamah et al., 2010). Poorer integrity of

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<sup>43</sup> A response that can be measured by EEG soon after an error (Bernstein, Scheffers & Coles, 1995).

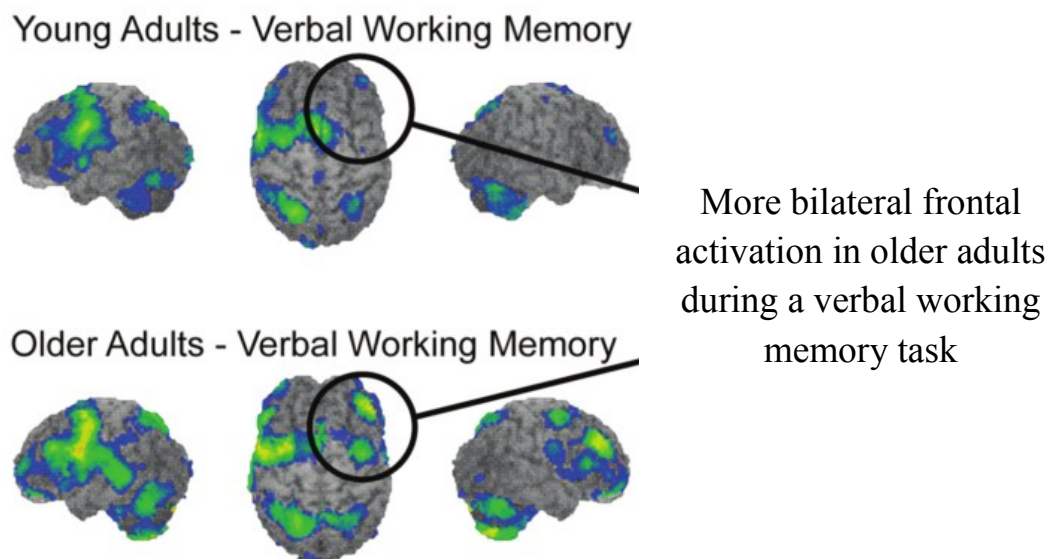
<sup>44</sup> For which there is no measure in the LBC1936.

the ATR and the inferior longitudinal fasciculus (ILF) has been associated with poorer performance on the Trail Making Test part B (Pérez-Iglesias et al., 2010). The implication of the ILF in tests thought to rely on fronto-parietal integration is unusual, given that this tract connects parietal and occipital lobes (Catani et al., 2003, Nolte & Angevine, 1995), and is generally linked to spatial memory and face perception (ffytche & Catani, 2005; Fox, Iaria & Barton, 2008; Ross, 2008). However, Pérez-Iglesias and colleagues used cluster-based analysis; the ILF is difficult to distinguish from other tracts that occupy the same posterior white matter regions such as the inferior front-occipital fasciculus (Catani & de Schotten 2008), it is difficult to infer which tract has been identified in such cases. It should also be noted that the participants used by Mamah et al. (2010) and Pérez-Iglesias et al., (2010) comprised both healthy controls and schizophrenic patients in early middle-age, and so may not be directly generalizable to the current sample.

#### *8.1.4 Cortical De-differentiation in Ageing*

As discussed previously, structural changes in the brain take place with increasing age and are thought to underlie observed cognitive decline. Yet functional imaging studies that compare activation patterns between young and old show that old age is accompanied by “over-recruitment”; that is, greater cortical activation both in those regions engaged by young subjects, and also in a more distributed network of regions (reviewed in Craik & Rose, 2012; Goh, 2011; Park & Reuter-Lorenz, 2009). Some authors have posited that it reflects an attempt to supplement the functioning of a failing network and thus makes a positive compensatory contribution to memory performance (Cabeza, 2002; Park and Reuter-Lorenz, 2009). Others have proposed

that such differences could reflect changes that are detrimental to cognitive performance, either through general breakdown in the functional specialization of the cortex (Li, Brehmer, Shing, Werkle-Bergner & Lindenberger, 2006) or an inability to shut down activity not related to the cognitive task at hand (Logan, Sanders, Snyder, Morris, & Buckner, 2002).



*Figure 8.1.* Increased frontal bilaterality during verbal memory in old age. fMRI images from Reuter-Lorenz et al. (2000). Image adapted from Park & Reuter-Lorenz (2009).

Though there has been little work contrasting BOLD response patterns of young and old for the specific frontal tests selected for the current study, immediate and delayed verbal memory tests have been a specific foci of study. One region that has been shown to exhibit such age-related over-recruitment in verbal memory encoding is the right prefrontal cortex (PFC; Figure 8.1). Activation of the right PFC has been reported in old, but not young participants, in addition to the expected BOLD response in components of the well-characterised memory network (outlined

above) during both immediate (Reuter-Lorenz et al., 2000; Logan et al., 2002) and delayed (Cabeza et al., 2002; Duverne, Motamedinia, & Rugg, 2009; Morcom et al., 2003; de Chastelaine et al., 2011) verbal recall tasks. Moreover, these additional rightward-frontal activations are not necessarily present in every individual within the older group, but are associated with poorer memory performance (Duverne et al., 2009; de Chastelaine et al., 2011; Persson et al., 2006). In other words, the older individuals that tend to perform more poorly on memory encoding tasks are also the members of their age group who exhibit the greatest additional right PFC activity.

This is not intuitively consistent with the view that over-recruitment reflects a compensatory response to a lifetime of accumulated insult to the network shown in young adults to subserve memory processes. One possible interpretation is that of partial compensation (Rossi et al., 2004), which suggests that whatever auxiliary processing is facilitated by this additional activation is not sufficient to fully replicate a normally-functioning network, but would lead to much poorer performance if this alternative cognitive route were not available, though it could also still reflect an inability to direct neural resources to the task at hand (Logan et al., 2002). An examination of the structural underpinnings of memory performance in old age could offer a novel perspective. Using structural MRI measures (cortical volume and tract diffusion parameters) for each component of the large-scale memory network where disruption to one or more regions can disrupt the state of normal parallel processing necessary to support unhindered performance (Bressler & Menon, 2010; Mesulam, 1990) allows a set of predictions to be tested based on the current theories of over-recruitment during verbal memory processing in old age.

On the one hand, the partial compensation hypothesis would predict that poorer integrity of the area providing auxiliary processing (in this case the right frontal lobe) would negatively affect memory functioning. On the other, performance would be reliant on inhibition of right frontal activation and therefore would not positively correlate with auxiliary regions, but would rather depend upon the integrity of the inhibitory pathway through which inhibition is effected. A candidate pathway for facilitating shut-down of right frontal activation is via left lateral PFC inhibitory signals through the corpus callosum (Logan et al., 2002; Persson et al., 2006; Sullivan & Pfeferbaum, 2006); thus an age-related loss of left lateral PFC or callosal integrity could impair transcallosal inhibition, leading to additional right-sided frontal activations (de Chastelaine et al., 2011).

#### *8.1.5 Summary and Aims*

In addition to cross-study differences in the tracts investigated and the methods used to do so, the terminology and underlying tests from which latent variables are created vary between studies. The latent variable approach is an extremely useful technique for identifying tracts and cortical regions that might be common to multiple tasks. Nevertheless, there is little work examining neural correlates in ageing that pertain to specific tasks (although this is often due to the need to minimise the number of comparisons in modest sample sizes; Zahr et al., 2009). To this end, the neural correlates of cognitive performance are assessed in the current chapter. Examining the relationships between variations in brain structure and cognition in a cohort with a narrow age range offers a novel perspective on the possible functional ramifications of age-related brain changes. The results of this analysis are also of

central importance to the overall research question of this thesis that the relationship between cortisol levels and function will be partially mediated via brain structure. In order to identify candidates for such analysis, an understanding of how brain structure and cognitive variables correlate is essential.

A summary of the hypothesised structure-function relationships is shown in Table 8.1. Consistent with the lesion and functional imaging data from patient and healthy adults, it is hypothesised that larger volumes of the DLPFC (which combines lateral superior frontal gyrus and middle frontal gyrus) will correlate most strongly with better performance on the Tower and SOPT task. Larger dACC volume will be related to a larger Simon Effect and greater post-error slowing, larger vACCs with slower and less utilitarian responses on the Dilemmas task, and larger OFC volume with higher scores on the Reversal Learning and Faux Pas tasks. Immediate and delayed memory recall will both exhibit positive relationships with hippocampal volume and left lateral PFC (DLPFC and IFG). Delayed recall will also show correlations with the dorsal and ventral ACC. General cognitive ability will positively correlate with DLPFC, ACC, frontal pole<sup>45</sup>, but not OFC.

Relatively little is still known about the roles of major white matter tracts in cognition, particularly how individual differences in anisotropy and diffusivity in old age might relate to performance on specific frontal lobe tests. However, it is likely that limbic connectivity via the uncinate fasciculus will facilitate the integration of

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<sup>45</sup> Little work has been done on the functioning of the frontal pole apart from Paul Burgess' group. A meta-analysis of functional imaging studies suggests a lateral-medial split (Gilbert et al 2006). Medial areas appear to be involved in tasks that require mentalizing ("attending to one's own mental states or the states of others" pp.932). Lateral areas were involved in working and episodic memory tasks. As there is no medial/lateral split in the current volumetric protocol making directional hypotheses for DLPFC, ACC and OFC –type tasks difficult to test. Furthermore, as stated in the parcellation review, this does not mean that the frontal pole measure should be excluded from structural measurement.



visceral information necessary for performance on the Reversal Learning and Faux Pas tasks. Similarly, the arcuate, inferior longitudinal and cingulum fasciculi are likely to support the integration of fronto-parietal connectivity necessary for the SOPT and Tower tests. The cingulum, callosal fibres will be of particular importance to the variables measured by the Simon and the Dilemmas task. Differentiation between these two tasks could be reflected in the differential involvement of the arcuate (Simon Task) and uncinate (Dilemmas) fasciculi, based on the type of information involved and integration with other related regions. Better integrity of the corpus callosum and ATR will correlate with memory performance, and with *g* (as some memory sub-tests were used to derive it using factor analysis). *g* will correlate with similar tracts to those correlating with the SOPT and Tower tests, given their putative cerebral overlap in the DLPFC. General speed of processing is likely to correlate to general tract integrity, but may also be related to the ACC, given its dense and complex connectivity profile. Finally, the inferior longitudinal fasciculus is included as a control tract. It does not extend to the frontal lobes and therefore is likely to show little relationship to cognitive performance measures in the current study.

There is little evidence on which to base hypotheses of laterality for the structural imaging analysis for numerous tests, as functional imaging work in old age is scarce for specific frontal lobe tests. For memory performance, evidence suggests that dedifferentiation is present in only some older participants (de Chastelaine et al., 2011), but without analogous research for the other tests used in this study, it is impossible to predict what proportion of the current sample might exhibit such a pattern, to what degree, and in which tasks. Nevertheless, given the evidence that

aspects of endocrine regulation may be lateralised (e.g. Czéh et al., 2008) and the need to localise both function and cortisol levels onto brain structure to adequately address the main research question of the thesis, the analysis of brain structure and cognitive functioning is split into left and right in the current chapter.

Finally, an examination of frontal hemispheric laterality during immediate and delayed verbal memory will be conducted, using an *a priori* selection of network components based on the extant literature (DLPFC, IFG, hippocampus and corpus callosum). Consistent with the partial compensation hypothesis, right frontal lobe measures should be correlated with performance on the immediate and delayed verbal memory measures for the low, but not high performers. Further, the correlation between right frontal lobe volume and memory score should be of a significantly greater magnitude in lower, compared to higher performers. Contrary to the hypothesis of inhibitory breakdown, poorer performers will not have significantly smaller left frontal volumes or poorer integrity of the genu of the corpus callosum (contrary to the hypothesis posited by Logan et al., 2002; Persson et al., 2006; Sullivan & Pfeferbaum, 2006). Rather, higher correlations between memory score and right lateral frontal lobe in low-performers will be accompanied by smaller hippocampi, supporting the hypothesis that anterior frontal changes are in response to failing hippocampal function (e.g. Davis, Dennis, Dasellar, Fleck & Cabeza, 2007; Park and Reuter-Lorenz 2009).

*Table 8.1.* Hypothesised relationships between cognitive task score and brain structure.

Cognitive Task	ROI Volume	Tract Integrity
Tower	DLPFC	Arcuate, ATR, Cingulum
SOPT	DLPFC	Arcuate, ATR, Cingulum
Faux Pas	OFC	Uncinate
RL errors	OFC	Uncinate
PES	dACC	Arcuate, CC, Cingulum
Simon Eff	dACC	Arcuate, CC, Cingulum
SE Direction	dACC	Arcuate, CC, Cingulum
Dilem. MRT	vACC	Cingulum, Uncinate
Dilem %End	vACC	Cingulum, Uncinate
<i>g</i>	dACC, DLPFC, FP, HC	Arcuate, ATR, Cingulum
Speed	ACC	all tracts
Immediate	DLPFC, HC	CC, ATR
Delayed	ACC, DLPFC, HC	CC, ATR

Tower: Total Tower score, SOPT: Mean number of repetitions made on the Self-Ordered Pointing Task, Faux Pas: Faux Pas score; RL Errors: total errors on the Reversal Learning Task, PES: Post-Error Slowing during the Simon task, Dilem. MRT: Dilemmas mean reaction time, Dilem. %End: Percentage of Dilemma endorsements, Speed: general speed of processing, Immediate: mean z-score of immediate verbal memory recall, Delayed: mean z-score of delayed verbal memory recall, FP: Frontal pole, dACC: dorsal anterior cingulate, vACC: ventral anterior cingulate, mSFG: medial superior frontal gyrus, MFG: middle frontal gyrus, IFG: inferior frontal gyrus, OFC: orbitofrontal cortex, HC: hippocampus. ATR: anterior thalamic radiation, CC: corpus callosum, ILF: inferior longitudinal fasciculus.

## 8.2 Methods

The variables used in this chapter were volumetric measures of frontal gyri derived from manual parcellation, measures of tract integrity and cognitive test scores.

### 8.2.1 Cognitive Test Scores

Measures of immediate and delayed memory recall were also included in the analysis, given that the association between high cortisol levels and poorer memory functioning is one of the most consistent findings in the human ageing literature (discussed in Chapter 4). Immediate verbal memory was assessed using Logical Memory I and the total initial recall score from the Verbal Paired Associates; both taken from the Weschler Memory Scale III<sup>UK</sup> (WMS-III; Weschler, 1998). Delayed verbal memory was assessed using Logical Memory II and the verbal paired associates (delayed recall score), also from the WMS-III). Highly statistically significant Pearson's correlations between tests for scores of immediate recall [ $r(87) = .56, p < .001$ ] and delayed recall [ $r(87) = .50, p < .001$ ] suggested that the test scores could be combined into two overall measures. Z-scores were created and averaged to yield two scores of memory ability for each participant; one of immediate ( $M = -.01, SD = .09$ ) and one of delayed recall ability ( $M = -.01, SD = .89$ ). One participant did not complete the Verbal Paired Associates test, and so the z-score for logical memory performance was used in place of an average. Full cognitive testing and scoring procedures are detailed in Chapter 5 and Appendix D.

### *8.2.2 Sub-regional Volumes*

Eight manually-traced frontal lobe sub-regions and the hippocampus in each hemisphere were derived from T1 MRI images, and are reported in mm<sup>3</sup>. Details of the development, reproducibility and protocol can be found in Chapters 3 and 5. Signal noise due to movement artefacts was present in the anterior slices of two of the 90 acquired images. The ROI volumes for these images were not included in analysis (as brain matter, meninges, skull and signal noise could not be reliably differentiated). This left 88 T1 images for the following 7 sub-regions per hemisphere: frontal pole (FP), dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), inferior frontal gyrus (IFG), medial superior frontal gyrus (mSFG), dorsal anterior cingulate cortex (dACC) and ventral anterior cingulate cortex (vACC). Automated segmentation of the hippocampi failed in one case, leaving 89 manually-edited hippocampal volumes.

### *8.2.3 DTI Tractography*

Seven tracts of interest were identified using neighbourhood tractography from diffusion tensor imaging (DTI). Fractional anisotropy (FA) and mean diffusivity (MD) are reported measures of water diffusion within these tracts. High FA and low MD are generally considered to represent coherent directional water diffusion within the tracts, and are therefore thought to be useful indices of tract integrity (see Methods). A first wave of examination was conducted as part of the entire LBC1936 protocol by Dr. Mark Bastin (Reader in Medical Physics) and Dr. Susana Muñoz Maniega (Research Fellow) at the Brain Research Imaging Centre, University of

Edinburgh. Tracts affected by partial volume effects of CSF contamination or other measurement confound - such as difficulty identifying the correct tract - were removed from analysis. Tract measures were available for the following seven tracts (numbers in brackets): genu (83) and splenium of the corpus callosum (87), arcuate fasciculus (left: 85, right: 77), anterior thalamic radiation (ATR; left: 73, right: 81), cingulum (left: 85, right: 83), uncinate fasciculus (left: 76, right: 81), and inferior longitudinal fasciculus (ILF; left: 86, right: 86).

#### *8.2.4 Statistical Analysis of Sub-Regional Brain Volumes*

All brain imaging measures were controlled for intracranial volume (ICV; reflecting maximal healthy brain size) in order to account for individual differences in brain size and atrophy. The volume measurement in  $\text{mm}^3$  was entered as the dependent variable in a linear regression with ICV as the independent variable; the resultant unstandardised residuals were used in all further analysis. Outlier ( $\pm 3\text{SD}$ ) and normality checks were performed on the frontal lobe volumes. The object maps of the outlying values were inspected (without knowledge of any other values) to double-check the measurement for error. One marginal outlier for the left orbitofrontal gyri was examined and deemed to be a valid measure, so winsorized.

Measurement of the hippocampus was conducted by Ms. Natalie Royle (Brain Imaging Development Technician, CCACE/ Imaging Research Associate, Brain Research Imaging Centre, University of Edinburgh) using manual editing of automated segmentations (full details in the Methods section). A single marginal outlier was identified in both left and right hippocampi, but these were winsorized

following examination of the object maps by Ms. Royle. All variables showed normal distributions and were also analysed using Pearson's correlations.

#### *8.2.5 Statistical Analysis of DTI Tractography data*

Measures for Fractional Anisotropy (FA) and Mean Diffusivity (MD) for seven major long-range tracts were: genu and splenium of the corpus callosum, arcuate fasciculus, anterior thalamic radiation (ATR), anterior cingulum bundle, uncinate fasciculus and inferior longitudinal fasciculus. These variables were examined for outliers ( $\pm 3$  SDs) and normality in consultation with Drs Bastin and Maniega.

Outliers were examined and removed from both FA and MD measures (as both are derived from the same tract) if they did not represent a valid measure (measurement confounds as above). One outlier was removed for the splenium, left arcuate, left ATR, and two from the left cingulum bundle. Marginal outliers for the FA of the right arcuate and right ATR were checked and were not due to measurement error.

The variables generally showed a normal distribution following log transformations of LATR MD. Single marginal outliers for right arcuate fasciculus FA, and right ATR FA were winsorized. However, both FA and MD of the left ILF, and the MD of the right ILF exhibited non-normal distributions. Correlation coefficients were calculated using Pearson's product-moment for all parametric data, and using Spearman's rank order for all non-parametric comparisons.

#### *8.2.6 High and Low Memory Performance*

The following regions were selected *a priori*, consistent with the previous literature regarding competing theories of age-related over-recruitment during memory performance (de Chastelaine et al., 2011; Duverne et al., 2009): DLPFC, hippocampal and IFG volumes and callosal integrity (genu and splenium). Analysis addressed the hypothesis that poorer memory scores are related to poorer integrity of the right PFC, and that there are no group differences in anterior callosal integrity and LIFG volume. Hierarchical linear regression was used to examine the contribution each region made to the variance in memory performance (mean z-scores of immediate and delayed verbal memory). Regions were entered step-wise into the model based on correlation magnitude (largest first) to establish that each region uniquely explains some variance in the score, consistent with concepts of large-scale brain networks (Bressler & Menon, 2010; Mesulam, 1990).

In the second part of the analysis, participants were split ( $z$ -scores = 0) into high and low performers to examine differences in structural correlates, and to test the hypothesis that low performers showed a significantly larger association between the right PFC volume and memory score than high performers. Variables split by score for immediate and delayed recall showed normal distributions and no outliers ( $\pm 3$  SDs). Group differences in correlation magnitudes were tested using INDEPCOR.EXE (Crawford et al., 1996). Finally, the group means of the structural variables (DLPFC, IFG, callosal integrity and hippocampus) were compared using  $t$ -tests.

#### 8.2.7 Correction for Multiple Comparisons



Due to the large number of comparisons, the one-stage false discovery rate (FDR) method was used in order to control for type I errors (Pike, 2011).

## 8.3 Results

### 8.3.1 Descriptive Statistics

Descriptive statistics and reliability of the cognitive scores are described in Chapter 7. Sub-regional volumes are summarised in Table 8.2, and the fractional anisotropy and mean diffusivity for the different tracts are displayed in Table 8.3 and 8.4 respectively. Figures 8.2 and 8.3 illustrate the variability of the volumetric and tract-based measures respectively.

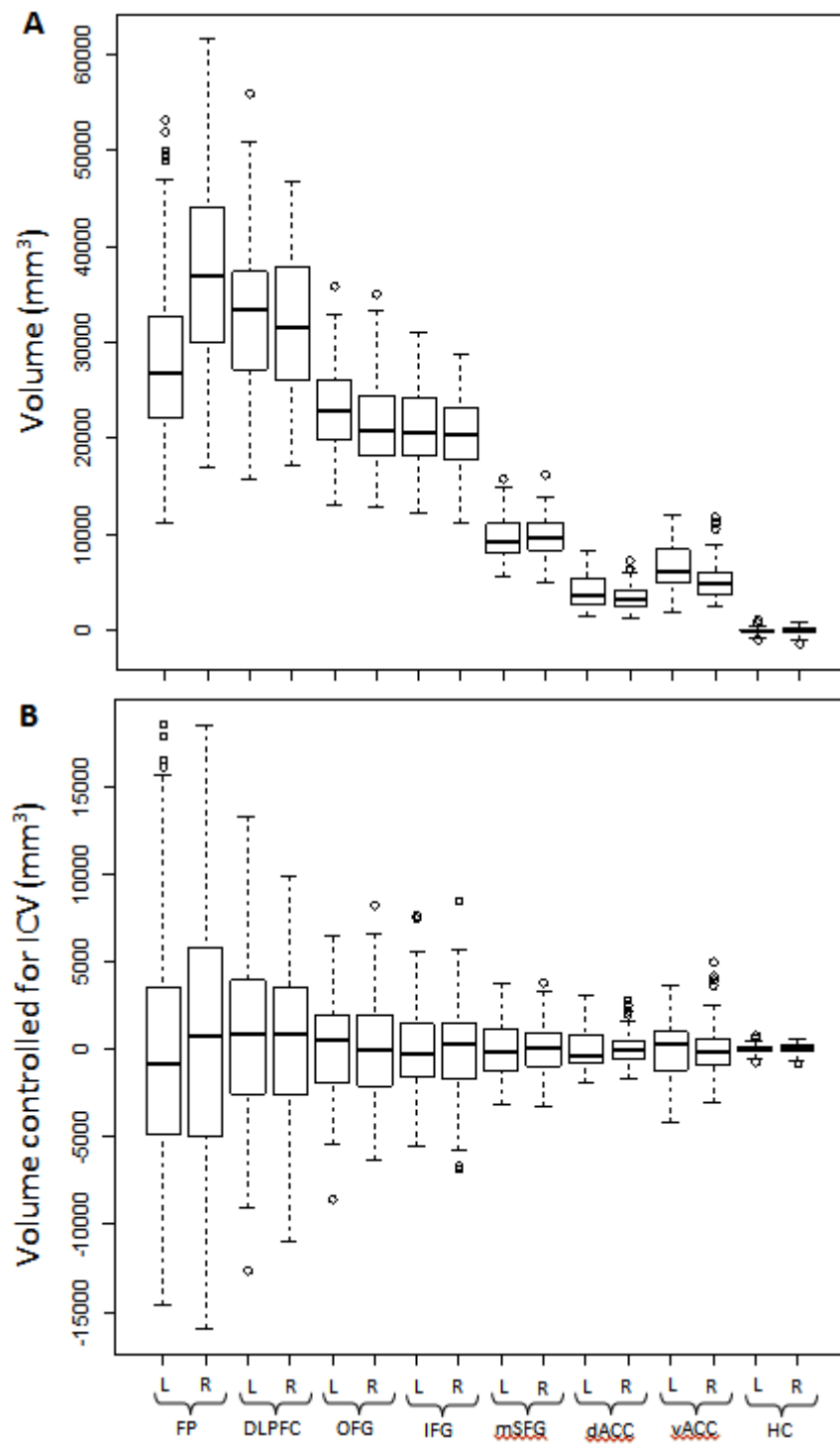
The frontal poles were the largest sub-region, but the dorsal and ventral ACC measures showed the most inter-individual variability, as indexed by a large standard deviation as a percentage of the mean volume. Dorsolateral and frontopolar volumes also showed wide variations, with the orbital, IFG and hippocampal volumes showing the least.

On average, the splenium of the corpus callosum was the tract with the highest fractional anisotropy (FA), and also the highest mean diffusivity (MD) and the arcuate fasciculus tended to have the lowest average MD. In general, the inferior longitudinal, cingulum and callosal fibres showed the most variation between subjects, once the characteristic diffusion of each tract was taken into account.

Table 8.2. Raw volumes of brain sub-regions ( $n = 88$ ).

Region	Side	Mean Volume (mm <sup>3</sup> )	SD	Min	Max	SD % of Volume
<b>Frontal Pole</b>	L	28447	9117	11252	53231	32.05
	R	36775	10182	16844	61623	27.69
<b>Dorsolateral</b>	L	32583	7379	15867	55979	23.65
	R	31820	7073	17230	46866	22.22
<b>Orbitofrontal</b>	L	22854	4754	13087	35911	20.80
	R	21578	4606	12736	35001	21.35
<b>Inferior Frontal</b>	L	21109	3851	12247	31000	18.24
	R	20430	4067	11278	28691	19.91
<b>mSFG</b>	L	9740	2322	5589	15856	23.84
	R	9809	2185	5112	16154	22.28
<b>Dorsal ACC</b>	L	4052	1638	1481	8193	40.42
	R	3490	1259	1377	7277	36.07
<b>Ventral ACC</b>	L	6534	2456	1888	11956	37.59
	R	5188	2003	2499	11879	38.61
<b>Hippocampus</b>	L	3080	392	1985	4347	12.73
	R	3376	412	1918	4398	12.20

mSFG: Medial superior frontal gyrus, ACC: anterior cingulate cortex, L: Left, R: Right.



*Figure 8.2.* Sub-regional volumes (mm<sup>3</sup>) before (A) and after (B) controlling for intracranial volume. FP: Frontal pole, DLPFC: dorsolateral prefrontal cortex, OFG: orbitofrontal gyri, IFG: inferior frontal gyrus, mSFG: medial superior frontal gyrus, ACC: anterior cingulate gyrus, HC: hippocampus.

Table 8.3. Fractional anisotropy of white matter tracts.

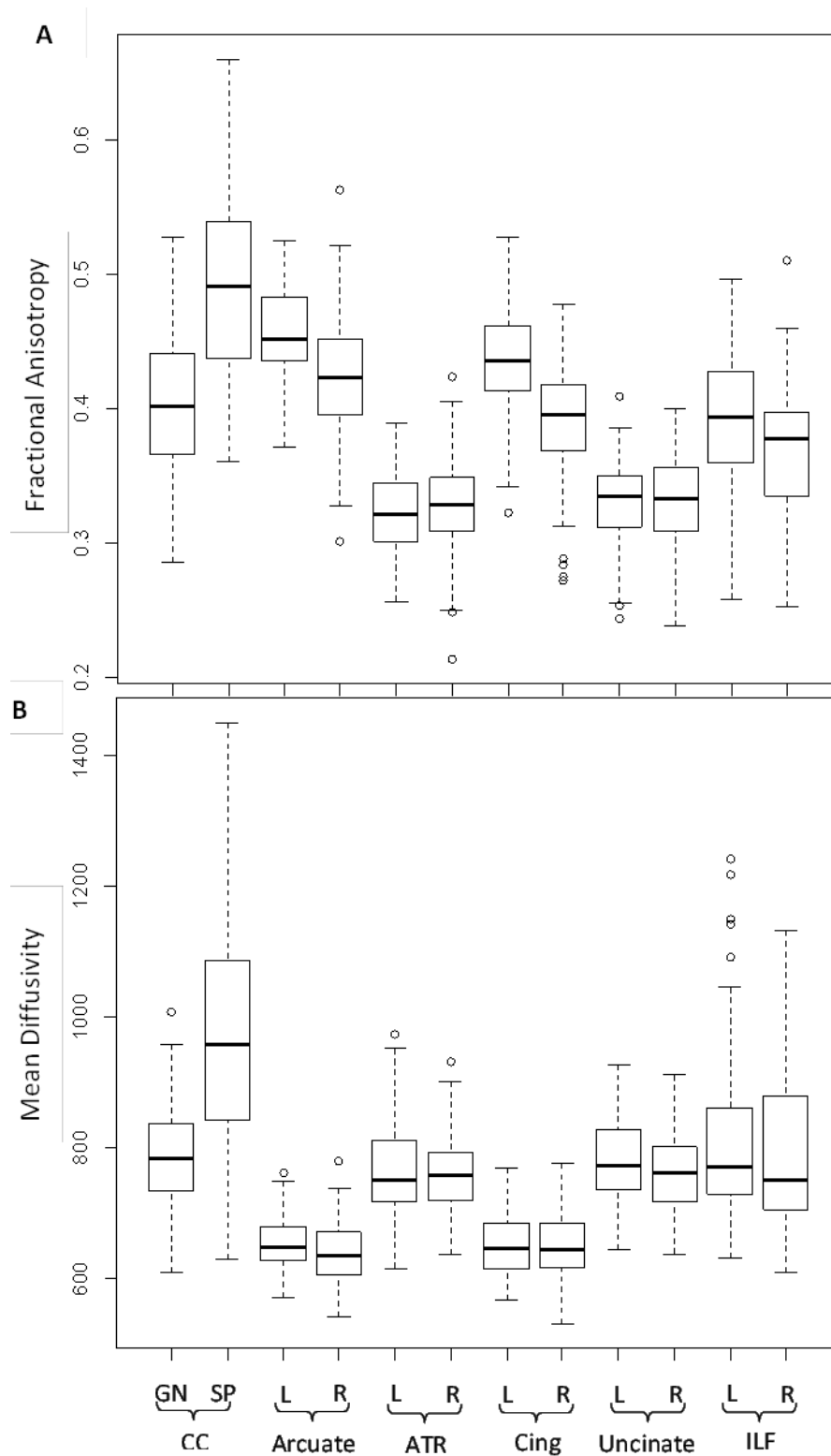
Tract	<i>n</i>	Side	mean FA	SD	Min	Max	SD % of mean FA
<b>Genu</b>	83		.40	.05	.29	.53	12.50
<b>Splenium</b>	86		.49	.07	.36	.66	14.29
<b>Arcuate</b>	84	L	.46	.04	.37	.53	8.70
	77	R	.42	.04	.30	.56	9.52
<b>ATR</b>	72	L	.32	.03	.26	.39	9.38
	81	R	.33	.04	.21	.42	12.12
<b>Cingulum</b>	83	L	.43	.04	.32	.53	9.30
	83	R	.39	.04	.27	.48	10.26
<b>Uncinate</b>	76	L	.33	.03	.24	.41	9.09
	81	R	.33	.03	.24	.40	9.09
<b>ILF</b>	86	L	.39	.05	.26	.50	12.82
	86	R	.37	.05	.25	.51	13.51

ATR: Anterior thalamic radiation, ILF: inferior longitudinal fasciculus, FA: fractional anisotropy, L: left, R: right.

Table 8.4. Mean diffusivity of white matter tracts.

Tract	<i>n</i>	Side	mean MD	SD	Min	Max	SD % of mean MD
<b>Genu</b>	83		786.76	76.32	610.21	1007.43	9.70
<b>Splenium</b>	86		977.17	176.51	630.55	1450.05	18.06
<b>Arcuate</b>	84	L	655.44	39.94	573.04	761.69	6.09
	77	R	642.29	50.60	543.22	780.17	7.88
<b>ATR</b>	72	L	767.44	69.14	616.34	974.40	9.01
	81	R	762.13	62.93	637.33	931.65	8.26
<b>Cingulum</b>	83	L	648.92	46.38	569.11	770.76	7.15
	83	R	653.88	49.40	531.93	776.59	7.55
<b>Uncinate</b>	76	L	780.88	65.45	643.40	927.39	8.38
	81	R	756.19	54.72	637.60	912.33	7.24
<b>ILF</b>	86	L	811.44	125.51	631.91	1240.86	15.47
	86	R	792.60	116.25	610.20	1132.00	14.67

ATR: Anterior thalamic radiation, ILF: inferior longitudinal fasciculus, MD: mean diffusivity, L: left, R: right.



*Figure 8.3.* DTI measures of FA (A) and MD (B) for white matter tracts. GN: genu, SPL: splenium of the corpus callosum, ATR: anterior thalamic radiation, ILF: inferior longitudinal fasciculus.

### 8.3.2 Sub-regional volumes and cognitive performance

Table 8.5 and Figure 8.4 present correlations between regional brain volumes corrected for ICV and cognitive performance (neuropsychological tests scores, g, speed and memory). Overall, significant correlations followed the same expected direction: higher volumes correlated with higher cognitive scores, or fewer errors. A larger left ACC was associated with better performance on the both the Tower test ( $r(86)=.22, p=.043$ ) and SOPT ( $r(84)=-.29, p=.006$ ). Fewer SOPT errors was also associated with larger left vACC ( $r(84)=-.22, p=.043$ ), a trend with the left DLPFC ( $r(84)=-.21, p=.057$ ) and the right hippocampus ( $r(85)=-.25, p=.019$ ). Contrary to our hypothesis, neither left nor right DLPFC volume correlated with performance on the Tower test (a putative DLPFC measure).

Larger left dACC and IFG volumes were also correlated with better scores on the two OFC tasks: the Faux Pas task ( $\rho(86)=.26, p=.016$ ;  $\rho(86)=.22, p=.043$ ) and Reversal Learning (RL;  $\rho(83)=-.26, p=.015$ ;  $\rho(83)=-.23, p=.033$ ). However, a larger left mSFG predicted more RL errors ( $\rho(83)=.25, p=.021$ ). A similar contradiction was evident for post-error slowing (PES), whereby greater slowing was predicted by a larger right frontal pole ( $r(84)=.24, p=.028$ ), but smaller volumes of both right dorsal (trend;  $r(84)=-.19, p=.080$ ) and ventral ( $r(84)=-.31, p=.004$ ) ACC. For the Simon Effect, a smaller right frontal pole predicted a larger difference between congruent and incongruent reaction times ( $r(85)=-.25, p=.017$ ), whereas smaller volumes of all other right-sided frontal regions apart from the mSFG correlated with a smaller Simon Effect. The time taken to arrive at decisions during

the Dilemmas task increased with smaller bilateral dACC (left:  $r(82)=-.23, p=.037$ ; right:  $r(82)=-.26, p=.018$ ) and left DLPFC volumes  $r(82)=-.22, p=.041$ ). The directional Simon Effect and the percentage of actions endorsed in the Dilemmas task showed no significant correlations with any regional volume.

However, the measures of general cognitive ability and verbal memory showed a pattern of correlations with ROI volumes generally consistent with our hypotheses. Larger left DLPFC, left dACC and right hippocampal volumes tended to correlate with higher  $g$ , speed, immediate and delayed verbal memory scores. Left hippocampal volume also showed a significant positive relationship with  $g$  ( $r(87)=.33, p=.001$ ) and speed ( $r(87)=.27, p=.012$ ). However, the left DLPFC correlations showed only a trend toward significance for  $g$  ( $r(86)=.19, p=.080$ ) and immediate recall ( $r(86)=.20, p=.060$ ), and were not significant for speed of processing ( $r(86)=.16, p=.128$ ). The predicted relationship between both verbal memory scores and the left IFG were non-significant. A relationship between larger right mSFG and poorer  $g$  showed a trend towards significance ( $r(86)=-.20, p=.061$ ), but there was no correlation between  $g$  and the frontal pole (although there was a positive non-significant relationship with the right frontal pole;  $r(86)=.18, p=.10$ ).

Table 8.6 and Figure 8.5 show correlations between PC1, PC2 and PC3 derived from principal components analysis in the previous chapter and frontal lobe regional volumes. The neural correlates of the first principal component (PC1) were left DLPFC ( $r(75) = .24, p<.05$ ), left dorsal ACC ( $r(75) = .36, p<.01$ ) and left ventral ACC ( $r(75) = .23, p<.05$ ). PC2 significantly correlated with right DLPFC ( $r(75) = -.41, p<.001$ ), right dorsal ACC ( $r(75) = -.43, p<.0001$ ), right ventral ACC ( $r(75) = -.26, p<.05$ ) and right frontal pole ( $r(75) = .30, p<.05$ ). Post-hoc tests for



lateralisation found that PC1 correlations with the dorsal and ventral ACC were significantly left lateralised ( $t(74) = 3.05, p=.003$ ;  $t(74) = 2.03, p=.046$ ) but the difference between magnitudes for left and right DLPFC was non-significant ( $t(74) = 1.49, p=.141$ ). Correlations between PC2 and brain structure were significantly right-lateralised for the DLPFC ( $t(74) = 2.11, p=.039$ ), dACC ( $t(74) = 3.24, p=.002$ ), vACC ( $t(74) = 2.54, p=.013$ ) and frontal pole ( $t(74) = 2.23, p=.029$ ). PC2 did not correlate with speed of processing, immediate or delayed memory scores (all  $r<.11$ , *ns*). PC3 did not significantly correlate with any frontal regional volumes.

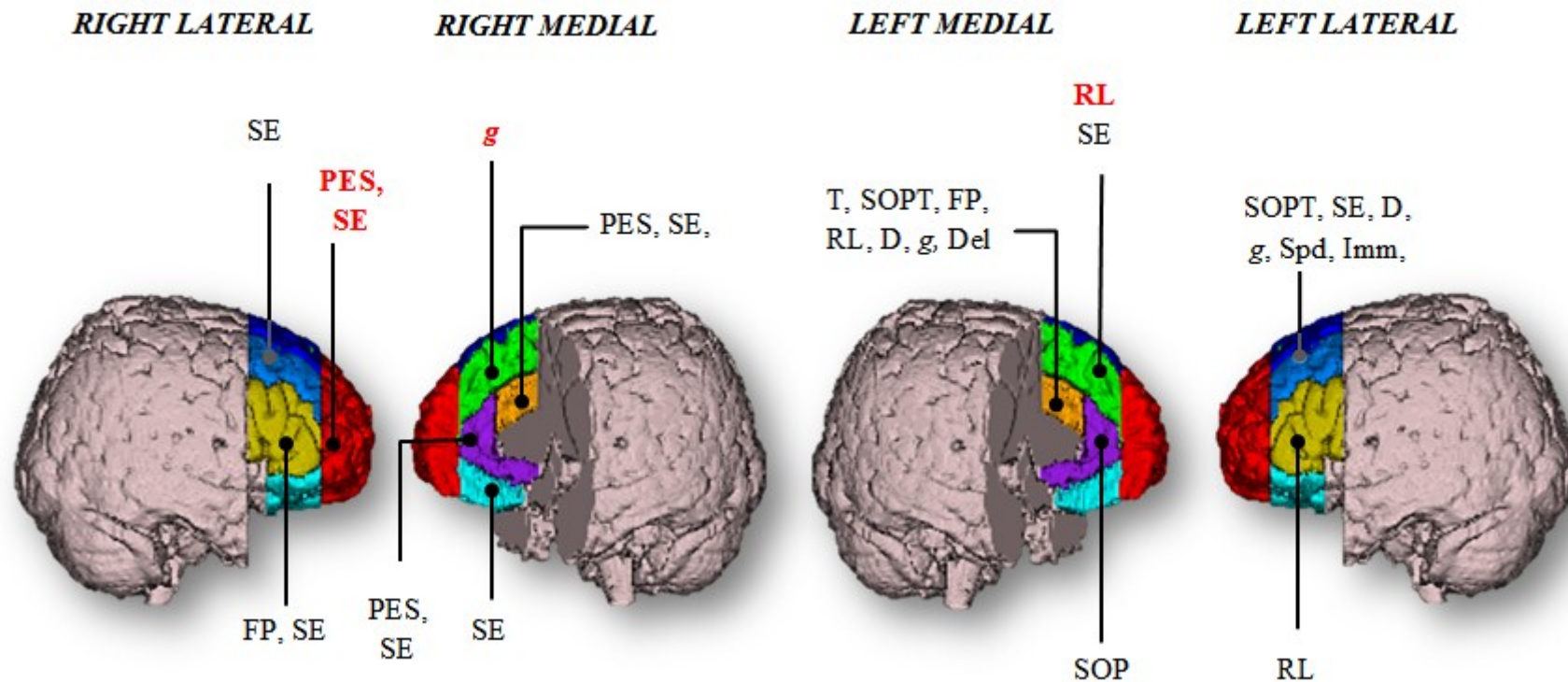
In summary, the two tasks selected for their sensitivity to DLPFC functioning did not strongly correlate with DLPFC regions, and the two tasks sensitive to orbital regions did not correlate with the OFG volumes. Tasks thought to be sensitive to anterior cingulate functioning did, however, correlate with cingulate volumes, although the Dilemmas task correlated with the dorsal and not ventral ACC, which was contrary to predictions. When common components of test score variance are considered, PC1 (which can be considered *g*) correlates strongly with left DLPFC and left ACC and PC2 (orthogonal to PC1) strongly correlates with the right FP, right DLPFC and right ACC. Post-hoc tests of laterality suggest that only the PC1-left DLPFC relationship was not significantly lateralised.

Table 8.5. Correlations between sub-regional volume and cognitive performance.

	FP		dACC		vACC		mSFG		DLPFC		IFG		OFG		HC	
	L <sup>a</sup>	R	L <sup>a</sup>	R <sup>a</sup>	L	R <sup>a</sup>	L	R	L	R	L	R	L	R	L	R
Tower	-.02	.13	<b>.22*</b>	-.04	.11	-.06	-.11	-.05	.10	.04	.13	.13	.02	-.03	.14	.10
SOPT	.17	-.13	<b>-.29**</b>	-.06	<b>-.22*</b>	.10	.08	.12	<b>-.21<sup>†</sup></b>	-.04	-.09	-.11	.04	.03	-.19	<b>-.25*</b>
Faux Pas <sup>◇</sup>	.01	.02	<b>.26*</b>	.08	.07	-.06	-.09	-.12	.19	.12	.13	<b>.22*</b>	.08	.05	.09	<b>.20<sup>†</sup></b>
RL errors <sup>◇</sup>	-.03	-.06	<b>-.26*</b>	.10	-.14	-.11	<b>.25*</b>	.08	.11	.11	<b>-.23*</b>	-.07	.06	.05	-.13	-.13
PES	-.09	<b>.24*</b>	.02	<b>-.19<sup>†</sup></b>	.05	<b>-.31**</b>	.13	.10	.12	-.07	.09	-.05	.18	-.08	.01	-.01
Simon Eff	-.11	<b>-.26*</b>	.11	<b>.37***</b>	-.01	<b>.19<sup>†</sup></b>	<b>.21<sup>†</sup></b>	.15	<b>.24*</b>	<b>.44***</b>	.03	<b>.25*</b>	.15	<b>.22*</b>	.16	-.04
SE Direction	-.08	.09	.13	.01	.11	-.03	.11	-.01	.18	-.06	.15	.13	.08	-.04	.01	-.07
Dilem. MRT	-.12	.01	<b>-.23*</b>	<b>-.26*</b>	-.02	-.06	-.04	-.01	<b>-.22*</b>	-.17	-.12	-.14	.05	-.09	-.04	-.08
Dilem %End	-.05	.13	-.07	.00	-.09	-.13	.09	-.11	.01	.00	-.04	.03	.14	-.09	-.10	-.17
g	-.10	.18	<b>.23*</b>	.01	.11	-.14	-.03	<b>-.20<sup>†</sup></b>	<b>.19<sup>†</sup></b>	-.03	.04	.03	.05	-.10	<b>.29**</b>	<b>.32**</b>
Speed	-.07	.18	<b>.19<sup>†</sup></b>	.00	.09	-.16	-.01	-.12	.16	-.03	.09	.02	.03	-.15	<b>.23*</b>	<b>.27*</b>
Immediate	-.11	.10	.15	-.03	.10	-.06	.00	-.09	<b>.21<sup>†</sup></b>	.02	.03	.11	.05	.10	.14	<b>.26*</b>
Delayed	-.14	.09	<b>.22*</b>	-.04	.13	-.05	.00	-.02	<b>.23*</b>	.07	.10	.16	.08	.09	.17	<b>.25*</b>

Pearson's  $r$  unless  $\diamond$  non-parametric variable (Spearman method used). \*\*\* $p < .001$ , \*\* $p < .01$ , \* $p < .05$ , <sup>†</sup> trend ( $.05 < p < .08$ ), <sup>a</sup> denotes variable is square root transformed.

Tower: D-KEFS Tower score, SOPT: Mean number of repetitions made on the Self-Ordered Pointing Task, Faux Pas: score on the Faux Pas test, RL Errors: total errors on the Reversal Learning Task, PES: Post-Error Slowing during the Simon task, Simon Eff: Simon Effect of congruency, Dilem. MRT: mean Dilemmas task decision time, Dilem. %End: Percentage of Dilemma endorsements, Speed: general factor of processing speed, Immediate: mean z-score of immediate verbal memory, Delayed: mean z-score of delayed verbal memory, FP: Frontal pole, dACC: dorsal anterior cingulate, vACC: ventral anterior cingulate, mSFG: medial superior frontal gyrus, MFG: middle frontal gyrus, IFG: inferior frontal gyrus, OFG: orbitofrontal gyri, HC: hippocampus. Significant and trend findings are shown in bold type-face, italicised results survived FDR correction.

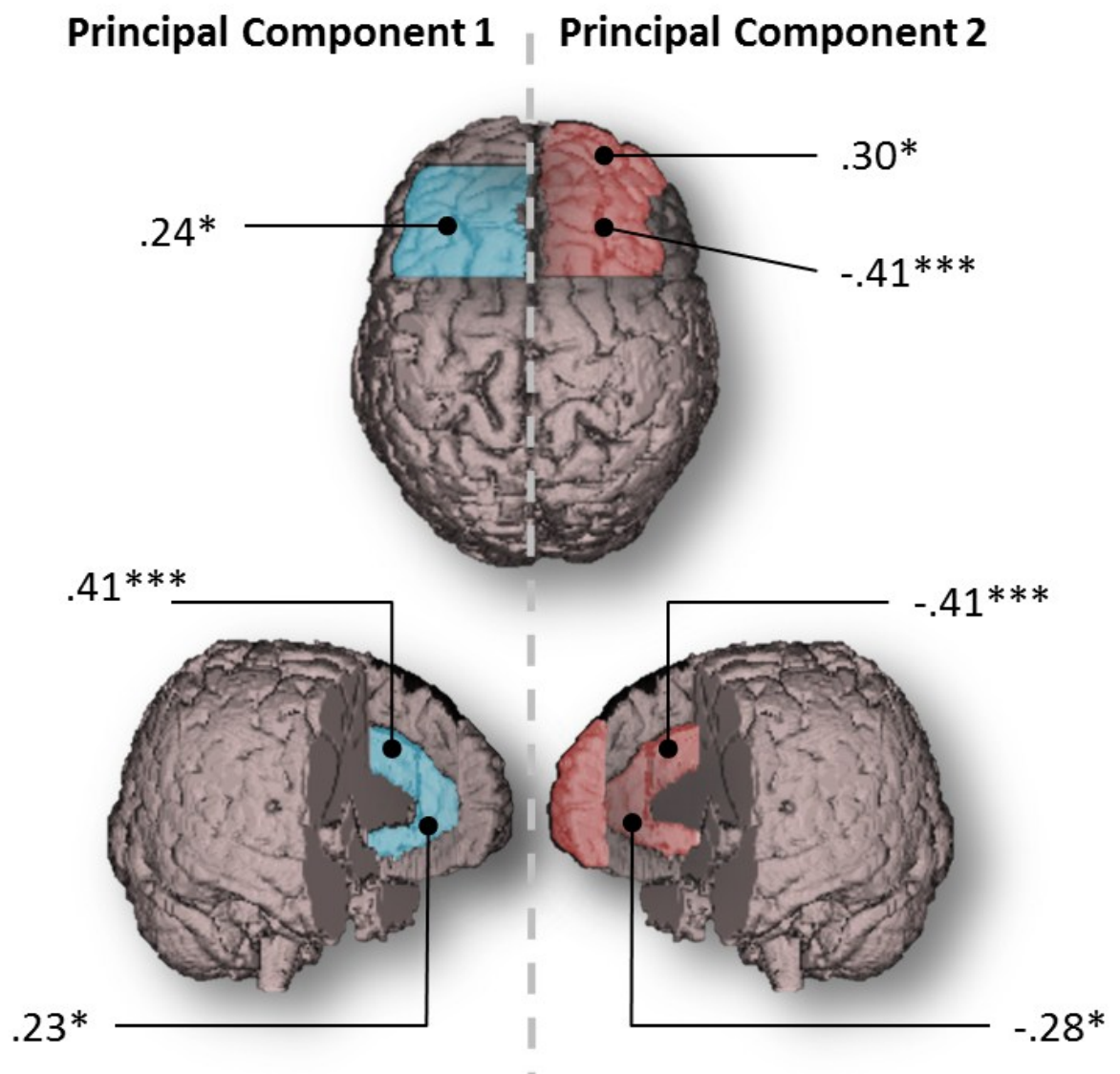


*Figure 8.4.* Correlations between sub-regional frontal volumes and cognitive scores on a 3D rendering of the current parcellation protocol. Red bold text indicates that larger volume predicts worse score. T: tower, SOPT: self-ordered pointing task, PES: post-error slowing, SE: Simon effect, D: dilemmas mean reaction time, *g*: general cognitive ability, Spd: general factor of processing speed, Imm: immediate verbal memory, Del: delayed verbal memory. Blue: dorsolateral prefrontal cortex, yellow: inferior frontal gyrus, red: frontal pole, green: medial superior frontal gyrus, orange: dorsal anterior cingulate, purple: ventral anterior cingulate, cyan: orbitofrontal cortex.

Table 8.6 Correlations between frontal lobe regional volumes and principal components derived from frontal tests and intelligence.

	FP		DLPFC		dACC		vACC		IFG		OFC		mSFG		HC	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
PC1	-.15	.15	<b>.24*</b>	.09	<b>.41***</b>	.07	<b>.23*</b>	-.03	.20	.19	.10	.00	-.12	-.11	.26*	.33**
PC2	-.00	<b>.30*</b>	-.21	<b>-.41***</b>	-.05	<b>-.41***</b>	.04	<b>-.28*</b>	-.04	-.18	.05	-.15	-.20	-.02	-.05	.03
PC3	-.02	.13	.02	.02	-.10	-.05	-.20	-.12	-.08	-.09	.16	-.05	.09	-.03	.01	.00

*Note.* PC = principal component; FP = frontal pole; DLPFC = dorsolateral prefrontal cortex; dACC = dorsal anterior cingulate cortex; vACC = ventral anterior cingulate cortex; IFG = inferior frontal gyrus; OFC = orbitofrontal cortex; mSFG = medial superior frontal gyrus; L = left; R = right. \* $p < .05$ , \*\*\* $p < .001$ . Italicised correlations survived one-stage FDR correction for multiple comparisons.



*Figure 8.5* Correlations between frontal lobe regional volumes and principal components one (blue) and two (red) derived from frontal test scores and *g*. \* $p < .05$ , \*\*\* $p < .001$ .

### 8.3.3 Tract Integrity and Cognitive Performance

The correlations between cognitive scores and tract FA and MD are shown in Tables 8.7 and 8.8 respectively. There were unexpectedly few significant correlations between test scores and FA or MD of the major tracts. Contrary to our hypotheses, measures of the arcuate, cingulum bundles and the ATR did not correlate with scores on the Tower task or SOPT, except for a trend between fewer SOPT errors and higher RATR FA ( $r(77)=-.20, p=.073$ ). Neither uncinate FA nor MD showed significant relationships with Faux Pas task or Reversal Learning scores, in contrast to our predictions. There was an unanticipated significant correlation between lower Reversal Learning errors and better integrity of the left cingulum bundle (FA:  $\rho(78)=.23, p=.037$ ; MD:  $\rho(80)=-.25, p=.025$ ).

However, there was a striking pattern of significant correlations between indices of better tract integrity and a greater sensitivity to errors, as measured by a longer PES during the Simon Task. Higher FA and lower MD of the bilateral arcuate, cingulum, uncinate and the genu of the corpus callosum each correlated with greater post-error slowing. Additional correlations were significant between higher PES and lower MD, but not higher FA, in the bilateral ATR, though there appeared to be a general trend towards higher FA and greater PES for the bilateral ATR.

There were no significant associations between tract integrity and any other ACC measure, though there was a trend for greater congruency effects on the Simon Task with lower FA of the right cingulum bundle ( $r(80)=-.20, p=.077$ ), and for more utilitarian Dilemmas endorsements with lower left uncinate MD ( $r(71)=-.21, p=.080$ ).

Measures of *g*, speed, immediate and delayed memory ability showed significant positive associations with higher FA of corpus callosum splenium. This pattern was also true for the FA of the right ATR, though only only a trend with *g* ( $r(79)=.20, p=.072$ ), and Immediate ( $r(79)=.20, p=.074$ ). These four cognitive tests showed similar patterns of association with MD values of these same tracts, with poorer performance relating to higher MD of splenium and right ATR. In spite of the consistent direction, correlations between speed and splenium MD ( $r(84)=-.16, p=.132$ ) were not significant. There was also a trend for faster speed of processing with better integrity of the left uncinate (FA:  $r(74)=.23, p=.051$ ; MD:  $r(74)=-.22, p=.054$ ) and right cingulum (FA:  $r(81)=.21, p=.055$ ; MD:  $r(81)=-.19, p=.078$ ), and these tracts did not correlate with *g*, Immediate or Delayed.

No tract-cognition associations survived correction for multiple comparisons using FDR.

Table 8.7. Spearman correlations between tract fractional anisotropy and cognitive performance.

	Genu	Splenium	Arcuate		ATR		Cingulum		Uncinate		ILF	
			L	R	L	R	L	R	L	R	L <sup>◇</sup>	R
Tower	.05	.14	.05	.05	-.05	.10	.06	.11	.11	-.03	-.10	.15
SOPT	.04	-.04	.08	.05	-.04	<b>-.20<sup>†</sup></b>	-.05	-.11	.03	.06	.06	.06
Faux Pas <sup>◇</sup>	.09	.11	-.01	-.18	.01	.06	-.05	-.00	-.01	-.04	-.08	<b>-.21<sup>†</sup></b>
RL Errors <sup>◇</sup>	-.08	-.02	-.05	-.03	.09	.08	<b>.23*</b>	.05	-.18	-.03	-.05	.10
PE Slow	<b>.22*</b>	.09	<b>.31**</b>	<b>.30**</b>	.11	.17	<b>.29**</b>	<b>.22*</b>	<b>.33**</b>	<b>.22<sup>†</sup></b>	<b>.27*</b>	.18
Simon Eff	-.16	-.01	.08	-.10	.19	-.15	-.08	<b>-.20<sup>†</sup></b>	-.20	-.08	.01	-.06
SE Direction	.20	.13	.09	.06	.15	-.04	.17	.07	-.03	-.02	.14	-.02
Dil. MRT <sup>a</sup>	.01	.00	.02	-.05	-.01	.09	-.15	.12	.01	.08	.14	.18
Dil. %End.	.04	-.11	-.02	-.08	-.19	.02	-.05	-.08	.14	.08	.17	.14
<i>g</i>	-.03	<b>.32**</b>	-.03	-.05	.02	<b>.20<sup>†</sup></b>	-.01	.00	.09	.03	.02	.01
Speed	.09	<b>.31**</b>	.12	.11	.03	<b>.31**</b>	.19	<b>.21<sup>†</sup></b>	<b>.23<sup>†</sup></b>	.12	.09	.05
Immediate	-.04	<b>.28**</b>	-.01	-.02	.14	<b>.20<sup>†</sup></b>	.06	.10	.11	.06	.04	.06
Delayed	-.01	<b>.32**</b>	.10	.05	.08	<b>.27*</b>	.04	.11	.09	.15	.11	.13

Pearson's *r* shown unless <sup>◇</sup> non-parametric variable (Spearman method used), \*\*\**p*<.001, \*\**p*<.01, \**p*<.05, <sup>†</sup> trend (.05<*p*>.08), bold-face indicates a significant correlation <sup>a</sup> natural log transformed, SOPT: Mean number of repetitions made on the Self-Ordered Pointing Task, RL Errors: total errors on the Reversal Learning Task, PE Slow: Post-Error Slowing during the Simon task, Dilem. MRT: mean Dilemmas task decision time, Dilem. %End: Percentage of Dilemma endorsements, FRONTAL: Second rotated component score from principal components analysis of frontal tests and *g*. ATR: Anterior thalamic radiation, ILF: inferior longitudinal fasciculus.



Table 8.8. Spearman correlations between tract mean diffusivity and cognitive performance.

	Genu	Splenium	Arcuate		ATR		Cingulum		Uncinate		ILF	
			L	R	L <sup>a</sup>	R	L	R	L	R	L <sup>◇</sup>	R <sup>◇</sup>
Tower	-.01	-.09	-.10	-.04	-.05	-.11	.00	-.11	.02	-.01	-.01	-.10
SOPT	-.07	.07	-.12	-.18	.13	.12	-.04	-.07	-.02	-.07	-.12	-.09
Faux Pas <sup>◇</sup>	.02	-.08	-.01	.06	.02	-.07	.05	.00	.03	.05	.03	.09
RL errors <sup>◇</sup>	-.11	-.09	-.18	-.02	.05	-.08	<b>-.25*</b>	-.08	-.04	-.04	.18	.03
PE Slow	<b>-.25*</b>	.04	<b>-.36**</b>	<b>-.36**</b>	<b>-.30**</b>	<b>-.27*</b>	<b>-.30**</b>	<b>-.32**</b>	<b>-.41***</b>	<b>-.23*</b>	-.18	<b>-.20<sup>†</sup></b>
Simon Eff	.07	-.06	-.00	.01	-.07	.15	-.02	.10	.13	.11	-.05	-.15
SE Dir	.03	-.04	-.01	.06	-.10	.06	.06	.09	.06	.06	-.17	.04
Dil. MRT <sup>a</sup>	-.01	-.03	.13	.03	-.04	-.07	.08	.04	.03	-.07	-.03	-.12
Dil %End.	-.08	.17	-.11	-.06	.10	.03	-.16	.03	<b>-.21<sup>†</sup></b>	-.19	-.07	-.04
<i>g</i>	-.08	<b>-.27*</b>	-.01	-.03	-.17	<b>-.29**</b>	-.05	-.09	-.15	-.10	.02	.03
Speed	-.15	-.16	-.16	<b>-.25*</b>	<b>-.28*</b>	<b>-.39***</b>	-.18	<b>-.19<sup>†</sup></b>	<b>-.22<sup>†</sup></b>	-.19	-.13	-.09
Immediate	-.01	<b>-.21<sup>†</sup></b>	-.06	-.01	-.17	<b>-.25*</b>	-.04	-.13	-.13	-.07	.03	-.03
Delayed	.02	<b>-.24*</b>	-.05	-.05	-.14	<b>-.24*</b>	.01	-.07	-.04	-.06	.00	-.03

Pearson's *r* shown unless <sup>◇</sup> non-parametric variable (Spearman method used), \*\*\**p*<.001, \*\**p*<.01, \**p*<.05, <sup>†</sup> trend (.05<*p*>.08), bold-face indicates a significant correlation <sup>a</sup> natural log transformed, SOPT: Mean number of repetitions made on the Self-Ordered Pointing Task, RL Errors: total errors on the Reversal Learning Task, PE Slow: Post-Error Slowing during the Simon task, Dil. MRT: mean Dilemmas task decision time, Dil. %End: Percentage of Dilemma endorsements, FRONTAL: Second rotated component score from principal components analysis of frontal tests and *g*. ATR: Anterior thalamic radiation, ILF: inferior longitudinal fasciculus.

### 8.3.4 High and Low Memory Performance

As reported in Tables 8.6, 8.7 and 8.8, variability in participants' immediate and delayed memory recall are positively correlated with the volume of the right hippocampus, left dorsolateral prefrontal cortex (LDLPFC) and integrity of the splenium of the corpus callosum (CC), although only a trend towards significance exists for the relationship between the LDLPFC and Immediate Recall. When entered into a linear regression, variability in these regions predicted 16% of the variance in Immediate Recall (Table 8.9), and 19% of the variance in Delayed Recall performance (Table 8.10) for the overall sample. Each step-wise iteration showed an increase in  $R^2$  over the previous model.

*Table 8.9. Hierarchical linear regressions for immediate recall in the whole sample*

Covariates	SE	F	df	R <sup>2</sup>	p
+Splenium_FA	.89	7.20	1, 84	.08	.009
+Splenium_FA+ Right Hippocampus	.83	6.37	2, 82	.13	.003
+Splenium_FA+ Right Hippocampus + Left DLPFC	.83	5.16	3, 79	.16	.003

FA: Fractional anisotropy, DLPFC: dorsolateral prefrontal cortex.

*Table 8.10. Hierarchical linear regressions for delayed recall in the whole sample*

Covariates	SE	F	df	R <sup>2</sup>	p
+Splenium_FA	.86	7.56	1, 84	.10	.003
+Splenium_FA+ Right Hippocampus	.81	7.01	2, 82	.15	.001
+Splenium_FA+ Right Hippocampus + Left DLPFC	.80	6.22	3, 79	.19	.0007

FA: Fractional anisotropy, DLPFC: dorsolateral prefrontal cortex.

None of the brain imaging variables were significantly associated with immediate recall performance for the high-performing group, whilst measures of the splenium and bilateral dorsolateral PFC were significantly correlated in the low group. Only right DLPFC volume was a significantly better predictor of performance in the low than the high group on Immediate Recall ( $z = 2.051, p < .05$ ; Table 8.10). Compared to high performers, low performers had significantly smaller right hippocampi ( $t(56.06) = -2.82, p < .01$ ) but not left PFC nor callosal integrity (Table 8.11 and Figure 8.6).

Table 8.11. Neural correlates of high- and low-performing groups immediate recall.

Mean Z-Score	DLPFC		IFG		CC GENU		CC SPLENIUM	
	Left	Right	Left	Right	FA	MD	FA	MD
Immediate Recall HI (log)	0.11	-0.05	0.13	0.13	-0.06	0.10	0.20	-0.11
Immediate Recall LO	<b>0.39*</b>	<b>0.39*</b>	0.15	0.22	0.24	-0.21	0.31 <sup>†</sup>	<b>-0.34*</b>
INDEPCOR z	1.34	<b>2.05*</b>	0.09	0.41	1.30	-1.33	0.52	-1.07

\* $p < .05$ , <sup>†</sup> trend ( $.05 < p < .08$ ), bold-face indicates a significant correlation. HI: high performers ( $z > 0$ ), LO: low performers ( $z < 0$ ), DLPFC: Dorsolateral prefrontal cortex; IFG: inferior frontal gyrus; MFG: middle frontal gyrus; SFG: superior frontal gyrus; CC: corpus callosum.

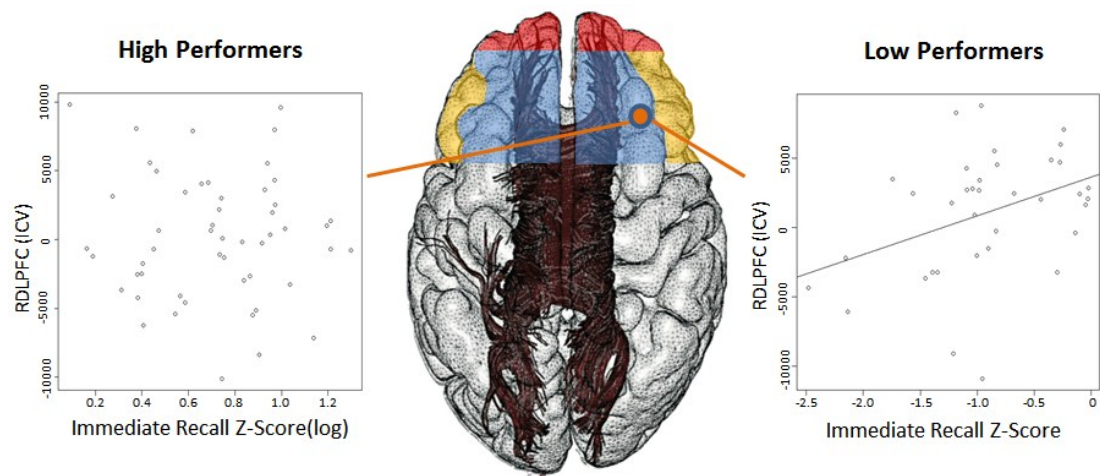


Figure 8.6. Correlations between immediate memory recall and dorsolateral prefrontal volumes (DLPFC) in high ( $z > 0$ ) and low ( $z < 0$ ) performers. Image modified from Catani & de Schotten (2008). Blue: DLPFC, yellow: inferior frontal gyrus, red: frontal pole, brown: corpus callosum.

For delayed memory performance, the right DLPFC was not a significant predictor of performance for the low-scoring group ( $r(34) = .28, p = .099$ ). Right IFG volume and Genu MD both showed significant positive associations with memory scores for the high group, whilst the splenium showed a negative association with performance for the low group (Table 8.12 & Figure 8.7). Whilst no single ROI was a significantly greater predictor of performance for one group than the other, the magnitude of association between right DLPFC volume and delayed memory score appeared larger in the low group compared to the high. Genu MD was a better predictor of performance for the high group at trend levels, and the Splenium MD exhibited the opposite trend. The groups did not differ in terms of the left DLPFC or IFG volume, or measures of callosal integrity, but low performers did have significantly smaller left ( $t(64.65) = -2.10, p < .05$ ) and right hippocampi ( $t(54.65) =$ ,  $p < .01$ ).

Table 8.12. Neural correlates of high- and low-performing groups delayed recall.

Mean Z-Score	DLPFC		IFG		CC GENU		CC SPLENIUM	
	Left	Right	Left	Right	FA	MD	FA	MD
Delayed Recall HI	0.21	0.15	0.15	<b>0.28*</b>	-0.19	<b>0.36**</b>	0.21	-0.11
Delayed Recall LO	0.21	0.28	0.20	0.22	0.03	0.01	<b>0.48**</b>	<b>-0.46**</b>
INDEPCOR z	0.00	0.61	0.23	0.28	0.94	1.55 <sup>†</sup>	1.34	-1.64 <sup>†</sup>

\*\* $p < .01$ , \* $p < .05$ , <sup>†</sup> trend ( $.05 < p < .08$ ), bold-face indicates a significant correlation. HI: high performers ( $z > 0$ ), LO: low performers ( $z < 0$ ), DLPFC: Dorsolateral prefrontal cortex; IFG: inferior frontal gyrus; MFG: middle frontal gyrus; SFG: superior frontal gyrus; CC: corpus callosum.

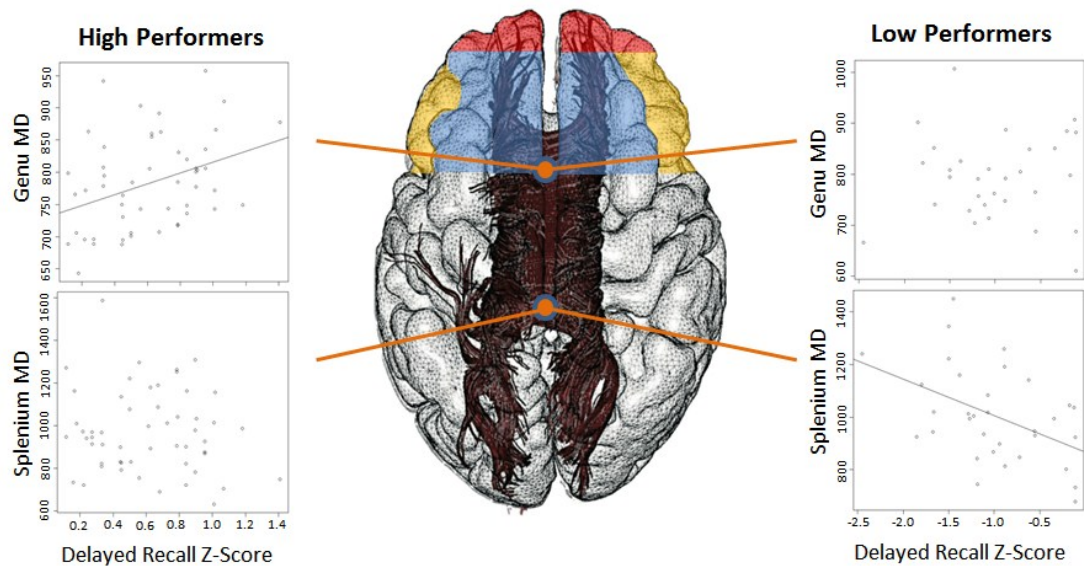


Figure 8.7. Correlations between delayed memory and callosal diffusivity in high ( $z > 0$ ) and low ( $z < 0$ ) performers. Image modified from Catani & de Schotten (2008). Blue: dorsolateral prefrontal cortex, yellow: inferior frontal gyrus, red: frontal pole, brown: corpus callosum.

## 8.4 Discussion

The results presented in this chapter illustrate how regional brain variance is related to individual differences in performance. The structural and cognitive measures allow a detailed and novel insight into the state of this relationship in old age, but also require a large number of comparisons. As previously mentioned, data reduction methods are commonly used in modest sample sizes in order to reduce potential family-wise error from large numbers of comparisons. However, it is possible that this method “*blurs the components that comprise the factors, potentially obscuring relevant correlations between neuropsychological test performance and fiber system metrics*” (Zahr et al, 2009, pp.1060). In this instance, the approach has been to provide a fine-grained and robust structural and functional consideration of the participants’ cognitive abilities, using false-discovery rate (FDR) analysis and biological plausibility to frame the findings of this novel study.

Only the associations between the Simon Effect and the right DLPFC, PCI and left DLPFC and both right DLPFC and ACC with PC2 survived correction for multiple comparisons using FDR. However, this may be overly conservative considering that sub-regional brain volumes and DTI measures are not entirely independent. For example, it is highly likely that the degree of age-related brain atrophy is – at least to some extent – common to multiple brain areas (e.g. some commonality of white matter integrity amongst different tracts in old age; Penke et al., 2012). In addition, the sub-regional boundaries of the frontal lobe ROIs are common to multiple regions such that no single region is entirely spatially independent of any others. Consequently, it is possible that conventional type I error correction, even in the form of FDR, may be overly-conservative because each new

test is not an entirely independent opportunity for type I error (Nyholt, 2001; Ott; 1999). Moreover, tract and cortical analysis have not been previously combined with this battery of tests in ageing participants. Therefore, it is worth interpreting these results in the light of our initial hypotheses and possible biological plausibility, with the caution that should be inherent when considering a preliminary study of relatively limited power.

In the majority of results reported here, selectively smaller ROI volume or poorer tract integrity correlates with poorer cognitive performance. However, neither the volumetric or tract-based correlations with cognitive performance were generally as predicted. The scores from the two putative DLPFC tasks (Tower and SOPT) and OFC tasks (Faux Pas and Reversal Learning) did not strongly correlate with their hypothesised regional volumes. Moreover, the Tower score, the number of SOPT repetitions, the Faux Pas score and the total Reversal Learning errors were not predicted by long-range tract integrity, either in terms of general diffusivity or directional cohesion. One possible interpretation could be that this emphasises the reliance of complex cognition on local, intra-lobar connectivity, but this is discussed below, along with details of the cognitive test scores and their neural correlates.

#### *8.4.1 Neural Correlates of Tower and SOPT Performance*

Performance on the Tower test and SOPT is associated with the DLPFC (Chapter 2). While the SOPT was associated with the left cingulate (ventral and dorsal), and showed a trend correlation with left DLPFC, the Tower test showed only a correlation with the left dACC, but not DLPFC. However, closer examination of the



might also suggest a weak relationship between the Tower score and the left DLPFC ( $r=.10$ ) and left vACC ( $r=.11$ ) which this study lacks the power to detect. Although correlations with the dACC were not entirely unexpected, the weak relationship between these tasks and the DLPFC is difficult to explain. It is noteworthy that the parcellation protocol did not include the entire length of the dorsal frontal gyri, but used a coronal cut-plane at the most anterior appearance of the precentral gyrus. Whilst this protocol is used because 3D surface modelling is not available to enable easy identification of the precentral sulcus, and is intended to exclude mainly premotor areas (Kates et al., 2002), it is possible that excluded posterior DLPFC areas were functionally pertinent to the Tower test and SOPT tasks. The extent of individual differences in the angle of the precentral gyrus in anatomically-aligned brains is unknown, and further work could usefully explore this, to give insight into the consistency of the region being excluded.

#### *8.4.2 Neural Correlates of Faux Pas and Reversal Learning Performance*

The two orbitofrontal tasks (the Faux Pas task and Reversal Learning) showed no correlations with OFC volumes, in contrast to the previously-discussed lesion and neuroimaging evidence linking this region to these tasks. Rather, larger volume of the left or right IFG was related to fewer RL errors and better Faux Pas score respectively. Although lesions to the OFC have been reported to impair Faux Pas and Reversal Learning performance, structural decline with ageing is a temporally and mechanistically distinct process. The right IFG is implicated as part of a wider cognitive network underlying social and emotional cognition, but has predominantly

been associated with emotional empathy via its role in the suggested mirror neuron system (Bastiaansen Thioux & Keysers, 2009; Hynes, Baird, & Grafton, 2006; Schulte-Ruther, Markowitsch, Fink & Piefke, 2007; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). The ability to experience the emotions of others is not thought to be necessary to determine the emotions or intentionality of others (Ghosh et al., 2012; Hynes et al., 2006; Lee et al., 2010). In spite of having removed the scores of empathy questions from the Faux pas score used here for this very reason, the association of the Faux Pas test with the right IFG in the current study is in line with some functional imaging that implicates the right IFG in perspective-taking (Hynes et al., 2006) and evidence that cortical loss in the right IFG in progressive supranuclear palsy correlates with impairments on the TASIT theory of mind test<sup>46</sup>, when compared to controls (Ghosh et al., 2012).

The IFG has also been implicated in Reversal Learning, though for the right, rather than left hemisphere (Ghahremani, Monterosso, Jentsch, Bilder, & Poldrack, 2010; Hampshire, Chamberlain, Monti, Duncan & Owen, 2010; Xue, Ghahremani, & Poldrack, 2008). However, previous work has suggested that the IFG is involved in the detection of important cues (Hampshire et al., 2010), irrespective of the relative value of available stimuli (Mitchell et al., 2009). Given that the number of stimuli was low in the Reversal Learning test (only 2 options), and value – based on trial-by-trial feedback – was the only criterion on which to base selection, it is counter-intuitive that variance in IFG but not OFC would predict performance. Nevertheless, it is possible that increased errors on this task were explained by an inability to

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<sup>46</sup> The TASIT (MacDonald et al., 2002; 2003) consists of a series of videos in which actors exhibit sincerity or sarcasm towards one another. Participants are then asked a series of scripted questions about the meaning of the exchange.

effectively identify the feedback as useful for updating the perceived value of stimuli and driving subsequent selections.

The comparable and opposite relationship of Reversal Learning errors with the left mSFG ( $\rho=.25$ ) and left dACC ( $\rho=-.26$ ) might be explained by considering the parcellation protocol. The spatial relationship between the cingulate and mSFG and morphological variation in their common boundary could potentially explain the differences in the direction of the correlations. However, this same pattern is not exhibited for the Simon Effect, where there is a trend relationship with the left mSFG and a non-significant relationship in the same direction with the left dACC. This suggests that associations for these regions are not just driven by positional shifts in their shared border. However, little work has been done on the specific functional and connective profile of the mSFG as distinct from other portions of the medial frontal wall. For example, the SFG is not included as a connective site for ACC clusters by either Beckmann et al. (2009) or Johansen-Berg et al. (2008). It is currently unclear why a larger mSFG might confer increased errors during Reversal Learning.

#### *8.4.3 Neural Correlates of Simon Task and Dilemmas Performance*

Measures of stimulus-response conflict correlated with ACC volume, corroborating a large body of previous work (reviewed in Chapter 2). For the Simon Task, post-error slowing (PES) and the Simon Effect are both thought to reflect instances levels of conflict; the former, a mismatch between the expected and actual outcome of a previous response; the latter, a spatial mismatch of stimulus and required response.

The Dilemmas task measures are also theorised to reflect conflict elicited between the social benefit and moral implications of a proposed action in a given context. Thus it was predicted that the Simon Task measures would correlate with the dorsal ACC, and Dilemmas measures with ventral ACC. Although both the Simon Task measures exhibit significant correlations with both dorsal and ventral ACC (as predicted) and the frontal pole, the Simon Effect appears more sensitive to a more global reduction in right frontal lobe volume that includes both lateral and orbital frontal regions. In contrast, PES shows significant correlations across the majority of the fibre systems whilst neither FA nor MD tract measures are generally correlated with the Simon Effect. The Dilemmas mean response time showed another distinct pattern, with significant relationships with bilateral dorsal cingulate, but not the ventral region, which contrasts with the lesion data (Ciaramelli et al., 2007; Koenigs et al., 2007; Moretto et al., 2010 ), and this cognitive measure did not show any significant correlations with tract measures.

While our results suggest that involvement of the dACC is common to each of these response conflict measures, we found divergent patterns of association with brain structure which one could infer are relevant to the types of conflict elicited between PES and the Simon Effect. For example, Snyder and Stoet (2008) assert that humans are able to minimise congruency effects by ‘locking in’ the response schema in advance – this results in higher task switching costs to ‘unlock’ the schema, but lower congruency costs, while primates show the opposite pattern of behaviour. Online tracking and modification of the prepotent response based on current task rules could be plausibly driven by the frontal cortex and local frontal lobe intraconnectivity. In contrast, PES may require rapid global signalling in response to

errors and enable PFC-driven top-down control of other brain regions (Danielmeier, Eichele, Forstmann, Tittgemeyer, & Ullsperger, 2011). The integrity of long range connectivity could be invaluable for the rapid communication to posterior brain regions to halt current behaviour or increase vigilance following errors (possibly detected by the ACC).

#### *8.4.4 Neural Correlates of g*

In general accord with cerebral models of the *g* network (Duncan et al., 2010; Jung & Haier, 2007) and structural imaging studies (Barbey et al., 2012; Colom et al., 2009; Glascher et al., 2010; Narr et al., 2007), larger volumes of the left ACC, left DLPFC and bilateral hippocampus predicted higher intelligence. Jung and Haier (2007) also identified the uncinate fasciculus as a plausible candidate for subserving the requisite long-range connectivity for this network, yet neither FA nor MD measures were significantly associated with *g* in the current study (the left arcuate was previously reported to relate to *g* in a larger sub-sample of the LBC1936, but only for carriers of the *rs1402714 ADRB2* SNP; Penke et al., 2010). Rather, better anisotropy and diffusivity in the right ATR was related to higher *g*, and better scores on both speed and memory abilities. This tract was not examined in relation to the full LBC1936 cohort (Penke et al., 2010) though it facilitates fronto-hippocampal connectivity via the thalamus. The frontal pole was also suggested as part of the *g* network by Jung & Haier (2007) based on their literature review, and also in two recent lesion-based mapping studies (Barbey et al., 2012; Glascher et al., 2010). There was a small association between *g* and the right frontal pole, but a larger sample would be

required for greater power to examine smaller relationships. The two lesion-based mapping studies also showed a striking relationship between left-sided lesions and *g*, which is partially consistent with the pattern of correlations here between left dACC, left DLPFC and left cingulum, but not with the right ATR or right mSFG.

#### *8.4.5 The Significance of the ACC*

The volume of the anterior cingulate cortex (ACC) was the most variable of all regional volumes, and the dorsal region appears to play a significant role in most measures of cognitive ability in this ageing cohort. Significant associations between *g* (speed, and verbal memory recall – constituents of *g*), both DLPFC tasks and both OFC tasks were limited to the left dACC, whereas the right-sided (dorsal and ventral) cingulate volumes correlated with PES and the Simon Effect. Furthermore, *g*, speed and memory positively correlated with hippocampal volumes and the splenium of the corpus callosum – which are two of very few regions not related to PES. This pattern is highly similar to the way in which the cognitive scores themselves covary, as reported in the previous chapter. The lack of overlap between putative ACC cognitive scores (the Simon Effect, PES and Dilemmas reaction time) and the scores on other tasks which showed intercorrelations (*g*, the ‘DLPFC’ and ‘OFC’ tasks – reported in the previous chapter) are also reflected in the pattern of structural MRI correlates, and as such offer a biological basis for the pattern of reported principal components loadings reported in Chapter 7.

The concurrence between structure-function relationships in this chapter and patterns of cognitive score covariance reported in the last chapter also follows for the

directional Simon Effect and the percentage of endorsed dilemmas. These did not correlate with any other cognitive score, nor any sub-regional volume, and were the main loadings on the third rotated principal component. Whilst both showed a single correlation with tract diffusivity (left uncinate with Dilemmas percentage endorsement, and right PCing with the directional Simon Effect), the general pattern of cognitive and neural covariation suggests that these variables have a limited cerebral basis and should be treated with caution.

Thus the ACC appears central to the covariance between common cognitive tasks and also the way in which they are distinguished via principal components analysis. How can one interpret the apparent significance of the ACC? There is evidence for increased ACC activity in a wide range of tasks including social and goal-based action selection (Bush, Luu & Posner, 2000; Mansouri, Tanaka & Buckley, 2009), motor control (Paus, 2001) and experience of pain (Vogt, 2005), but the rarity with which medio-frontal lesions arise (in otherwise normal patients)<sup>47</sup> with sufficient regional specificity makes it difficult to infer for which tasks the ACC is necessary (Fellows & Farah, 2005). The anatomy and hodology of the ACC place it at the centre of fronto-lobar activity, with several clusters each displaying distinct connective profiles with fronto-cortical, sub-cortical areas and the brainstem in humans (Beckmann et al., 2009; Johansen-Berg et al., 2008) and animals (Devinsky, Morrell & Vogt, 1995). Taking reduced volume relative to ICV as an estimate of age-related atrophy, these findings highlight the importance of preserved ACC integrity in superior performance on the majority of tasks studied here.

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<sup>47</sup> For example, patients with intractable pain showed little cognitive impairment following cingulotomy (Yen et al., 2009), but it is unclear how much of their pre-operative cognition was impaired due to chronic pain.

However, from the current results it cannot necessarily be inferred that the cingulate is equally important in young healthy humans (or indeed, in other ageing participants). In light of theories of de-differentiation or compensation in old age - in which older brains exhibit more distributed patterns of BOLD response compared to their young counterparts - the connectivity of the cingulate makes it well placed to facilitate information integration across a more diffuse network of frontal regions. Were this the case, deleterious effects of age on this specific structure would significantly disrupt such functioning - perhaps to a greater extent than it might in young participants who experienced a similar degree of insult. The ACC shows the largest variability of all the volumetric measures proportional to its size in this study, but normal healthy ageing has more often been characterised by either a non-specific frontal decline or accentuated DLPFC and OFC, but not ACC atrophy (Convit et al., 2001; Raz et al., 1997; Tisserand et al., 2002)<sup>48</sup>, though different methodologies are likely a confounding factor. For example, Tisserand and colleagues (2002) used different methods in the same study, and reported that manual methods indicated age-related volume reductions predominantly in DLPFC and OFC, whereas semi-automatic and voxel-based methods identified DLPFC and ACC as more susceptible to atrophy. More recently, increased ACC atrophy has been specifically linked to Alzheimer's Disease (AD). All portions of the cingulate gyrus were shown to be smaller in 10 familial AD patients compared to matched controls (Jones et al., 2006). Though this was not replicated in a recent study, which showed only posterior cingulate differences in incipient AD compared to controls (Pengas, Hodges, Watson, & Nestor, 2010), only a small portion of the ACC was measured, in contrast

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<sup>48</sup> And a recent study by Raz et al., 2010 did not measure the ACC at all.



to the entire volume of the cingulate gyrus by Jones and colleagues (2006). Another study suggests that while AD is characterised by a posterior-anterior profile of cingulate atrophy, fronto-temporal dementia (FTD) shows anterior-posterior cingulate changes (Barnes et al., 2007). Atrophy of the ACC is thought to be common to both FTD and semantic dementia (Rosen et al., 2002). Although smaller cingulate volumes do not necessarily indicate rates of atrophy, nor onset of clinical pathology, these studies also highlight the importance of the ACC in age-related pathologies of severe cognitive decline, and suggest that differential patterns of atrophy may be pertinent to different trajectories of cognitive decline amongst currently healthy ageing cohorts.

#### *8.4.6 Neural Correlates of Principal Components of Cognition*

An alternative perspective on the biologically relevant bases of complex cognition was to correlate frontal lobe regional volumes with the principal components derived in the previous chapter. The neural correlates of PC1 were generally consistent with the *g* factor derived using mainly Weschler subtests (section 8.4.4) and was related to left-sided ACC, left DLPFC and bilateral hippocampus. More interestingly, PC2 correlated with right-sided ACC, DLPFC and FP. The suggestion that *g* does not fully reflect all frontally-based contributions to complex cognition is not a new one (Barbey et al., 2012; Friedman et al., 2006; Gläscher et al., 2010; Robbins et al., 1998). However, the finding that these orthogonal components also relate – asymmetrically in most cases – to DLPFC and ACC volumes relative to maximal brain size in old age adds further support to this contention.

Having considered the neural underpinnings of these units of common variance, how might they be understood in terms of existing theories of cognitive ability? The finding of this partial left-right frontal asymmetry receives some support from other empirical evidence of lateralised functional segregation. Based on a large number of lesion and imaging studies, it has been proposed that the left lateral regions are involved in the capacity to form or select task-relevant rules (criterion setting) and right lateral regions are tasked with updating contingencies and fine-tuning performance of ongoing behaviours (monitoring) in order to optimise behaviour (Stuss & Alexander, 2007; Stuss, 2011; reviewed in Vallesi, 2012). Moreover, two recent lesion-symptom mapping studies found that left- but not right-sided frontal lesions were associated with poorer intelligence (Barbey et al., 2012; Gläscher et al., 2010). The test score loadings on the principal components in our study shows a plausible fit: in addition to a high intelligence loading on PC1, performance on the Tower test, SOPT and Reversal Learning all intuitively require the flexible acquisition and selection of rules. It could be argued that the Faux Pas and Dilemmas tasks also require the participant to quickly orient themselves within each scenario and select the appropriate social/moral rules. Likewise, for PC2, performance monitoring and contingency-updating are intuitively involved in resolving response conflict from competing stimulus cues (Simon Effect), and in response to feedback regarding errors where performance may subsequently need optimising (Post-Error Slowing). In addition to loading on PC1, the Tower test constantly requires updating of the next task-relevant sub-goal, the stimulus-reward contingencies are shifted during the Reversal Learning task, and the Dilemmas task requires the concurrent development and comparison of conflicting moral

perspectives. This finding adds to data indicating that complex cognitive abilities such as updating and inhibition may be partially independent of intelligence (e.g. Friedman et al., 2006 in young adults). Whether PC1 represents ‘g’ or ‘criterion setting’ (if such constructs are independent), and PC2 represents ‘monitoring’ is conjecture, but our results indicate that frontal tasks may require multiple parts of cognition which can be explained by their split loadings on these two neuroanatomically distinct frontal components.

#### *8.4.7 Neural Correlates of Verbal Memory in Old Age*

Overall, the correlations between memory performance and brain structure were as predicted, and the regions selected *a priori* based on previous work each accounted for some variance in performance, consistent with the idea that they form part of a memory network, and contribute uniquely to its functioning. Correlations for the whole group identified that better callosal integrity, larger left DLPFC and right hippocampus significantly correlated with better memory performance. Though bilateral hippocampi are central to memory performance, the correlations for the left hippocampi were non-significant, albeit in the same direction as for the right side. A larger study may have had sufficient power to detect significant associations with this region. Integrity of the genu in old age has previously been reported to correlate either directly with memory performance (Persson et al., 2006) or with prefrontal activations during verbal memory tests using fMRI (de Chastelaine et al., 2011), though not in all cases (Kennedy & Raz, 2009). The participants in the latter paper

included only 19 males (19-81 years) and a manual ROI approach to measuring tract integrity.

By splitting participants into high and low scoring groups on immediate and delayed memory performance, divergent structural correlates are apparent. The right DLPFC showed a significantly larger correlation with immediate recall performance in the low, but not the high group. Furthermore, the low group had significantly smaller hippocampi than their counterparts. The fact that the correlation between right DLPFC and memory score was positive supports the proposal that right frontal activations during fMRI are partially beneficial for memory processes. That this was only present for the low-scoring group (whose hippocampi were smaller) also supports the hypothesis that the right DLPFC is only required to supplement changes in posterior brain functioning, not in left frontal cortex.

However, analysis of delayed recall performance portrayed a slightly different picture. High and low performers showed a trend toward divergent structural correlates here too, though not with the hypothesised regions. Although the magnitude of the association with right DLPFC was larger for low-scorers than for high ( $r=.28$  versus  $r=.15$ ), this was not significant. As before, the high group had larger hippocampi, but only associations with callosal diffusivity appeared significantly different. The MD of the genu was a better predictor of performance for high than low performers, whilst the splenium MD showed stronger associations for the low than high group (though both showed only a trend towards being significantly different). Counter-intuitively, increased diffusivity of the genu predicted better memory performance in the high group, though this corroborates a previous finding that poorer genu anisotropy predicted the extent of right PFC BOLD

activity during verbal memory encoding, but it did not directly relate to memory performance (de Chastelaine et al., 2011). It is unclear why increased general diffusivity in the genu of the corpus callosum might be beneficial to memory performance for high performers, but both our findings and those of de Chastelaine and colleagues (2011) were analysed across relatively small groups, suggesting that these findings require replication in larger cohorts.

Nevertheless, the current study identifies possibly divergent neural correlates for immediate and delayed verbal recall amongst high and low performers in old age. We did not find evidence to suggest that poorer performers exhibit a breakdown in cross-hemisphere inhibition of the right PFC by the left PFC via the genu of the corpus callosum, as our lower performers for both immediate and delayed memory recall showed no significant differences in left PFC volumes or callosal integrity. However, this does not preclude the involvement of inhibitory breakdown in ageing memory performance, but rather suggests that frontal left-to-right via the corpus callosum might not be a relevant route in this instance. Although both functional and structural imaging have separately reported different neural correlates between high and low performers, care should be exercised when testing hypotheses and interpreting results in small samples and across methodologies.

The current basis for de-differentiation is primarily driven by functional imaging evidence during memory processing; additional frontal recruitment is often attributed to ‘age-related changes in ‘posterior brain regions’ (i.e. the hippocampus; this terminology is used by Cabeza et al., 2004; Craik & Rose, 2012; Davis et al., 2007; Goh, 2011; Park & Reuter-Lorenz, 2009). However, our understanding of cognitive decline with age would benefit from focus on other types of cognitive

process, comparing the pattern of sub-regional brain involvement in younger and older individuals, and between high and low performers, and preferably combining structural and functional imaging techniques. In this way, it might be possible to build a more comprehensive understanding of the structural underpinnings of cognitive ageing, and even to identify epidemiological factors underlying subtle changes in functional network integrity and composition.

#### *8.4.8 Further Limitations*

The use of anatomical landmarks and cut-planes to delineate brain structures has its own set of implications for interpreting these results. The aim of measuring sub-regional volume was to estimate the degree of age-related decline. However, it is impossible to say how much of individual differences in volume is due to age-related structural decline, and how much reflects variability in the positioning of relevant landmarks used in the parcellation. For example, the anterior point of the cingulate gyrus is used for the frontal pole. It is possible that the asymmetry between left and right frontal pole (see Figure 8.2) is driven by the tendency for the paracingulate gyrus to appear more often on the left than the right side (Fornito et al., 2004). Moreover, the tendency for the frontal pole to correlate in the opposing direction to other frontal measures with PES and Simon Effect could be driven by the size of the cingulate; the larger this region is, the more anteriorly it would encroach, thus reducing the size of the frontal pole volume. Likewise, the paracingulate gyrus (where present) was used as the dorsal border of the ACC. The opposite direction of the correlations of the ACC and mSFG with Reversal Learning might reflect an

excitatory versus inhibitory function of these two regions, but it could also reflect the fact that additional cingulate gyrification necessitates a smaller mSFG, as they share a border. However, were this the case, we would expect that for every positive correlation between the left dACC there is a comparable and opposite correlation with the mSFG. Such a pattern is not consistently present, and there are cases where a cognitive score shows significant correlations with the dACC but not mSFG (SOPT, Faux Pas, Dilemmas mean reaction time) or with the mSFG but not dACC (Simon Effect, *g*). Nevertheless, longitudinal volumetric measures would allow a more robust estimate of the variance accounted for by brain-related cortical changes, versus individual differences in general landmark position.

In addition, the volumetric measurements include shallow white matter. Whilst it is likely that the gyral white matter is highly relevant to the functioning of the adjacent cortical sub-regions, this does not give a pure measure of cortex alone. Volumetric measures cannot account for age-related changes in receptor density and distribution which may also change with increasing age (Park & Reuter-Lorenz, 2009). Moreover, our structural measures are relatively limited. Measures of non-fronto-cortical regions, sub-cortical structures, other major tracts such as the fornix (implicated in hippocampal-PFC connectivity; Metzler-Baddeley et al., 2011), and intra-lobar connectivity would allow a fuller account of structure-function relationships. Finally, our structural and functional measures are relatively novel – particularly the inclusion of social and emotional processing tasks and the novel frontal lobe parcellation protocol. When even variation in the test battery composition used to derive a *g* factor can yield significantly different scores (Haier et

al., 2009), generalizability to other studies of cognition and structure in old age may be partially limited.



## Chapter 9: The Relationships Between Cortisol and Brain

### Structure

#### 9.1 Introduction

Exposure to excess levels of glucocorticoids (GCs) can have a detrimental impact on brain structure and function. Administration of exogenous GCs, or chronic exposure to stress, has deleterious effects on brain structure and function in animals (Cerquiera et al., 2007; Cook & Wellman, 2004; McEwan, 1999, Wellman, 2001). The same outcome has been observed in Cushing's syndrome in humans (Patil et al., 2007; Starkman et al., 1999; Toffanin et al., 2011). Ageing in some animals and humans appears to be accompanied by an increase in cortisol levels both during the overall diurnal cycle, and in reaction to stress (discussed in detail in Chapter 4). Age-related chronic exposure to elevated levels could have similarly damaging effects on specific brain regions and tissue types to those observed in the laboratory or in clinical conditions (Landfield et al., 1978; Landfield et al., 2007; Sapolsky et al., 1986).

The hippocampus and prefrontal cortex are of particular interest, as these are both regions of the brain thought to be most susceptible to structural decline with age, and are also involved in higher functions such as memory, planning, monitoring and social cognition. Moreover, these regions are implicated in the regulation of hypothalamic-pituitary-adrenal (HPA) axis functioning. Both regions contain high levels of receptors to which GCs preferentially bind, facilitating negative feedback shutdown of further GC production. In addition, chronic stressors or GCs produce rearrangement of apical dendrites and reductions in dendrite branches in rodent

hippocampus and medial prefrontal cortex (Brown, Henning & Wellman, 2005; Cerqueira et al., 2007; Radley et al., 2004; Wellman, 2001). This remodelling is reflected in a volumetric reduction, although volumetry may be a conservative estimate of the detrimental effects of GCs, as it cannot account for other possible effects such synapse or receptor loss, or changes in neurotransmission (Tata et al., 2006; Patil et al., 2007).

In ageing rodents and non-human primates, associations of elevated levels of GCs with smaller hippocampi and medial prefrontal cortices are reported. In ageing humans, volumetric reductions of the hippocampus were associated with elevated basal cortisol in a five-year prospective study in a small sample ( $n = 11$  vs control group  $n = 5$ , Lupien et al., 1998), but cross-sectional studies have not replicated this (Gold et al., 2005; MacLulich et al., 2005, 2006; Kremen et al., 2010a). Explorations of cortisol levels and frontal lobe volumes in ageing humans are rare, and discrepant methodologies for brain and cortisol measures make a synthesis of findings difficult. Elevated cortisol levels in response to CRH administration were associated with a higher rating of visual atrophy and a trend towards lower volume for the entire frontal lobe (Gold et al., 2005). However, another study reported no relationships between total frontal lobe volume and post-dexamethasone cortisol levels (MacLulich et al., 2006). Moreover, two studies report different associations between frontal lobe sub-regions and cortisol levels, although direct comparison is confounded by different cortisol measures and MRI analysis methods (MacLulich et al., 2006; Kremen et al., 2010a). The findings of MacLulich and colleagues (2006) suggest that smaller left ACC volumes, but not right ACC or bilateral SFG accompany impaired dexamethasone suppression of cortisol release. In contrast,

Kremen et al., (2010a) found that mean diurnal cortisol output correlated with the cortical thickness of the bilateral SFG, and left lateral convexity of the frontal lobe, but not ACC. Although the implicated ROIs in these two papers do not overlap, left-sided regions are implicated in both studies. Cerebral influences on HPA activity may well be partially lateralised, although in which direction, and in relation to which aspects of GC production is currently unclear. In rodents, the left mPFC is implicated in the regulation of immediate stress response, whilst the right mPFC is thought to be involved in adapting behaviours to environmental conditions (Czeh et al., 2008). In humans, patients with left- but not right-sided stroke showed increased morning cortisol compared to control participants<sup>49</sup>, but lesions to either hemisphere, and particularly frontal involvement, blunted reactive responses (Lueken et al., 2009). Supra-hypothalamic influences on HPA activity may well be partially lateralised, although in which direction and in relation to which aspects of GC production is currently unclear.

The significance of white matter integrity has been relatively underplayed with respect to both models of HPA axis regulation, and the potential deleterious effects of GCs in the laboratory and old age. The limited data in rodents suggest that axonal sprouting in response to lesion is impaired by exposure to GR-specific steroid treatment, but not MR (Scheff & Cotman, 1982; Scheff & DeKosky, 1983). In rhesus monkeys, poorer MD but not FA in the corpus callosum, uncinate and cingulum bundles was associated with higher observational ratings of behavioural stress reactivity (but not directly with 12hr urinary cortisol (Wilette et al., 2011). These tracts, and the anterior thalamic radiation (which connects OFC and thalamus) are

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<sup>49</sup> Though it should be noted that the authors did not test for a significant difference between left and right patient groups.

plausible connective pathways through which supra-HPA axis cortisol regulation might operate.

Extant studies give conflicting reports of relationships between brain regions and cortisol levels in old age. As well as using different MRI measures, there is no standardisation of cortisol measurement. Numerous studies investigate “age-related HPA-axis dysregulation”, but the focus is on either reactive *or* diurnal cortisol. It is unclear whether dysregulation of both profiles is mutually inclusive within individuals. If all brain regions engaged in cortisol regulation or expressing GR and MR are subject to age-related deleterious effects of cortisol exposure, then we might expect to see a system-wide dysregulation, reflected in both diurnal and reactive profiles. However, current understanding of the human neuro-regulatory framework for cortisol (e.g. Dedovic et al., 2009) suggests that dysregulation of diurnal and reactive profiles could be dissociable to some degree. Selective damage to the network could yield selective impairment in one but not the other profile. Such individual differences would clearly raise important questions about the genetic and environmental influences at play, and effects on cognition in old age.

Extension of this work is required, as there are no studies to date examining volumes of all frontal lobe sub-regions and major white matter tracts with respect to both diurnal and reactive cortisol in old age. In this chapter, data on diurnal and reactive cortisol levels are presented and explored. Next, the relationships between cortisol measures and MRI variables are analysed to test the following hypotheses:

- (1) Elevated reactive and diurnal cortisol levels, and flatter slopes will be associated with smaller orbitofrontal, medial prefrontal and hippocampal volumes.
- (2) Elevated reactive and diurnal cortisol levels, and flatter slopes will be associated with poorer FA and MD in the corpus callosum, uncinate fasciculus, anterior thalamic radiation and cingulum bundle.

## 9.2 Methods

Variables used in this chapter are from assays of free salivary cortisol and brain imaging analysis. Details of data collection and processing are outlined in the Methods chapter.

### 9.2.1 Cortisol

As a measure of reactive cortisol production, saliva was collected before and after the cognitive testing appointment (approximately 90 minutes apart). These will be referred to as START and END. The appointment was expected to act as a mild cognitive stressor with higher levels at the start of testing, declining over the testing session due to HPA axis negative feedback regulation. On a separate day, saliva was collected at waking and at 10pm to represent the diurnal cortisol profile. These will be referred to as WAKING and EVENING. Mean sampling times (self-report for home samples) were:

WAKING: 7.52am ( $\pm 1$ hr; range 5-10am), EVENING: 10.02pm ( $\pm 21$  minutes, range 8-11pm), START: 10.30am ( $\pm 32$  minutes, range 9.15-11.55am), END: 12.06pm ( $\pm 137$  minutes, range 10.30am-1.35pm).

Slopes were calculated by subtracting the earlier measure (waking or start of testing) from the later measure (evening or end of testing). Thus a negative slope value denotes a decreasing slope. Cortisol is reported in units of nmols/l.

### *9.2.2 Sub-Regional Volumes*

Eight manually-traced frontal lobe sub-regions and the hippocampus in each hemisphere were derived from T1 MRI images, and are reported in mm<sup>3</sup>.

### *9.2.3 DTI Tractography*

Seven tracts of interest were identified using neighbourhood tractography from diffusion tensor imaging (DTI), and fractional anisotropy (FA) and mean diffusivity (MD) are reported measures of water diffusion within these tracts.

### *9.2.4 Statistical Analysis of Cortisol*

Prior to analysis, the data was examined for extreme values in consultation with Prof. MacLulich. Since two or three measures of each time point on separate days may more reliably characterise a person's cortisol profile (Kraemer et al., 2006) we were cautious when considering extreme single measurements and these were removed from further analysis. One participant was removed before analysis began due to unusually high cortisol levels (START: 343 nmols/l, END: 284 nmols/l; WAKING: 56 nmols/l; EVENING: 238 nmols/l). A high single outlier for the evening levels (69.41nmols/l) was also removed prior to analysis.

Outliers were classed as any points further than 3 standard deviations from the mean. For the EVENING sample, four outliers were identified (25.29 nmols/l, 29.59 nmols/l, 33.32 nmols/l and 26.09 nmols/l with an upper limit of 22.44 nmols/l) and removed. Following a log transformation, EVENING cortisol level data points

were normally distributed. Three high outlier values for cortisol at the START of cognitive testing (47.34 nmols/l, 49.98 nmols/l and 56.06 nmols/l with an upper limit of 47.34 nmols/l) were removed, before applying a log transformation. A log transformation rectified the skewed distribution for the END levels. All cortisol variables entered into further analysis were normally distributed, and therefore Pearson's product-moment correlations were performed between cortisol measures. All exclusions of outliers took place without any knowledge of the other variables.

#### *9.2.5 Statistical Analysis of ROI Volumes*

The same regions of interest, controlled for intracranial volume (ICV) were used as in the previous chapter (Chapter 8)

#### *9.2.6 Statistical Analysis of DTI Tractography*

Measures for Fractional Anisotropy (FA) and Mean Diffusivity (MD) were used as described in the previous chapter (Chapter 8).

#### *9.2.7 Laterality effects*

Post-hoc tests of the difference between independent correlations were conducted to examine whether associations between cortisol and structure were significantly lateralised.

#### *9.2.8 Correction for Multiple Comparisons*

Given the large number of simultaneous comparisons being computed, one-stage of False Discovery Rate (FDR) correction was used to identify potential type I errors.



### **9.3 Results:**

#### *9.3.1 Cortisol*

Descriptive statistics for salivary cortisol levels for diurnal (WAKING, EVENING and diurnal slope), and on the day of cognitive testing (START, END, and reactive slope) are shown in Table 1. In general, WAKING levels were high than EVENING levels ( $t = 17.67$ ,  $df = 100.47$ ,  $p < .001$ ), and START levels were higher than END levels ( $t = 3.97$ ,  $df = 145.80$ ,  $p < .001$ ). The average slope for participants was negative for both diurnal and reactive measures, although there were some participants with flat diurnal rhythms (maximum 0.26 nmols/l), and some with very positive reactive slopes, denoting increased cortisol over the course of the cognitive test battery (maximum 15.94 nmols/l).

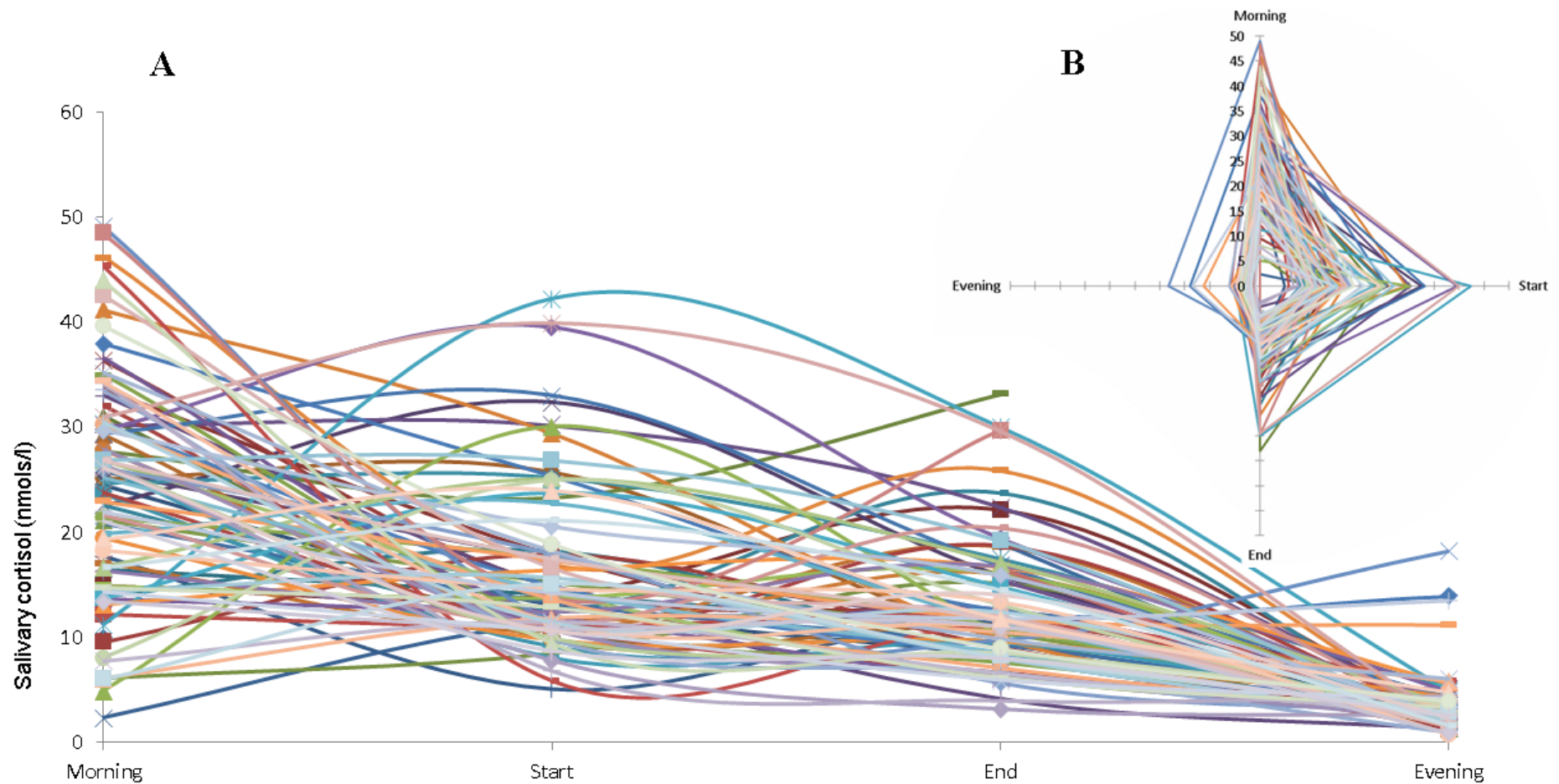
Correlations among cortisol measures are also presented in Table 9.1.

Although diurnal and reactive measures tended to intercorrelate, there were no significant relationships across diurnal and reactive data ( $r < .18$ ,  $p > .24$ ). Cortisol data are also plotted in Figure 9.2, showing participants' composite cortisol profiles (A), and separated into diurnal and reactive slopes (B).

Table 9.1. Descriptive data and intercorrelations for diurnal and reactive cortisol levels

		Descriptive Statistics					Correlations Between Cortisol Measures					
		<i>n</i>	Mean	sd	Max	Min	WAKING	EVENING <sup>a</sup>	Diurnal Slope	START <sup>a</sup>	END <sup>a</sup>	Reactive Slope
Diurnal	WAKING	89	24	10.59	49.09	2.38	-----	<b>.21†</b>	<b>-.96***</b>	-.04	-.01	.09
	EVENING <sup>a</sup>	84	3.47	2.75	18.20	0.80		-----	.04	.11	-.04	-.18
	Slope	84	-20.77	9.72	0.26	-43.91			-----	.05	.09	-.00
Reactive	START <sup>a</sup>	86	16.39	7.77	42.26	5.08				-----	<b>.45***</b>	<b>-.67***</b>
	END <sup>a</sup>	89	12.67	6.07	33.11	3.18					-----	<b>.30**</b>
	Slope	86	-3.87	7.19	15.94	-20.12						-----

\* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ , † trend ( $0.05 < p > 0.08$ ), <sup>a</sup> log transformed. Comparisons are Pearson's *r*. Descriptive units nmols/l.



*Figure 9.2.* Concentrations of salivary cortisol (nmols/l) are plotted to illustrate the relationship between diurnal and reactive levels by A) participant, and B) sampling point. Diurnal and reactive profiles were not correlated within participants. In general, morning levels were higher than evening levels, and start levels were higher than end levels. However, diurnal and reactive profiles were not correlated within participants.

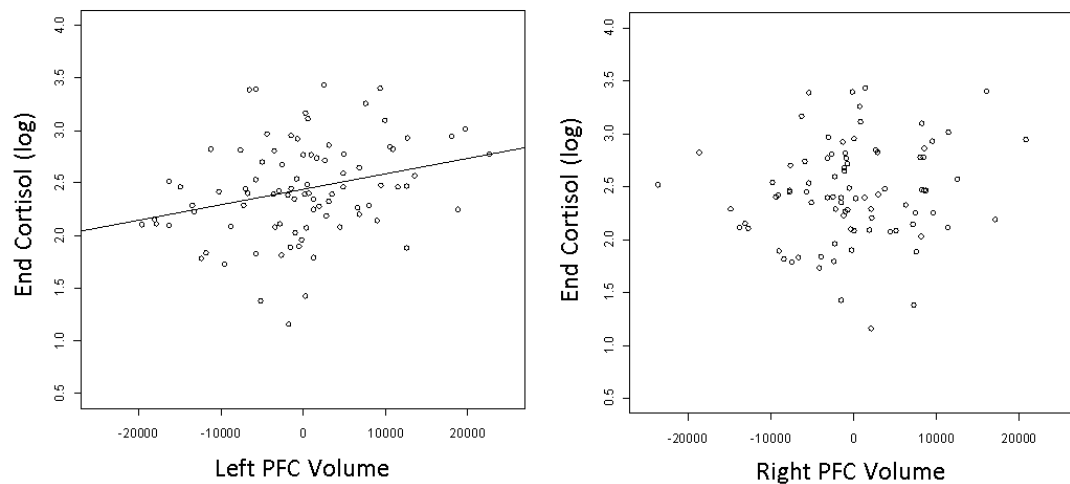
### 9.3.2 Cortisol Measures and Total Prefrontal Volume

Correlations were carried out between all six cortisol metrics and the measures of the whole frontal lobe, and left and right hemispheres (Table 9.2). There were no significant relationships between any diurnal measure and these volumes. START cortisol levels also showed no correlation with gross lobar measures. However, lower END values were significantly correlated with smaller total PFC volumes (Pearson's  $r(85) = .22, p = .032$ ). Analysis by hemisphere showed that this relationship was true for the left hemisphere ( $r(85) = .28, p = .008$ ) but not the right ( $r(85) = .12, p = .260$ ; Figure 9.3). Testing for effects of laterality indicated that these correlations were not significantly different ( $z(85) = 1.07, p = .285$ ).

Table 9.2. Pearson correlations between lobar volumes and cortisol levels.

		Cortisol (nmols/l)	Frontal Lobe Volume (ICV)		
			Total	Left	Right
Diurnal	WAKING		-.16	-0.13	-.17
	EVENING		-.06	-.12	.01
	Slope		.14	.10	.15
Reactive	START		.07	.06	.07
	END		.22*	.28**	.12
	Slope		.16	.21 <sup>†</sup>	.07

\* $p < .05$ , \*\* $p < .01$ , <sup>†</sup> trend ( $.05 < p < .08$ ).



*Figure 9.3.* Scatterplots showing the relationship between cortisol levels at the end of cognitive testing and left and right prefrontal brain volumes.

### *9.3.3 Diurnal Cortisol and Regional Volumes*

Pearson's product moment correlations are reported in Table 9.3. Smaller volumes of the left medial superior frontal gyrus (mSFG) were significantly correlated with higher WAKING ( $r(85) = -.23, p=.032$ ) and EVENING cortisol levels ( $r(80) = -.26, p=.018$ ). Higher EVENING levels were also associated with a larger left hippocampus ( $r(81) = .25, p=.021$ ). There were no significant correlations between the diurnal slope and any frontal ROI. The ACC and OFC did not significantly correlate with any diurnal cortisol measures.

### *9.3.3 Diurnal Cortisol and White Matter Tracts*

Correlations between diurnal cortisol and tract measures are reported in Table 9.4 (MD) and Appendix F (FA). There were no significant relationships between any diurnal measure and the FA of any tract, but there were two trend associations: lower FA in the left inferior longitudinal fasciculus (ILF) with higher EVENING levels

( $\rho(78) = -.22, p = .054$ ), and lower FA in the splenium of the corpus callosum with a flatter/more positive diurnal slope ( $r(78) = -.21, p = .064$ ).

Elevated WAKING levels did not significantly correlate with any tract measure, but higher WAKING cortisol generally correlated with increased MD. There was a trend for higher EVENING cortisol to correlate with higher MD of the bilateral arcuate fasciculus (left:  $r(77) = .21, p = .070$ ; right:  $r(69) = .22, p = .068$ ). Elevated evening levels were significantly correlated with increased MD in the left uncinate fasciculus ( $r(69) = .25, p = .036$ ) and although this pattern was the same for the right uncinate, the relationship did not reach significance ( $r(74) = .19, p = .010$ ). The diurnal slope did not correlate with the MD of any tracts.

#### *9.3.4 Reactive Cortisol and Regional Volumes*

High START levels were significantly correlated with smaller left mSFG volume only ( $r(82) = .26, p = .016$ ; Table 9.5). Contrary to our hypothesis, higher levels at the END of testing correlated with a *larger* volumes of the left frontal pole ( $r(85) = .25, p = .020$ ) and right orbitofrontal gyri ( $r(85) = .29, p = .007$ ). A flatter or more positive reactive slope was associated with larger volumes of the left mSFG ( $r(82) = .34, p = .002$ ) and bilateral DLPFC (left:  $r(82) = .23, p = .033$ ; right:  $r(82) = .21, p = .060$  – trend). The ACC did not significantly correlate with any reactive cortisol measures.

#### *9.3.5 Reactive Cortisol and White Matter Tracts*

Correlations between cortisol and tract measures are reported in Table 9.6 (MD), and Appendix F (FA). There were no significant correlations between any reactive cortisol measure and the FA of any tract. Cortisol START levels were generally

correlated with higher MD, though significantly positive correlations were found only with right cingulum ( $r(78)=.22, p=.046$ ), and bilateral uncinate fasciculus (left:  $r(72)=.27, p=.022$ ; right:  $r(76)=.24, p=.034$ ). Higher START levels also showed a trend for higher right anterior thalamic radiation MD ( $r(76)=.21, p=.070$ ).

There were no significant correlations between MD values and salivary END cortisol. Contradicting our hypothesis that a flatter or positive reactive profile would relate to lower limbic tract integrity, a positive slope was *negatively* correlated with the MD of the genu of the corpus callosum ( $r(79)=-.25, p=.027$ ), bilateral arcuate fasciculus (left:  $r(79)=-.34, p=.002$ ; right:  $r(79)=-.21, p=.078$  - trend), bilateral uncinate fasciculus (left:  $r(72)=-.32, p=.005$ ; right:  $r(76)=-.35, p=.002$ ), right anterior thalamic radiation ( $r(76)=-.26, p=.020$ ), right cingulum ( $r(78)=-.26, p=.018$ ) and left anterior thalamic radiation ( $r(81)=-.24, p=.027$ ).

### 9.3.6 Correction for Multiple Comparisons

No correlations survived False Discovery Rate correction for multiple comparisons.

### 9.3.7 Tests of Laterality

There were a larger proportion of correlations between cortisol levels and left-sided ROIs and tracts than with right, for diurnal, but not reactive cortisol. Post hoc tests of the difference between independent correlations found that their relationship with cortisol showed a significant leftward asymmetry for:

MSFG vs. evening cortisol ( $z(80)=-1.90, p<.05$ , one-tailed)

MSFG vs. start cortisol ( $z(82)=-2.05, p<.05$ , one-tailed)

FP vs. end cortisol ( $z(85)=2.54, p<.01$ , one-tailed)

And a significantly rightward asymmetry was found as follows:

OFC vs. end cortisol ( $z(85)=2.30$ ,  $p<.05$ , one-tailed) rightward asymmetry



Table 9.3. Correlations between diurnal cortisol levels and ROI volumes

	FP		ACC		vACC		Medial SFG		DLPFC		IFG		OFG		Hippocampus	
	L <sup>b</sup>	R	L <sup>b</sup>	R <sup>b</sup>	L	R <sup>b</sup>	L	R	L	R	L	R	L	R	L	R
Morning	-.03	-.11	.15	.00	.08	-.02	-.23*	-.06	-.03	-.07	-.16	.03	-.05	-.04	.09	.09
Evening <sup>a</sup>	-.14	-.06	.15	.04	.03	-.00	-.26*	.04	-.11	-.05	.02	.07	.14	.14	.25*	.11
Diurnal	-.04	.10	-.13	-.01	-.01	.04	.16	.02	.02	.06	.14	-.08	.16	.11	-.11	-.05

Significances not corrected for multiple comparisons, \* $p < .05$ , \*\* $p < .01$ , † trend ( $0.05 < p > 0.08$ ). <sup>a</sup> log transformed, <sup>b</sup> square root transformed, FP: frontal pole; ACC: anterior cingulate cortex; vACC: ventral anterior cingulate cortex; SFG: superior frontal gyrus; MFG: middle frontal gyrus; IFG: inferior frontal gyrus; OFG: orbitofrontal gyri. Diurnal denotes the slope, where a negative value reflects decreasing cortisol levels from the first to second time points.

Table 9.4. Correlations between diurnal cortisol levels and tract mean diffusivity

	Genu	Splenium	Arcuate		ATR		Cingulum		Uncinate		ILF	
			L	R	L <sup>a</sup>	R	L	R	L	R	L <sup>◇</sup>	R <sup>◇</sup>
Morning	.03	-.11	.07	.13	.13	.05	.02	.05	.08	.09	.02	-.01
Evening <sup>a</sup>	.15	-.02	.21†	.22†	.18	.12	.11	.08	.25*	.19	.11	.05
Diurnal	-.01	.17	-.09	-.05	-.04	-.02	-.05	-.00	-.09	-.09	-.02	.05

Significances not corrected for multiple comparisons, \* $p < .05$ , \*\* $p < .01$ , † trend ( $0.05 < p > 0.08$ ). <sup>a</sup> log transformed, <sup>◇</sup> non-parametric variable, Spearman method used. ATR: anterior thalamic radiation; ILF: inferior longitudinal fasciculus. Diurnal denotes the slope, where a negative value reflects decreasing cortisol levels from the first to second time points.

Table 9.5. Correlations between reactive cortisol levels and ROI volumes

	FP		ACC		vACC		Medial SFG		DLPFC		IFG		OFG		Hippocampus	
	L <sup>b</sup>	R	L <sup>b</sup>	R <sup>b</sup>	L	R <sup>b</sup>	L	R	L	R	L	R	L	R	L	R
Start <sup>a</sup>	.14	-.02	.12	-.09	-.02	.01	-.26*	.06	-.15	-.12	.11	.13	-.01	.16	-.14	-.02
End <sup>a</sup>	.25*	-.14	.00	.04	-.02	.14	.10	.18	.11	.07	.09	.12	-.06	.29**	-.04	.15
Reactive	.05	-.13	-.13	.10	.05	.13	.34**	.14	.23*	.21†	-.06	-.06	-.01	.12	.08	.12

Significances not corrected for multiple comparisons, \* $p < .05$ , \*\* $p < .01$ , † trend ( $0.05 < p > 0.08$ ). <sup>a</sup> log transformed, <sup>b</sup> square root transformed, FP: frontal pole; ACC: anterior cingulate cortex; vACC: ventral anterior cingulate cortex; SFG: superior frontal gyrus; MFG: middle frontal gyrus; IFG: inferior frontal gyrus; OFG: orbitofrontal gyri. “React.” denotes the slope, where a negative value reflects decreasing cortisol levels from the first to second time points.

Table 9.6. Correlations between reactive cortisol levels and tract mean diffusivity

	Genu	Splenium	Arcuate		ATR		Cingulum		Uncinate		ILF	
			L	R	L <sup>a</sup>	R	L	R	L	R	L <sup>◇</sup>	R <sup>◇</sup>
Start <sup>a</sup>	.15	.05	.18	.12	.12	.21†	.08	.22*	.27*	.24*	.18	.14
End <sup>a</sup>	-.09	.00	-.10	-.11	.02	-.01	-.05	.02	.03	-.04	-.07	.01
Reactive	-.25*	-.05	-.34**	-.21†	-.11	-.26*	-.17	-.26*	-.32**	-.35**	-.24*	-.17

Significances not corrected for multiple comparisons, \* $p < .05$ , \*\* $p < .01$ , † trend ( $0.05 < p > 0.08$ ). <sup>a</sup> log transformed, <sup>◇</sup> non-parametric variable, Spearman method used. ATR: anterior thalamic radiation; ILF: inferior longitudinal fasciculus. Reactive denotes the slope, where a negative value reflects decreasing cortisol levels from the first to second time points.

## 9.4 Discussion

In this chapter, relationships were examined between cortisol and brain structure, measured by frontal ROI volume and diffusion properties of major white matter tracts. Given previous animal and human work, we hypothesised that lower volumes of the ventral and medial PFC regions (OFG, ACC and mSFG) would be associated with higher cortisol levels and flatter diurnal and reactive slopes. The absence of a direct precedent in the human literature for relationships between tract integrity and cortisol in ageing meant that the hypotheses were guided by previous animal work and the relevance of candidate tracts to brain ROIs implicated in HPA axis functioning. It was predicted that limbic pathways such as the uncinate and cingulum bundles, the corpus callosum and anterior thalamic radiation (ATR) were most likely to be involved in cortisol regulation, and would exhibit higher MD and lower FA with higher cortisol.

### 9.4.1 Cortisol

The cortisol data showed the expected diurnal (WAKING>EVENING) and reactive (START>END) pattern, although there was variation in both slopes. Visualisation of all cortisol time-points by participant suggested that there was a large amount of variance in relationships between diurnal and reactive characteristics. A closer examination of the data confirmed that reactive and diurnal measures were not correlated. This finding is not intuitively consistent with the hypothesis that ageing is associated with dysregulation of the entire HPA axis feedback system, because individuals with flatter or higher daily cortisol did not necessarily also show a flatter or higher cortisol response to the cognitive test battery. This could suggest that diurnal and reactive regulatory networks are partially dissociable, in keeping with the neuroregulatory model proposed by Dedovic and colleagues (2009), where distinct brain regions deal with either physiological or psychological cortisol regulation. Our

estimates of cortisol may have been improved by increasing the number of samples taken from each subject. We only took a single cortisol sample for each time point on which to base our estimates of diurnal and reactive function in order to minimise the burden on an already well-studied group of participants, but Kraemer and colleagues (2006) suggest that a second set of diurnal measures reflect the diurnal slope more accurately. Regarding the reactive measures, additional variance could be ascribed to motivational state, coping mechanisms and performance perception, as well as possible other background/life stressors being experienced at the time sampling. In addition, this fact that cortisol levels were generally higher at START than END might as easily reflect a normal part of the diurnal rhythm as it might reflect reactivity and acclimatisation to a cognitive stressor. As described in Section 5.1, these participants have already attended two waves of cognitive testing and a 75 minute MRI scan. As such, it could be argued that the testing did not elicit a reaction that significantly altered their profile from its diurnal rhythm. However, participants were coming to a novel location to participate in the current study, and our results also indicate that diurnal and reactive measures did not significantly correlate. Obtaining an additional cortisol measure during a normal weekday at the same time as the cognitive test appointment could have adequately demonstrated that the testing appointment resulted in a significant rise from diurnal levels at that time of day.

#### *9.4.2 Cortisol vs. Brain Structure – Overview*

Next we performed correlations between brain imaging data (ROI volumes and DTI data) and salivary cortisol levels (three measures each for diurnal and reactive profiles). Treating the frontal lobe as a unitary structure did not support the hypothesis that higher cortisol levels correlate with smaller volumes. However, the direction of significant correlations amongst the detailed brain imaging data and EVENING cortisol provided some support for the

glucocorticoid hypothesis of ageing: higher EVENING levels were related to greater diffusivity, but there was no discernible pattern of smaller ROI volumes. Higher START levels also correlated with generally poorer diffusivity, (but no overall trend direction for the sub-regional volumes), which might suggest the raw circulating cortisol levels are more relevant than the relationship between morning and evening levels.

Individuals with a flatter/positive reactive slope had consistently larger ROI volumes and reduced tract MD; this was also found at the lobar level for END cortisol. This appears to partially contradict the findings of Gold et al. (2005), who found a trend towards lower left fronto-lobar volumes associated with impaired negative feedback following a combined DEX-CRH test<sup>50</sup>. If one takes greater diffusivity and smaller ROI volume<sup>51</sup> in old age as an index of poorer integrity, it appears that higher diurnal and predictive cortisol levels correlate with poorer integrity, but this data does not support the hypothesis that greater reactivity following a cognitive stressor is deleterious to brain structure. To better decipher the implications of these results, it is informative to re-consider what reactive cortisol measures and the testing conditions themselves might represent.

Our hypotheses assumed that high levels of cortisol at all time points indicate elevated exposure to cortisol, and therefore poorer integrity. Thus, increased cortisol at the start of testing would signify a response to a novel situation and mild cognitive stressor (leading to increased levels) whereas END levels might reflect the efficiency of the negative feedback loop in reducing these levels once the participant had become comfortable with the testing environment. However, it is possible that END levels and reactive slopes might not represent negative feedback efficiency in isolation, but also the continuing excitation of HPA axis activity in the face of continuing cognitive demand – particularly amongst a group of highly-

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<sup>50</sup> However, they observed this trend only in participants with hypertension, and the comparability of post-test cortisol to that following exogenous steroid administration is debateable.

<sup>51</sup> Calculated relative to ICV, and therefore taking account of individual differences in head size and age-related atrophic change.

motivated individuals. In this study, those with better integrity of certain brain areas were also those who exhibited increasing reactive levels. One interpretation of these data could be that superior integrity of such sites confers the ability to maintain elevated cortisol output during this specific type of stressor, possibly overriding the inhibitory signals of the negative feedback loop. In support of this finding, damage to anterior frontal regions in humans results in a blunted HPA axis response to a cognitive task when compared to controls, suggesting that some regions of the frontal lobe are important for producing the characteristic reactive GC increase (Lueken et al., 2009). Frontal lobe regions may be differentially responsible for excitatory and inhibitory roles on HPA axis functioning, dependent on the nature of the current environment. The plausibility of this concept in relation to specific regions and tracts is discussed in the following sections.

Although no results survived False Discovery Rate correction, the revised threshold was driven by the level of detail afforded by our cortisol and ROI protocols. This could suggest that some significant findings are likely to be false-positives. Yet, given the empirical non-independence of brain measures (see Chapter 8), the novelty of the current study and the lack of concurrence in the human literature to date, it is informative to also consider the analysis in terms of biological plausibility and the context of previous work rather than to conservatively reject all findings. For example, the fact that the majority of significant correlations were of a consistent direction within sampling points cannot be easily explained by chance. Likewise, specific ROIs and tracts were consistently correlated with cortisol across different cortisol measures. The nature and context of these relationships merits further discussion.

#### *9.4.3 Site-specific relationships with cortisol*

As predicted, high levels of MORNING, EVENING and START cortisol were correlated with a smaller left medial superior frontal gyrus (mSFG). Elevated EVENING and START also significantly correlated with greater MD left uncinate fasciculus. Right uncinate MD showed the same pattern, and was positively associated with START, though the association (in the same direction as both left mSFG and left arcuate) did not reach significance. Higher START also predicted significantly poorer MD in the right ATR and right cingulum. The cingulum and uncinate bundles facilitate reciprocal connections between hippocampus and PFC. The former runs beneath the cingulate cortex, connecting hippocampus with the ACC and other parts of the frontal lobe, whereas the latter arises lateral to the hippocampus and amygdala, connecting entorhinal cortex with the OFC, and OFC with temporal lobes through the temporal stem (Catani & de Schotten 2008; Nolte & Angevine, 1995). Increased MD in these tracts is associated with increased behavioural reactivity to stressful situations in rhesus monkeys (Willette et al., 2012), and rodent studies suggest that GCs adversely affect axonal recovery from insult (Scheff & Cotman, 1982; Scheff & DeKosky, 1983). Thus it is plausible that the integrity of these regions could affect the efficiency of HPA axis negative feedback regulation.

However, the ACC did not show any correlations with any measure of cortisol. A significant relationship between high diurnal cortisol output and the left medial frontal wall has been reported in two previous studies in ageing samples. Thinner bilateral superior frontal gyral cortex (but not ACC) correlated with mean diurnal cortisol levels (Kremen et al., 2010a), while MacLulich et al. (2006) found that left anterior cingulate gyrus volumes were smaller in a group who showed non-suppression to low dose dexamethasone compared to suppressors. Discrepancies regarding the precise location on the medial wall that associates with diurnal cortisol might be partially accounted for by different methodologies. Firstly,

MacLulich et al. (2006) used a dexamethasone suppression test and the analysis of extreme groups (10 suppressors vs. 10 non-suppressors). Secondly, we used a method of manual gyral segmentation as opposed to the automated measure of cortical thickness used by Kremen and colleagues. Thirdly, both studies included the paracingulate gyrus, where present, in their SFG measures (using protocols: Desikan et al., 2006; Rademacher et al., 1992; Yamasue et al., 2004) and did not divide the SFG into medial and lateral sections. In contrast, our method combined cingulate and paracingulate gyri and included a lateral/medial split of the SFG (though which of these methods is most anatomically, cytoarchitecturally and functionally plausible is a matter of debate, but see Chapter 3). Future work could potentially shed more light on the differential connectivity between medial frontal areas and other parts of the lobe, using the object maps generated from the ROIs to guide tract identification. A recent paper used DTI to map some of the intricate connectivity within the frontal lobes (Catani et al., 2012), but no-one has yet examined frontal intralobar tracts in relation to cortisol levels.

We also hypothesised that the volume of the OFG would negatively correlate with higher cortisol levels and steeper slopes, given its limbic connectivity and relation to reactive cortisol production (Pruessner et al., 2008; Wang et al., 2005; 2007) and other measures of stress (Dedovic et al., 2009b). This was not the case for any cortisol measures. However, higher END cortisol levels were positively correlated with right OFG volumes, as well as the left frontal pole. Functional imaging studies have reported bloodflow changes in both regions in response to stress paradigms, with the right ventral PFC showing continued activation long after the end of a stressful task (Wang et al., 2005), perhaps reflecting a prolonged state of heightened arousal (Dedovic, D'Aguiar, et al., 2009). In the context of this study, better integrity of these regions could well facilitate continued HPA axis activity in response to cognitive testing, although it is currently unclear why the volumes of these regions do not show a negative relationship with diurnal cortisol measures, though failure to appropriately



increase cortisol levels when needed may also be pathological and could be an interesting avenue for further study.

#### *9.4.4 Unexpected significant findings*

Significant associations between EVENING cortisol levels and the arcuate fasciculus were unanticipated. Both the connectivity and the functional role of this bundle are under research (Bernal & Ardila 2009) and it is not thus far been implicated in endocrine regulation.

Likewise, the inferior longitudinal fasciculus showed a general trend towards the same pattern of poor diffusivity with higher START, and the converse with a flatter reactive slope. It connects temporal and occipital lobes (Bergman et al., 2005; Catani & de Schotten, 2008), and neither lobe has been a significant focus of attention in the neuroendocrine literature aside from the medial temporal lobe.

Another unexpected finding was that elevated EVENING levels associate with a significantly larger left hippocampus, in direct opposition to a number of previous animal studies. However, only one human study has reported a negative relationship between diurnal cortisol levels and hippocampal volume in a healthy ageing sample ( $n=11$ ; Lupien et al., 1998). Subsequent studies have found no such relationship with diurnal cortisol or DEX suppression (Gold et al., 2005; MacLulich et al., 2005, 2006; Kremen et al., 2010a). One possible methodological explanation is our hippocampal parcellation was not sub-regional. Several animal studies used a sub-regional method for hippocampal parcellation or detailed histological examination, and linked areas CA1 and CA3 with GC levels (Magarinos et al., 1996; Widenmayer et al., 2006; Zhao et al 2007; reviewed by McEwan 2007) but not in all cases (Vollman-Honsdorf et al., 1997).

However, the absence of an inverse relationship between cortisol and hippocampal volumes in this and other human studies (in contrast to the well-replicated finding in rodents)

could also reflect cross-species differences. In stark comparison to the rodent, the rhesus hippocampus contains a relative absence of GR (Sanchez et al., 2000), which could intimate that hypothalamic and neocortical areas are more focal targets of the deleterious effects of GCs with age in humans. This explanation is not intuitively consistent with the finding of an inverse relationship between cortisol and memory ability in human ageing (Lupien et al., 1998; MacLulich et al., 2005; Lee et al., 2007; Gerritsen et al., 2009), though not in all studies (Kuningas et al., 2007). There is little doubt that the hippocampus is intimately involved in memory functioning (Van Petten, 2004), but it is also one part of a large-scale brain network that facilitates these complex encoding and retrieval processes. As a result, it is possible that age-related GC remodelling could be affecting other regions of this network; this is a hypothesis that will be returned to in a later chapter.

The almost complete absence of significant findings with tract FA is conspicuous when compared to the MD results. Once again, this does not fit with a patterning of significant findings due to chance. We found that cortisol levels are generally related to the average level of water diffusion within certain tracts, but not with the directional cohesion of the diffusing water molecules. In the only other study of cortisol and DTI data, there was a significant interaction between behavioural stress reactivity and urinary cortisol in the MD, but not FA in rhesus limbic tracts. There is continuing debate surrounding the biological significance of MD and FA (Hasan, 2006), but this pattern of findings might reflect slight tissue damage, sufficient to increase the amount of intracellular water, but not to significantly affect the fibre coherence and consequent directional diffusion of water (MacLulich et al., 2009). MacLulich and colleagues report poorer MD but not FA of normal appearing white matter in association with higher blood pressure. They contend that hypertension could increase blood-brain barrier (BBB) permeability, resulting in an increase in extracellular water. Glucocorticoids are also thought to be intimately involved in BBB permeability

(Lubrich, Spleiss, Gebicke-Haerter, & van Calcar, 2000), but an acute increase in GC levels *decreases* BBB permeability (Förster et al., 2005). However, the effects of chronic GC exposure on the BBB are unknown, and merit further investigation. Thus, it is unclear whether ageing confers some breakdown in the mechanisms through which GC acts on the BBB, or whether elevated cortisol production might simply be a by-product of the deleterious effects of hypertension or other mechanisms on brain structures involved in HPA axis activity. These are potential routes for further investigation.

#### *9.4.5 Other Considerations*

This study uniquely combines diurnal and reactive cortisol measures with a detailed manual measurement of frontal lobe sub-regions and major white matter tracts. In spite of its several novel features, there are other limitations in addition to those already discussed. The rationale for combining hippocampal, prefrontal and tract data was to get a more global picture of potential large-scale brain network(s) relating to HPA axis activity. However, the temporal, parietal or occipital lobes and sub-cortical regions were not measured, including the amygdala (for which there is significant evidence of HPA axis feedback involvement – discussed in the Cortisol introductory chapter). The measures of frontal gyri include both cortex and some local white matter, and therefore it is currently impossible to relate cortisol to cortical volume alone – future work could usefully remove previously segmented white matter from the gyral masks to rule out any influence of white matter volume on the putative cortex - cortisol relationship.

Furthermore, Tata et al. (2006) reported that GC-related synapse loss in rodents occurred independent of hippocampal volume measures, suggesting that volume measures may provide a conservative estimate of GC effects on the brain (Patil et al., 2007). The cross-sectional design here precludes direct comment on the causal relationship between cortisol

and brain structure in old age. Although the data partially fits with previous work, a prospective design would be necessary to adequately address this issue. Finally, the self-selecting group of males studied here are likely to be highly motivated, and were selected for their relative good health, meaning that age-related brain changes may be comparatively modest. It is possible that our results are a conservative estimate of the relationship between cortisol and brain structure in the ageing population.

## Chapter 10: The Relationships Between Cortisol and Cognitive

### Function

#### 10.1 Introduction

The hypothesis that cognitive decline with age is partially determined by prolonged exposure to high levels of glucocorticoids (GCs) by facilitating damaging processes in the brain (Landfield et al., 2007; Sapolsky et al., 1986) has received some support from both animal and human studies. As discussed at length in Chapter 4, administration of exogenous GCs or exposure to various types of stressor over a long period has been frequently associated with damage to brain structure and poorer cognitive functioning. In particular, regions with limbic connectivity such as the hippocampus, amygdala and parts of the frontal cortex (which are implicated in GC regulation) are reported to show markers of GC-driven structural remodelling in animals (e.g. Cerquiera et al., 2007; Landfield et al., 1978; McEwen & Gianaros., 2010; Sapolsky 1985, 1986), though the picture is much less clear in humans. Likewise, the relationship between cortisol levels and cognition in ageing humans is not entirely consistent, though several studies using moderate to large sample sizes report impairments in a spectrum of cognitive domains associated with higher diurnal and reactive cortisol measures ( $97 \leq n \leq 1154$ ; Comijs et al., 2010; Gerritsen et al., 2009; Kuningas et al., 2007; Lee et al., 2007, MacLulich et al., 2005). These studies have examined the relationship between cortisol and core cognitive domains in ageing, but concentrating on major cognitive domains precludes an understanding of cortisol's relationship with specific abilities. It also limits assessment of the functional ramifications of any specific cortisol-brain structure covariance. By using tasks thought to show sensitivity to damage in specific brain regions (and combining this with brain MRI measures), it is hypothesised that a finer-grained mapping between cortisol, brain structure and cognitive function may be elucidated.

### *10.1.1 Associations Between Diurnal Cortisol and Cognition with Age*

Associations between diurnal cortisol levels and cognition in old age are informative because they may index the functional implications of long-term exposure to cortisol levels. An initial longitudinal study by Lupien and colleagues (1998) reported that 11 elderly humans that showed increasing diurnal cortisol levels (average 24hr serum levels, sampled once per hour, once a year over five years) had decreasing hippocampal volumes and concomitant declines in delayed, but not immediate memory performance, when compared to a group with stable cortisol. Whereas subsequent studies have replicated the relationship between cortisol and the hippocampus in healthy ageing (Coluccia et al., 2008; Gold et al., 2005; Kremen et al., 2010a; MacLulich et al., 2005, 2006, 2012; Wolf et al., 2002) and also in depression in old age (O'Brien et al., 2004; Vythilingham et al., 2004), associations between cortisol and cognition show some general concordance that some form of cognitive impairment is generally associated with higher cortisol levels with age. However, there is not total consistency in the literature regarding the types of cognition that might be affected, which might be partly attributed to between-study differences in design, such as a variety of cortisol measures, cognitive tests, age and health status of participants, prospective or cross-sectional sampling.

As an example of this inconsistency, one study used a single measure of global cognitive function, reporting that it was not correlated with morning cortisol (Kalmijn et al., 1998). Using more detailed cognitive testing, morning cortisol levels were negatively associated with *g*, processing speed and logical memory recall (MacLulich et al., 2005). Morning cortisol levels have also been reported to show no association with verbal memory

ability, but were negatively related to global cognitive function<sup>52</sup> and processing speed (Kuningas et al., 2007). Other apparently contradictory results report higher morning levels were associated with poorer executive functioning (Kuningas et al., 2007; Beluche et al., 2010), better executive functioning (Evans et al., 2012) reduced 4-year decline in immediate verbal memory only for those carrying the *APOE*  $\epsilon$ 4 allele (Gerritsen et al., 2009). Higher morning cortisol has also been related to poorer cross-sectional verbal memory performance, but not with increased change over 6 years ( $n=1154$ ; Comijs et al., 2010). Evening levels are less well-studied, but Gerritsen and colleagues (2009) also found that higher evening levels and flatter diurnal slopes for the entire cohort were associated with poorer immediate and delayed verbal memory at both baseline and follow-up, but not steeper decline over 4 years ( $n=911$ ). In contrast, higher evening cortisol at baseline predicted a 3 year decrease in immediate and delayed memory recall and executive functioning in another ageing cohort ( $n=46$ ; Li et al., 2006).

Higher total daily cortisol output estimated by urine sampling has been associated with worse delayed verbal memory in females but not males (Seeman et al., 1997) and increased risk of cognitive impairment over 7 years (using a brief mental state exam; Karlamangla et al., 2005). In contrast, it has also shown no association with measures of processing speed, verbal fluency, reasoning, visual or verbal memory, or their change over 6 years (MacLulich et al., 2012). As MacLulich et al. (2012) point out, the period over which the urine was collected in their study (24 hours) differed from that of Karlamangla and colleagues (2005; 12 hours), as did the sample composition and number of participants. After indexing diurnal cortisol as a slope or mean (calculated using morning and evening anchor points), higher levels or a flatter slope correlate with poorer executive function (Beluche et

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<sup>52</sup> It could be argued, however, that the Mini Mental State Exam used by Kalmijn et al. (1998) and Kuningas et al. (2007) to measure global cognition does not offer sufficient sensitivity to detect subtle cognitive deficits; as a dementia diagnosis tool, there are only 6/30 points between normal cognition and possible dementia.

al., 2010), poorer immediate and delayed verbal recall (Gerritsen et al., 2009), and a 3 year decline in delayed (but not immediate) verbal recall and executive function (Li et al., 2006). Daily exposure to cortisol has also been examined via an alternate method. Comparing arthritis sufferers who had been on a five-year course of the GC prednisone, with those who had not ( $n=13$  vs. 11 respectively), no significant group differences for immediate and delayed verbal memory performance were observed (Coluccia et al., 2008). However, both groups were comparatively young (aged c.50-60 years), and it is unclear how prednisone compares with the magnitude and mechanisms of endogenous GC exposure in older individuals.

In summary, building up a picture of how diurnal cortisol measures and cognitive function in old age covary is made difficult by the wide variety of study designs. There appears to be least clarity regarding associations between morning cortisol levels and cognition, and studies that measured diurnal slope in large ageing samples indicate that a flatter profile is associated with poorer cognitive function, though the cognitive abilities tested vary between studies (Beluche et al., 2010; Gerritsen et al., 2009; Li et al., 2006).

#### *10.1.2 Associations Between Reactive Cortisol and Cognition with Age*

Measurement of cortisol at various times following dexamethasone (DEX) administration is thought to measure the ability of the HPA axis negative feedback loop to identify high GC levels and reduce further production. Thus, the ability to suppress cortisol production (denoted by low post-DEX cortisol) represents effective regulation, and is thought to reflect the overall HPA axis regulatory efficiency in response to natural challenge and endogenous



GC production<sup>53</sup>. In old age, non-suppression has been associated with poorer global cognitive function (Kalmijn et al., 1998; O'Brien et al., 1994), but not  $g$ <sup>54</sup>, or logical memory, but a trend-level association with processing speed (MacLulich et al., 2005).

Additionally, individual differences in the reactivity of the cortisol response have been measured before, during and after various types of mild cognitive stressor. Exposure of participants to such procedures results in elevated cortisol, and variance amongst individuals increases with age (Otte et al., 2005). Higher reactive cortisol was associated with poorer immediate verbal memory recall, but not with non-declarative delayed verbal memory in an early study with low numbers ( $n=14$ , Lupien et al., 1997). Higher pre-test cortisol, mean levels and area under the curve (over the entire laboratory testing visit) correlated negatively with scores in the cognitive domains of language, processing speed, hand-eye coordination, executive function, verbal and visual memory (Lee et al., 2007). Cortisol measures during or after testing showed no correlations with any cognitive domain.

Finally, several placebo-controlled double-blind crossover studies have administered steroids to older individuals and examined the short-term dose response on cognitive performance. No age effects were found for either immediate or delayed recall, attention or Stroop task performance in a small study (young  $n=9$ ; elderly  $n=11$ ) of low-dose cortisol administration (Wolf et al., 2001). Another small study ( $n=16$ , age range 69-82) showed no dose response on a wide range of cognitive tests including immediate and delayed verbal and visuospatial memory, and a continuous performance test (Porter et al., 2002). A more recent small study ( $n=24$ ) did report a significant effect of 5mg of prednisone on both immediate and delayed verbal memory scores. The participants were arthritis sufferers, younger than the

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<sup>53</sup> Though some exogenous steroids may not adequately replicate the actions of cortisol – see Chapter 4.

<sup>54</sup>  $g$  is distinct from global cognitive function. The former is a latent variable derived from multiple cognitive tests whose scores tend to be highly correlated. The latter is a score on a single cognitive test which is generally insensitive to less subtle differences in cognitive ability, and more often used to detect dementia.

majority of ageing studies in cortisol (age= c.50-60 years), making comparison with other studies problematic (Coluccia et al., 2008).

### *10.1.3 Summary and Aims*

Cortisol exposure may be one determinant of accumulating insult to the brain and its functioning over the lifespan. Although not entirely consistent, there is evidence that individual differences in both cortisol's diurnal rhythm and the HPA axis response to challenge may reflect the degree of long-term GC exposure. Verbal memory functioning has been intensively studied, primarily due to the reported association between the hippocampus and chronic GC levels. Whereas this latter relationship does not appear so robust in the human literature as in animals, there is some converging evidence that higher cortisol does relate to poorer memory functioning in ageing humans. However, no meta-analysis currently exists to formally examine these relationships in the light of sample and effect sizes. This could usefully be extended to other cognitive measures too, though few studies have examined other cognitive functions, and the methods used to assess them rarely overlap. Major cognitive domains such as general intelligence and processing speed—which are also highly relevant to ageing effects—have been included in some more recent studies. Specific measures such as attention, conflict processing and planning are even more rarely investigated, making it challenging to clearly summarise the cortisol-cognition relationship in old age.

Moreover, studies examining the relationship between cortisol and measures of social and emotional processing are notably absent. Such tasks are thought to tap the functioning of limbic brain regions, such as the orbitofrontal cortex (OFC). Given the implication of limbic brain structures as possible targets for the negative effects of cortisol exposure, it is possible

that performance on these tasks may therefore be reduced with higher cortisol levels.

Although there have been some reports that social cognition does not necessarily decline with age (Keightley et al., 2006; MacPherson et al., 2002), or might be superior in old age (Happé et al., 1998), several studies have reported negative effects of age on theory of mind abilities (German & Hehman, 2006; Maylor, Moulson, Muncer, Taylor, 2002; McKinnon & Moscovitch, 2007; Phillips, McLean & Allen, 2002) and reward-based decision-making (Denburg, Tranel, & Bechara, 2005; Marschner et al., 2005; Mell et al., 2005; Weiler, Bellebaum, & Daum, 2008). Therefore, cortisol exposure may be a determinant of these cognitive abilities in old age.

The present study examines the cognitive correlates of cortisol levels that characterise (i) diurnal rhythm and (ii) reactivity to a mild cognitive stressor in the LBC1936 sub-sample described earlier (Chapter 5). As well as measures of memory, speed of processing and general intelligence, the new tasks that are included are thought to show differential sensitivity to the integrity of frontal lobe sub-regions. Having presented evidence that higher cortisol levels and flatter slopes reflect HPA axis dysfunction, and may index greater exposure over the lifecourse (Chapter 4), it is hypothesised that higher diurnal and reactive cortisol levels and flatter slopes will be predominantly associated with poorer performance on indices of cognition including those measuring social and emotional decision-making.

## 10.2 Methods

The cortisol and cognitive measures are as described in Chapters 5, 8 and 9. Further details on data collection and analysis can also be found in Appendix D. Briefly, the cognitive measures comprise *g*, speed of processing, the mean *z*-scores of immediate and delayed verbal memory recall, each derived from scores on the main LBC1936 test battery.

Additional neuropsychological measures are scores on the Tower, Self-Ordered Pointing Task (SOPT), Faux Pas, Reversal Learning, the Simon Task (post-error slowing and the Simon effect) and the mean reaction time taken during the Dilemmas task. Given previous findings that the percentage endorsement during the Dilemmas task and the directional Simon Effect did not correlate with any other cognitive score (Chapter 7), and minimally with any structural variable (Chapter 8), these measures were not included in the current chapter.

Diurnal salivary cortisol measures were taken on waking and at 10pm at home, from which the slope was derived. Reactive salivary cortisol was sampled at the start and end of the cognitive testing appointment, from which the reactive slope was also obtained. For ease of reference the cortisol sampling, cognitive tests, associated cognitive domains and abbreviations are presented in Table 10.1.

Table 1. Details and abbreviations of cognitive and cortisol measures.

<b>Cognitive Tests</b>	<b>Abbreviation</b>
general cognitive ability	<i>g</i>
speed of processing	Speed
z-score of immediate verbal memory recall	Immediate
z-score of delayed verbal memory recall	Delayed
total score on the D-KEFS Tower test	Tower
mean number of repetitions for the Self-Ordered Pointing task	SOPT
score on the Faux Pas test, minus empathy and factual questions	Faux Pas
total number of errors made during the Reversal Learning test	Reversal Learning
Post-Error Slowing: MRT on trials following an error/MRT on trials following correct response during the Simon Task	PES
MRT on incongruent trials/MRT on congruent trials during the Simon Task	Simon Effect
Mean time taken to respond during the Dilemmas Task	Dilemmas MRT
<b>Cortisol measures</b>	<b>Abbreviation</b>
Salivary cortisol sampled on waking at home	WAKING
Salivary cortisol at 10pm at home	EVENING
Morning – Evening (thus negative slope indicates a diurnal decrease)	Diurnal Slope
Salivary cortisol at the start of the neuropsychological test battery	START
Salivary cortisol at the end of the neuropsychological test battery	END
End – Start (thus negative slope indicates a reactive decrease)	Reactive Slope

MRT: Mean reaction time.

### 10.2.1 Statistical Analysis

Firstly, t-tests were conducted to compare start, end and reactive slope cortisol values between the two halves of the group who had received the tests in forward or reverse order. This was done to test whether the order in which the cognitive battery had been presented to participants was related to their reactive cortisol profile.

Pearson's product-moment correlation tests were performed between all variables except for those involving the non-normally distributed scores for the Faux Pas and Reversal Learning tests. In these cases, Spearman's rank-order correlation coefficients were calculated.

### 10.3 Results

There were no significant effects of test battery order on cortisol measures for the start ( $t(80.22)=-.60, p=.550$ ), end ( $t(85.26)=-.40, p=.688$ ) or reactive slope ( $t(80.15)=.22, p=.823$ ).

#### 10.3.1 Diurnal Cortisol vs. Cognition

Correlations between the three measures of diurnal cortisol (WAKING, EVENING and slope) and cognition were generally not significant. Although the associations were in a consistent direction (Table 10.1 and Figure 10.1), this direction was not necessarily as predicted. They indicated that higher levels of cortisol on WAKING correlated with better cognitive scores or fewer errors, whereas a flatter slope was generally associated with a lower score or increased errors on cognitive tests. Fewer repetitions during the Self-Ordered Pointing Task (SOPT) showed a trend toward association with a negative diurnal slope ( $r(85)=.21, p=.053$ ) and higher WAKING cortisol ( $r(85)=-.21, p=.053$ ). Better Immediate memory was also associated with higher WAKING levels of cortisol ( $r(87)=.21, p=.045$ ), and a more steeply declining diurnal slope ( $r(82)=-.25, p=.023$ ). Likewise, a more negative diurnal slope also correlated with a better Delayed memory score ( $r(82)=-.22, p=.047$ ). No other relationships between cognitive scores and any diurnal measure of cortisol reached significance.

#### 10.3.2 Reactive Cortisol vs. Cognition

There were also very few significant or trend associations between reactive cortisol measures and cognitive performance on the frontal lobe tests. However, in keeping with the direction of associations between cognitive scores and diurnal slope, higher START and END levels were

generally associated with lower scores and increased errors, whereas there were no significant associations between reactive slope and cognitive score (Table 10.1 and Figure 10.1). Decreased sensitivity to errors, measured by post-error slowing during the Simon Task, tended to correlate with higher START ( $r(82) = -.21, p = .055$ ) and END cortisol ( $r(85) = -.25, p = .060$ ). High START cortisol correlated significantly with poorer immediate verbal memory ( $r(84) = -.22, p = .039$ ) and showed a similar trend for delayed verbal memory ( $r(85) = -.20, p = .062$ ). Individuals with slower speed of processing also had higher start ( $r(84) = -.23, p = .030$ ) and end ( $r(85) = -.21, p = .046$ ) cortisol levels. The consistency of this pattern for poorer scores with high cortisol at both START and END of testing was also apparent with scores on the Tower, SOPT, *g* (and memory scores with end levels), though no correlation reached significance. There was a trend for individuals with higher cortisol to take less time to decide during the Dilemmas task ( $r(83) = -.19, p = .079$ ). The reactive slope showed no significant correlations with any measure of cognitive performance.

Table 10.1. Correlations between cortisol levels and cognitive scores

	Tower	SOPT	Faux Pas <sup>◇</sup>	RL Errors <sup>◇</sup>	PE Slow	Simon Effect	Dilem. MRT <sup>a</sup>	<i>g</i>	Processing Speed	Immediate Memory	Delayed Memory
Waking	.02	<b>-.21<sup>†</sup></b>	.04	-.13	-.00	-.14	.05	.13	.05	<b>.21*</b>	.17
Evening <sup>a</sup>	.09	-.19	-.08	-.08	-.05	-.13	.07	-.04	-.02	-.04	-.05
Diurnal	-.01	<b>.21<sup>†</sup></b>	-.03	.09	-.00	.08	-.09	-.17	-.09	<b>-.25*</b>	<b>-.22*</b>
Start <sup>a</sup>	-.15	.16	.08	.05	<b>-.21<sup>†</sup></b>	-.04	-.06	-.12	<b>-.23*</b>	<b>-.22*</b>	<b>-.20<sup>†</sup></b>
End <sup>a</sup>	-.17	.15	-.09	.15	<b>-.20<sup>†</sup></b>	.13	<b>-.19<sup>†</sup></b>	-.16	<b>-.21*</b>	-.17	-.17
Reactive	-.01	-.03	-.19	.03	.06	.10	-.10	-.04	-.03	.08	.04

<sup>a</sup> variable log transformed, <sup>◇</sup> non-parametric variable (Spearman method used, otherwise, Pearson's *r* is reported). Significance levels are not corrected for multiple comparisons, \* $p < .05$ , <sup>†</sup> trend ( $.08 < p < .05$ )





## 10.4 Discussion

This part of the study examined covariance between cortisol levels and complex cognitive functioning. Diurnal measures were taken because of the evidence that WAKING, EVENING and diurnal slope measures relate to the general diurnal cortisol rhythm of an individual. Likewise, measures at the START and END of testing, and the reactive slope were, based on prior evidence, thought to reflect an individual's cortisol response in anticipation of, and response to mild cognitive stressor. It was predicted that poorer cognitive performance would correlate with higher cortisol levels and flatter slopes, consistent with the hypothesis that increased cortisol levels in old age are detrimental to brain structure and function (Landfield et al., 2007; Sapolsky et al., 1986).

In general, higher WAKING levels showed consistent directions of association with better cognitive performance, although the magnitudes only reached significance for the number of repetitions on the SOPT, and Immediate memory score. In contrast, a flatter diurnal slope, and higher START and END levels showed consistent directions of association with poorer cognitive performance, though significant results were restricted to poorer memory ability and slower speed of processing. No associations survived correction for multiple testing using False Discovery Rate. Therefore it is likely that the results contain some type I error, but it is unlikely that all findings are due to chance. The fact that the direction and clustering of relationships across tests and cortisol time points were consistent is worth noting, and encourages attempts at replication with larger samples. Whilst this preliminary study may not have sufficient power to identify what are probably small

effect sizes, it is worth considering the general pattern of cognition-cortisol results in light of our initial hypotheses and other work.

#### *10.4.1 Diurnal Cortisol*

Higher WAKING salivary cortisol was significantly correlated with better Immediate memory and a trend towards fewer SOPT errors. A flatter diurnal slope significantly correlated with poorer Immediate and Delayed memory scores, and fewer SOPT errors. Both cognitive scores represent the ability to maintain information in mind (verbal details, or previously-chosen abstract designs, respectively), though it is unclear why the Tower test (a test thought to require holding and manipulating task goals and rules in order to plan ahead) did not show a similar pattern. Previous studies have reported that elevated morning cortisol levels correlate with poorer executive functioning (Beluche et al., 2010; Kuningas et al., 2007), *g* (MacLulich et al., 2005) and processing speed (MacLulich et al., 2005; Kuningas et al., 2007). Higher morning cortisol was also reported with poorer verbal memory scores in some studies (Gerritsen et al., 2009; MacLulich et al., 2005), but not others (Kuningas et al., 2007; Evans et al., 2011; 2012) in ageing cohorts. One possible reason for this apparent contradiction might be that MORNING levels were taken at the start of a lab visit for several of these cited studies (Beluche et al., 2010; Comijs et al., 2010; Kuningas et al., 2007; MacLulich et al., 2005), as opposed to just after waking (Evans et al., 2011; 2012; Gerritsen et al., 2009; the current study). As such, these levels may well be more representative of the predictive stress associated with attending an unfamiliar location in anticipation of unknown procedures. This argues

that a comparison of these studies' findings with our 'start' cortisol measures may be more appropriate (see Reactive Cortisol section below).

Gerritsen et al. (2009) did not find any significant association between waking levels and memory performance for their entire ageing cohort ( $n=911$ ). For carriers of the *APOE*  $\epsilon 4$  allele only, they report that lower morning levels predicted decline in memory function, but there is a lack of clarity in the literature regarding the significance of waking cortisol levels. Some previous studies have linked high waking levels to negative psychological or physiological states, whereas others indicate that a blunted wakening response may also indicate adverse outcomes. On the one hand, increased waking cortisol is an indicator of neuroendocrine disturbance in central obesity, as it correlates positively with cholesterol and waist-hip ratio (Steptoe et al., 2004; Wallerius et al., 2003). A higher cortisol awakening response (CAR)<sup>55</sup> is also associated with depressive symptoms amongst the currently or previously depressed (Bhagwager et al., 2005; Pruessner et al., 2003; Vreeburg et al., 2009). On the other hand, healthy subjects showed a larger CAR than those with disease or chronic health problems over a large age range (4-75 years,  $n=179$ ; Kudielka & Kirschbaum, 2003). Blunted CAR is also associated with persistent pain (Geiss, Varadi, Steinbach, Bauer & Anton, 1997), burnout (Pruessner et al., 1999, but see Sjors et al., 2012), brain damage (Wolf et al., 2005), depression (Stetler & Miller, 2005), and hypertension (Wirtz et al., 2007). More recently, higher CAR has been associated with higher overall  $g$  (Evans et al., 2011)<sup>56</sup>, and better executive function in a sample of healthy older individuals (Evans et al., 2012). Thus *lower*

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<sup>55</sup> Which typically indicates the increase of cortisol levels between waking and 30 minutes after waking, when cortisol tends to rise rapidly in healthy individuals.

<sup>56</sup> Though this did not survive correction for age within the elderly cohort ( $n=50$ , age range 60-91 years).

waking cortisol levels could plausibly denote HPA axis dysfunction in the current sample of healthy, non-depressed elderly males. Although our single WAKING measure differs from the CAR (which quantifies a change in cortisol between waking and post-waking), it is possible that participants were not able to strictly take the sample on waking. Given the large number of possible factors influencing the CAR, the comparatively small participant numbers used and inter-study variation in screening criteria (including this one), a well-powered study with a sufficiently broad spectrum of health phenotypes in old age is required to adequately address the interesting question of the relationship between cognition and the waking and morning cortisol profile.

We did not find any significant correlations between cognitive function and EVENING levels, but a flatter diurnal slope predicted poorer Immediate memory, Delayed memory and SOPT scores. This is in accord with studies linking flatter diurnal cortisol profiles with poorer memory and executive function (Beluche et al., 2010; Gerritsen 2009; Li et al., 2006).

#### *10.4.2 Reactive Cortisol*

Higher levels at either START or END of the cognitive test battery generally correlated with poorer test scores. This general pattern was evident for post-error slowing, Immediate and Delayed memory scores, though only correlations of start levels with immediate recall and processing speed reached significance. There were no significant associations between any cognitive variable and reactive cortisol slope,

suggesting that the raw cortisol levels, rather than their temporal dynamics, are of relevance to cognitive function.

As mentioned in the Diurnal Cortisol section above, cortisol levels taken in the morning at the beginning of a testing appointment at the laboratory are more likely to represent stress due to anticipation, and the effort involved in attending an appointment in a novel location on time. As such, our finding that higher START levels correlate with poorer cognitive functioning are in line with previous publications (Beluche et al., 2010; Comijs et al., 2010; Kuningas et al., 2007; Lee et al., 2007; Lupien et al., 1997; MacLulich et al., 2005). However, while associations between cognitive function and END cortisol levels tended to follow the pattern as for START cortisol, Lee et al. (2006) did not report any relationships between cortisol at the end of testing and cognitive domains of language, processing speed, eye-hand coordination, executive function, verbal memory or visual memory in a sample of 967 individuals aged 50-70.

#### *10.4.3 Summary*

In summary, although there was a general trend for higher reactive cortisol levels and a flatter diurnal slope to correlate with poorer cognitive function, and for higher morning levels correlate with better scores, few associations reached statistical significance. In general agreement with the current literature, correlation coefficients between cortisol measures and cognitive scores for memory (Immediate and Delayed) and speed of processing-related variables (Speed and PES) were generally of the largest magnitude, replicating several previous studies linking cortisol levels

with memory and speed abilities. General cognitive ability also directly followed this same pattern but did not reach significance, possibly due to study power. The SOPT – thought to tap the DLPFC, and a test of working memory ability – also followed the same pattern as outlined above. However, there were no significant correlations between any cortisol measure and either test of emotional processing. Although this does not fit with the hypothesis that the structure and functioning of limbic brain regions are targets of GC-driven remodelling, this is a coherent finding in the broader context of this thesis, as these tests did not correlate with the ICV-controlled volumes of the OFC (Chapter 8), nor were the actual neural correlates of these tests related to higher cortisol levels (Chapter 9).

#### *10.4.4 Limitations*

Previous studies have tended to show, albeit inconsistently, that elevated diurnal and reactive cortisol levels are related to poorer complex cognitive abilities in old age. The overall pattern of results presented here is not inconsistent with the literature, but few results reached statistical significance, and these results did not survive correction for multiple comparisons. As previously mentioned, a single cortisol sample for each time point may not accurately characterise an individual's cortisol profile (Kraemer et al., 2006). Although this protocol was adopted in order to minimise the burden on an already well-tested cohort, so as to maximize participation from a low number of potential participants (118), additional diurnal samples would have provided a more robust estimate of diurnal cortisol. Moreover, the level of compliance during cortisol sampling at home is unknown. Self-report

from the sampling form and feedback when participants were explicitly asked indicated a high degree of adherence to instructions, in agreement with a highly detailed study of cortisol measurement in the elderly (Kraemer et al., 2006). However, cortisol levels reach a peak around 30 minutes post-wakening. Therefore, even relatively small variance in the post-wakening sampling time might have led to misclassification of the morning samples as all waking, when some are in fact waking+30 minutes, and so on. Likewise, reactive measures may be affected by the nature of the participant's journey to the testing appointment, and possibly its timing in relation to an individuals' circadian rhythm. Although this is not likely to have been a source of systematic error, this factor may have contributed to the general measurement noise, resulting in weaker correlation estimates (Gerritsen et al., 2009).

In addition to the long-term structural changes that chronic cortisol exposure may bring about in the ageing brain, cognition is also affected by rapid non-genomic effects (Arnsten, 2009; Strelzyk et al., 2012). The exact time course of these effects, and their neurophysiological and functional correlates have not been well studied in old age, making it unclear what proportion of the variance in cognitive scores might be driven by structural brain changes (facilitated through genomic effects of cortisol exposure), and what proportion relates to rapid effects via such mechanisms as dopamine and noradrenaline increase during stress, and possible individual differences in their sensitivity (Arnsten, 2009).

In conclusion, although a general pattern was observed such that higher morning cortisol was associated with generally better cognitive function in the direction of association, and higher reactive levels went with poorer performance, few relationships were statistically significant, and several possible confounding



factors advocate a cautious interpretation of results. The novel comparison of tests of social and emotional processing (the Faux Pas and Reversal Learning tests) with cortisol did not provide strong evidence that scores for either test were modulated by either diurnal or reactive measures.

## Chapter 11: Mediation Analysis

### 11.1 Introduction

This thesis has been primarily concerned with the hypothesis that chronic exposure to cortisol levels correlates with deleterious changes to brain structure, which affects cognitive functioning (Landfield et al., 2007; Sapolsky et al., 1986). Previously presented evidence indicates increased variance in the diurnal and reactive cortisol profiles amongst the elderly, and higher levels in this age group may reflect chronic exposure to high levels. Thus, this thesis has sought to examine the covariances between cortisol, cognition and the ageing brain, with focus on the relatively neglected frontal lobes and relevant frontally-projecting white matter connections. More specifically, it was hypothesised that brain regions and tracts with limbic connectivity and the functions they are thought to subserve would show stronger negative relationships with cortisol levels, given their implication in HPA axis negative feedback regulation. The previous four chapters have examined assumptions about cognitive tests, their relationships to each other, and to brain structure. The latter two chapters then reported correlations between cortisol and brain structure, and then cortisol and cognitive function. Although correlational analysis cannot offer any explanation of cause and effect, implications of causal hypotheses can usefully be investigated using correlational data (Salthouse, 2011). One way in which the hypothesised causative relationship of these findings can be formally tested is with mediation analysis.

Previous studies of cortisol in ageing have tended to either examine cognitive function or brain structure. Of the few that have examined both, no direct tests of the

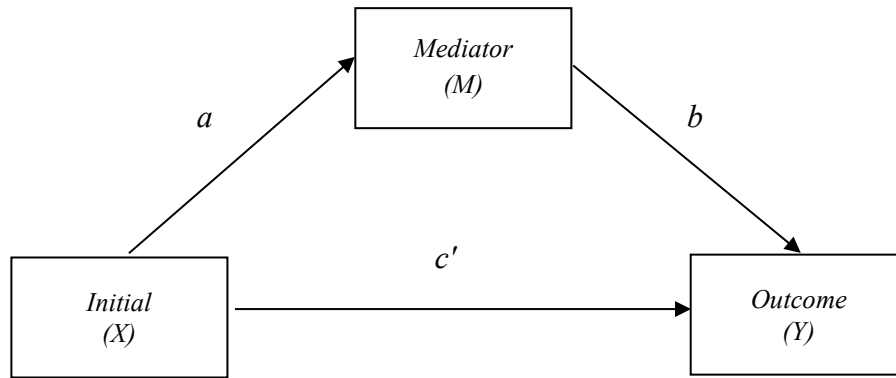
mediation effects of brain structure on cortisol-function correlations have been conducted<sup>57</sup>. Mediation analysis allows a more formal examination of the hypothesis that cognition is related to cortisol because it affects brain structure; in other words, brain structure mediates the relationship between cortisol and cognition. The most commonly-used mediation approach was proposed by Baron and Kenny (1986). They outline the following causal steps which would allow a specific causal model to be examined using correlational data:

Let  $X$  be the independent or initial variable (e.g. cortisol), let  $Y$  be the dependent or outcome variable (e.g. cognition) and let  $M$  be the mediator (e.g. brain structure; Figure 11.1):

1. The total effect of  $X$  on  $Y$  must be significant.
2. The effect of  $X$  on  $M$  must be significant.
3. The effect of  $M$  on  $Y$  controlled for  $X$  must be significant.
4. The effect of  $X$  on  $Y$  controlled for  $M$  must be smaller than the total effect of  $X$  on  $Y$ .

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<sup>57</sup> Analysis of very similar relationships have been examined however. Mediation effects of hippocampal volume on the relationship between cortisol and personality has been examined, but was not significant (Pruessner et al., 2005). MacLulich et al. (2012) conducted mediation analysis involving a measure of 11 $\beta$ -HSD1 activity, ventricular volume and processing speed.



The causal steps strategy stipulates that mediation is present if the  $X \rightarrow Y$  relationship attenuates to non-significance when accounting for  $M$ , or that partial mediation is present when the magnitude of  $X \rightarrow Y$  is reduced after  $M$ . However, rather than concluding that mediation is present through observation, it is possible to test the statistical significance of the difference between total ( $X \rightarrow Y$ ) and direct ( $c'$ ) effects. As Preacher & Hayes (2004) observe, such a test can usefully guard against instances where the change from significance to non-significance is accompanied by a negligible decrease in coefficient size (Type I error), or where a large change in coefficient size is accompanied by no ostensible change in significance (Type II error). The most common method for gauging the mediation effect of  $M$  on the relationship between  $X$  and  $Y$  is to conduct a Sobel test (Baron & Kenny, 1986; Sobel, 1982). This is calculated by dividing the indirect effect (the product of  $a$  and  $b$ ) by its standard error. This value is then compared to a critical value based on the assumption that the sampling distribution of  $ab$  is normal (Preacher & Hayes, 2004; Sobel, 1982). However, methodologists do not advocate this method in small

samples because the sampling distribution of  $ab$  is often not normal, particularly for small samples (Bollen & Stine, 1990; MacKinnon Lockwood & Williams, 2002; Preacher & Hayes, 2004). Instances where the Sobel test contradicts observations using Baron and Kenny's causal steps could be attributed to reduced power based on this assumption of normality. It has been proposed that this can be rectified by bootstrapping<sup>58</sup> the sampling distribution of  $ab$  a large number of times, because it makes no assumptions about distribution normality (Preacher & Hayes, 2004).

In summary, correlational analysis has been the mainstay of studies in the human literature seeking to test the hypothesis that elevated cortisol facilitates deleterious effects of the brain and cognitive functioning. The general absence of formal tests of this hypothesis through mediation analysis is partially because the majority of studies collect only two out of the three requisite variable types, and also perhaps due to the disconnect between cortisol-structure and cortisol-function relationships where studies do possess cortisol, brain structure and cognitive measures. This study offers a fine-grained perspective on all three categories of variable, and offers a good chance of identifying meaningful three-way associations that can be formally tested. This chapter therefore reports the identification of candidates for mediation analysis, and application of both the causal steps strategy (Baron & Kenny, 1986) and a formal test of the mediation effect using bootstrapping (Preacher & Hayes, 2004; 2008) to test the hypothesis that brain structure (negatively related to cortisol levels) mediates the negative relationship between cortisol levels and cognitive functioning.

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<sup>58</sup> Bootstrapping involves computing the indirect effect ( $ab$ ) in a large number of samples, each of  $n$  equal to that of the study in question. Each sample set is sampled with replacement, making the estimate of  $ab$  simply the mean computed over all of the sets sampled.

## 11.2 Methods

The measures of salivary cortisol, brain structure and cognitive function herein are the same as previously discussed in Chapters 5, 7 8 and 9. Based on the hypothesis that the relationship between cortisol levels and cognitive function would be mediated by brain structure, we identified candidates for analysis initially based on the relationship between cortisol levels and cognitive scores, consistent with Baron and Kenny's (1986) causal steps. Next, we identified instances for which steps 1 and 2 were true. This yielded thirteen candidates for analysis, and the structural measures were notably tract integrity measures (FA: fractional anisotropy; MD: mean diffusivity) rather than volumes of brain sub-regions. Furthermore, three of the four cognitive test scores were not those in the battery of frontal tests:

Start cortisol → Right Uncinate Fasciculus MD → Post-error Slowing

Start cortisol → Left Uncinate Fasciculus MD → Post-error Slowing

Start cortisol → Right Anterior Thalamic Radiation MD → Post-error Slowing

Start cortisol → Right Cingulum Bundle MD → Post-error Slowing

Start cortisol → Left Uncinate Fasciculus MD → Speed

Start cortisol → Right Anterior Thalamic Radiation MD → Speed

Start cortisol → Right Cingulum Bundle MD → Speed

Diurnal cortisol slope → Splenium FA → Immediate memory

Start cortisol → Right Anterior Thalamic Radiation MD → Immediate memory

Diurnal cortisol slope → Splenium FA → Delayed memory

Start cortisol → Right Anterior Thalamic Radiation MD → Delayed memory

Each of these three-way relationships was in accord with the hypothesis that higher cortisol levels were associated with poorer tract integrity (higher MD, or lower FA), and poorer cognitive performance (decreased sensitivity to error, speed of processing, or lower verbal memory score), and that poorer integrity was related to poorer cognitive performance. The association between the splenium of the corpus callosum FA and diurnal cortisol slope showed only a trend towards significance ( $r(78) = -.21, p = .064$ ), as did the correlation between right anterior thalamic radiation MD and start cortisol ( $r(76) = -.21, p = .066$ ). Therefore, step 2 was not entirely fulfilled in two of the analyses<sup>59</sup>. Given that memory recall is the subject of much interest in relation to cortisol and ageing, it was decided to pursue mediation analysis with verbal memory. All candidates were then tested as per step 3. Finally, parametric partial correlations between  $X$ - $Y$ , partialling out  $M$ , were performed as step 4. The INDIRECT macro in IBM SPSS 19 was used to statistically assess mediation effects using 5000 bootstrapped samples. Based on our directional

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<sup>59</sup> It should also be noted that the relationship between cortisol levels at the start of testing and post-error slowing, and between start levels and delayed memory recall were also only trend levels. However, meeting the criterion of Step 1 is not an absolute requisite for mediation analysis, particularly if a path from initial to outcome variable is implied by Steps 2 and 3 (Kenny, Kashner & Bulger, 1998).

hypotheses, one-tailed tests were conducted specifying 90% confidence intervals (A. Hayes: <http://www.afhayes.com/macrofaq.html>). Mediation effects are present if the 90% confidence interval (C.I.) span does not include zero (Preacher & Hayes, 2008).



### 11.3 Results

Table 11.1 shows the partial correlations for Step 3 (the relationship between the mediator and outcome variable should remain significant after controlling for the initial variable). All relationships between structure and function remained significant after partialling out cortisol, except for the relationship between post-error slowing and right uncinate MD, processing speed and left uncinate MD, and between processing speed and right cingulum MD. These relationships were not examined for mediation effects. The results of the mediation analysis (Step 4) are presented in Table 11.2 and Figure 11.2. In only three instances were the correlations between initial and outcome variables attenuated to  $p > .05$  (and the coefficient by more than 20%). These were:

Start cortisol → Left Uncinate Fasciculus MD → Post-error Slowing

Diurnal cortisol slope → Splenium FA → Immediate memory

Diurnal cortisol slope → Splenium FA → Delayed memory

*Table 11.1* Step 3 partial correlations between mediator and outcome, partialling out the independent variable (cortisol measure).

	<i>n</i>	<i>r</i>	<i>p</i>
PE Slow ~ R Unc MD	77	-.23	.066
PE Slow ~ R Unc MD   start	76	-.19	.087
PE Slow ~ L Unc MD	73	-.41	.000
PE Slow ~ L Unc MD   start	73	-.37	.001
PE Slow ~ R ATR MD	77	-.27	.018
PE Slow ~ R ATR MD   start	76	-.24	.035
PE Slow ~ R Cing MD	79	-.32	.004
PE Slow ~ R Cing MD   start	78	-.28	.011
Speed ~ L Unc MD	74	-.22	.053
Speed ~ L Unc MD   start	74	-.17	.146
Speed ~ R ATR MD	79	-.39	.000
Speed ~ R ATR MD   start	78	-.34	.001
Speed ~ R Cing MD	81	-.19	.078
Speed ~ R Cing MD   start	80	-.12	.283
Immediate ~ Splenium FA	84	.28	.008
Immediate ~ Splenium FA   diurnal	80	.24	.029
Immediate ~ R ATR MD	79	-.25	.026
Immediate ~ R ATR MD   start	78	-.29	.009
Delayed ~ Splenium FA	84	.32	.003
Delayed ~ Splenium FA   diurnal	80	.29	.009
Delayed ~ R ATR MD	84	.32	.003
Delayed ~ R ATR MD   start	80	.29	.009

PE Slow: Post-error slowing, Immediate: immediate verbal memory recall; Delayed: delayed verbal memory recall; L Unc MD: mean diffusivity of the left uncinate fasciculus; ATR: anterior thalamic radiation, Cing: cingulum bundle; Splenium FA: fractional anisotropy of the splenium of the corpus callosum, start: cortisol levels at the start of cognitive testing, diurnal: cortisol diurnal slope (evening minus morning). Grey type denotes relationships that were not significant when cortisol levels were partialled out.

*Table 11.2.* Step 4 partial correlations between initial and outcome, partialling out the mediator variable.

Initial (X)	Outcome (Y)	Mediator (M)	<i>n</i>	<i>Y~X</i>		<i>Y~X   M</i>		% <i>r</i> attenuation
				<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	
Start	PE Slow	L Uncinate	73	-.21	.055	-.12	.300	43
Start	PE Slow	R ATR	76	-.27	.018	-.24	.004	11
Start	PE Slow	R Cingulum	78	-.32	.004	-.28	.011	13
Start	Speed	R ATR	78	-.39	.000	-.34	.001	13
Diurnal	Immediate	Splenium	84	-.25	.023	-.20	.075	20
Start	Immediate	R ATR	78	-.25	.026	-.29	.009	-16
Diurnal	Delayed	Splenium	84	-.22	.047	-.16	.122	27
Start	Delayed	R ATR	78	-.24	.029	-.27	.012	-13

PE Slow: Post-error slowing, Immediate: immediate verbal memory recall; Delayed: delayed verbal memory recall; L Uncinate: mean diffusivity of the left uncinate fasciculus; R ATR: mean diffusivity of the right anterior thalamic radiation; R Cingulum: mean diffusivity of the right cingulum bundle; Splenium: fractional anisotropy of the splenium of the corpus callosum, start: cortisol levels at the start of cognitive testing, diurnal: cortisol diurnal slope (evening minus morning).

Bootstrapping statistics suggested significant mediation of the association between start cortisol and post-error slowing by left uncinate fasciculus MD (bootstrapping coefficient = -.039 [90% C.I.s: -.087,-.009]). The mediation of the association between diurnal cortisol slope and immediate memory recall was also significant, as the bootstrapping confidence interval did not contain zero at its upper limit (bootstrapping coefficient = -.005 [90% C.I.s: -.014,-.001]). The FA of the Splenium significantly mediated the relationship between diurnal cortisol and delayed memory recall (bootstrapping coefficient = -.006 [90% C.I.s: -.014, -.001]).

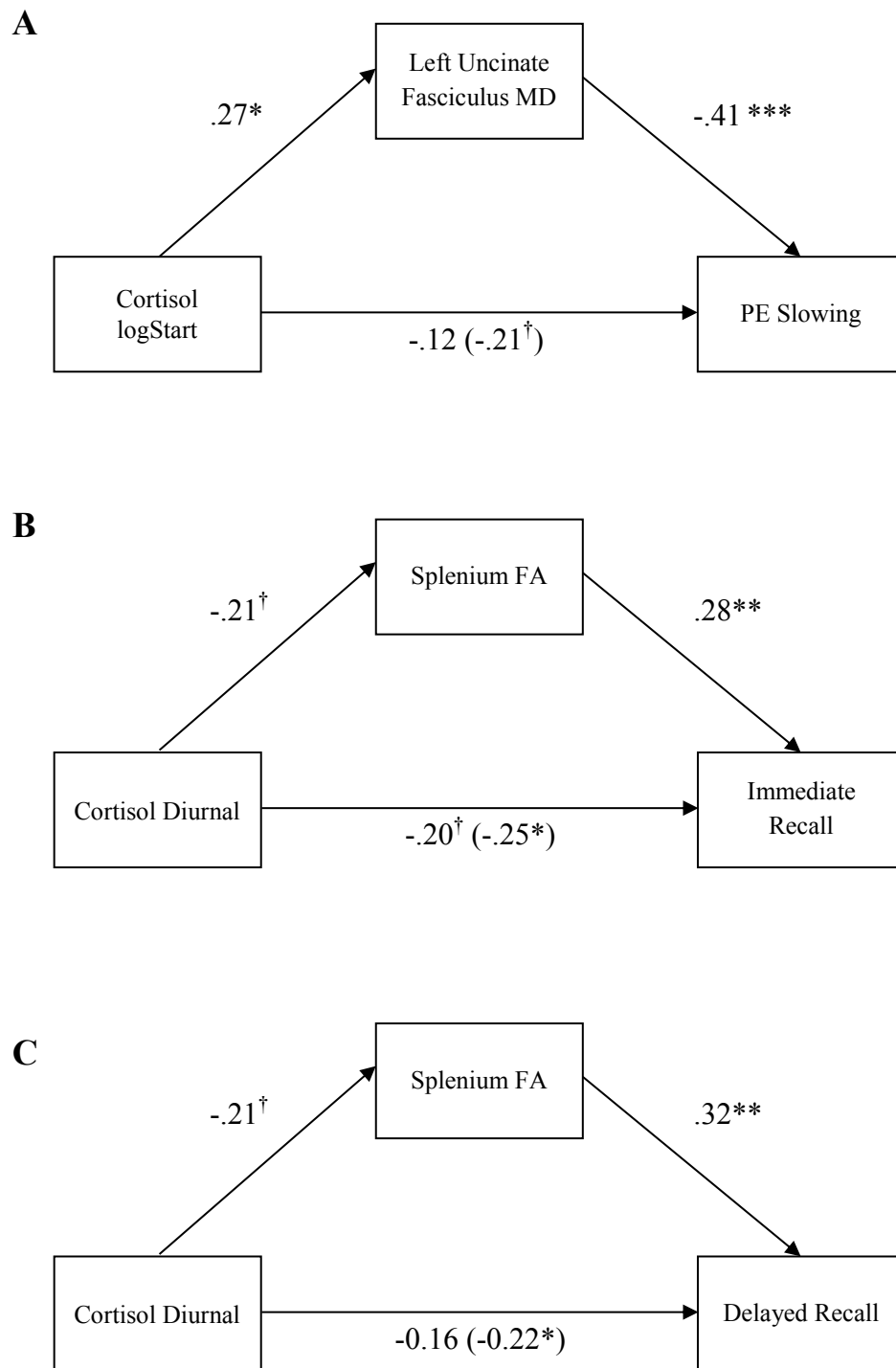


Figure 11.2. The mediating role of white matter integrity in the association between cortisol measures and A: Post-error slowing, B: Immediate verbal memory recall, and C: Delayed verbal memory recall. \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ , † trend ( $.08 < p < .05$ ). Values in parentheses denote correlation magnitude prior to mediation.

## 11.4 Discussion

This chapter aimed to directly test the hypothesis that the relationship between higher cortisol levels/flatter profiles and poorer cognitive scores reported in Chapter 10 were mediated by their mutual associations with poorer brain structural integrity (reported in Chapters 8 and 9). Mediation analysis based on both Baron and Kenny's observational step 4, and on more formal bootstrapping tests gave some support to our initial causative hypothesis for each of these cognitive abilities. However, before the implications of these findings are discussed in any detail, it is important to place them in the context of the entire study.

Firstly, the majority of significant findings did not survive correction for the large number of multiple comparisons conducted throughout this thesis. As a consequence, there is a possibility that some of the associations amongst the candidate variables for mediation have occurred by chance. Secondly, there were very few candidates for mediation analysis, even when searching uncorrected associations. Nevertheless, few studies have included measures of cortisol, brain structure and cognition function (as discussed in Chapter 4), and none have tested for mediation effects or have included tract measures. The absence of a clear precedent makes it difficult to judge the plausibility of our findings in a wider context. Thirdly, mediation analysis is asymmetric because a non-significant finding can be seen as model falsification, but a significant finding in mediation analysis only suggests support for the proposed hypothesis, but may also be consistent with other models (Penke & Deary, 2010; Salthouse, 2011) and does not rule out alternative configurations of causation between these three variables (so-called specification

error). For example, in a simple mediation model, it is possible that all three variables are inter-correlated because they are reflections of a single common factor, or that there is an alternative causal direction (e.g. better cognitive performance indicates healthier lifestyle choices, causing reduced HPA-axis regulatory disturbance by damaging the brain less). In addition, the specified models are rudimentary compared to the myriad factors that are likely to determine our cognitive decline. Finally, the measures of cortisol, cognition and brain structure are all likely subject to a large proportion of measurement error. A detailed critique of the methods has been outlined in previous chapters, and there is reasonable cause to scrutinise assumptions about i) the functional homogeneity of old, young and lesioned brains, ii) the accuracy and fidelity with which neuroimaging methods estimate underlying biology, and iii) the generalizability of our single time-point cortisol measures.

Nevertheless, the findings in this chapter represent the culmination of a detailed study, and a novel mediation perspective on the glucocorticoid (GC) hypothesis of human cognitive ageing. Landfield et al. (2007) proposed that ageing increases susceptibility to damaging GC-driven processes in certain tissue types, leading to poorer cognitive functioning. Animal and human studies suggest a role for limbic regions in HPA axis regulation (Dedovic et al., 2009; Herman et al., 2005), with rodent models and early human research supporting the role of elevated GCs in ageing as a mechanism of hippocampal damage and memory impairment (Lupien et al., 1998; Sapolsky et al., 1986). There is also some evidence that the medial and orbital prefrontal cortex, and axonal repair may be vulnerable to the damaging effects of chronically elevated GCs (e.g. Cerquiera et al., 2007; Diorio et al., 1993;

MacLulich et al., 2006; Scheff, Bernardo & Cotman, 1980). It was hypothesised that poorer performance on tests of social and emotional processing would show stronger associations with higher cortisol levels than other cognitive scores. Further, these associations would be mediated by the common associations of cortisol and social and emotional tests with orbital and cingulate frontal volumes, and the integrity of associated tracts (such as the uncinate and cingulum). However, the absence of any social and emotional tests, or any frontal lobe volumes among the candidates for mediation analysis does not provide support for this hypothesis. Instead, the analyses suggest that the relationship between lower memory function and a flatter diurnal slope is mediated by poorer callosal integrity. A number of studies have been presented which report reduced memory functioning with higher cortisol levels in ageing humans (Comijs et al., 2010; Gerritsen et al., 2009; Lee et al., 2007; Li et al., 2006), but the presence of these deficits in the absence of cortisol associations with hippocampal volume in old age may suggest that the hippocampus may not be primary mediator of this association amongst healthy ageing humans (Coluccia et al., 2008; Gold et al., 2005; Kremen et al., 2010a; MacLulich et al., 2005, 2006, 2012), although formal tests of this have not been reported. The corpus callosum is implicated as another memory network component (e.g. de Chastelaine et al., 2011) which our data seem to support (Chapter 8), and therefore the current results could represent a biologically plausible alternative explanation of the previously-reported relationship between cortisol and memory performance in old age. This alternative explanation could be usefully examined in a much larger study.

Our second finding of note is that the association between lower sensitivity to errors and higher cortisol at the start of testing was partially mediated by the integrity

of the uncinate fasciculus. This measure has not previously been reported in relation to cortisol levels in ageing, but similar bivariate (but not mediation) relationships between cortisol and general processing speed (with which PES was correlated) have been reported elsewhere (MacLulich et al., 2005; Lee et al., 2007; Kuningas et al., 2007). Though it was predicted that elevated cortisol levels would correlate with poorer integrity of the uncinate fasciculus, this tract was not specifically linked *a priori* with post-error slowing. From the examination of structure-function covariance in Chapter 8, it appears that post-error slowing may be a sensitive index of the integrity of several tracts. As such, it is conceivable that this finding reflects cortisol as a possible mechanism through which one component of the connective network underlying post-error slowing might disrupt performance via elevated cortisol levels.

For both types of cognitive performance, the finding that white matter integrity - not cortical volume - is the mediator of a cortisol-function relationship is novel, but is at odds with our prediction that limbic cortical areas and corresponding task performance would be predominantly affected by elevated cortisol. Given the limitations of the current study, a replication of these results in a larger sample would be necessary for firm conclusions to be drawn. Further research should also examine possible mechanisms by which white matter integrity might be affected by cortisol levels in humans, as the sparse research relating white matter integrity to elevated GCs (Scheff et al., 1980; Willette et al., 2011) is restricted to animals. Consequently, further work could attempt to replicate this finding in a larger study sample. However, it is uncertain why the same mechanism would affect different cognitive abilities (memory and post-error slowing), different tract measurements (FA for the



splenium and MD for the uncinate), at different time points (diurnal slope versus start levels). Previous work suggests that different supra-hypothalamic influences on HPA axis activity may be dissociable, dependent upon the type of stress (Dedovic et al., 2009), and it is possible that our findings simply reflect this, but it is equally possible that such discrepancies are an artefact of conducting a large number of multiple comparisons, such that some or all of the mediation candidates are the result of cumulative type I error.

In conclusion, we report the mediation of selective cortisol-function associations by brain structure, in accordance – at a general level - with our directional hypotheses. These data provide some support for the GC hypothesis of cognitive ageing, but only for memory functioning and PES. While we did find selectively smaller frontal regions in relation to cortisol levels, these relationships did not appear to be relevant to our measures of cognitive function. Rather, the present evidence might suggest that cortisol-function relationships are partially mediated by white matter integrity. Further to the methodological criticisms that can be levelled at our measurement and analysis techniques, the simplicity of the specified mediation model (with cortisol as the sole determinant under consideration), and the absence of alternative initial variables must also be acknowledged. Model parsimony is encouraged in small sample sizes (Penke & Deary, 2010), but the proceeding chapter will identify other variables that might index individual differences to cortisol sensitivity, and other possible determinants of cognitive ageing that could be part of more complex and comprehensive models for future study.

## Chapter 12: General Discussion & Future Directions

The overall aim of this thesis was to characterise the relationships amongst measures of cortisol, brain structure and cognitive function with particular emphasis on the prefrontal cortex. There is evidence that GC production is increasingly varied with age in humans, and chronic exposure to high levels is hypothesised to result in cognitive decline via cerebral remodelling (Landfield et al., 2007; Sapolsky et al., 1986). However, studies of GC exposure in older humans are scarce and methodological differences confound cross-study comparison. Furthermore, there has been little focus on the effects of GCs on the frontal lobes and key white matter tracts in the ageing brain. It was hypothesised that elevated cortisol levels would correlate more strongly with poorer integrity of limbic sub-regions (such as the OFC and medial structures). This thesis therefore examined relationships among cortisol levels, structural brain measures and cognitive performance in 90 healthy, elderly community-dwelling males from the Lothian Birth Cohort 1936.

## 12.1 Summary of Findings

Salivary cortisol samples characterised diurnal (morning and evening) and reactive profiles (before and after a cognitive test battery). Structural variables comprised Diffusion Tensor Imaging measures of major brain tracts and a novel manual parcellation method for the frontal lobes. The latter was based on a systematic review of current manual methods in the context of putative function and cytoarchitecture. Manual frontal lobe brain parcellation conferred greater spatial and volumetric accuracy when compared to both single- and multi-atlas parcellation at the lobar level. Cognitive ability was assessed via tests of general cognitive ability, and neuropsychological tests thought to show differential sensitivity to the integrity of frontal lobe sub-regions. The majority, but not all frontal lobe test scores shared considerable overlap with general cognitive ability, and cognitive scores correlated most consistently with the volumes of the anterior cingulate. This is further discussed below, in light of the diverse connective profile of the cingulate and a need to integrate information over more diffuse cognitive networks according to proposed de-differentiation or compensation in ageing. Individuals with higher morning, evening or pre-test cortisol levels showed consistently negative relationships with specific regional volumes and tract integrity. Participants whose cortisol levels increased between the start and end of cognitive testing showed selectively larger regional volumes and lower tract diffusivity (correlation magnitudes  $<.44$ ). The significant relationships between cortisol levels and cognition indicated that flatter diurnal slopes or higher pre-test levels related to poorer test performance. In contrast, higher levels in the morning generally correlated with better scores (correlation magnitudes  $<.25$ ). Interpretation of all findings was moderated by sensitivity to type

I error, given the large number of comparisons conducted. Though there were limited candidates for mediation analysis, cortisol-function relationships were partially mediated by tract integrity (but not sub-regional frontal volumes) for memory and post-error slowing. Thus, the presented work offers a novel perspective on the complex interplay among glucocorticoids, cognition and the structure of the ageing brain.

## 12.2 Discussion and Further Work

As cortisol is only one of many potential determinants of cognitive ageing, it is unlikely to explain a large proportion of the variance in brain structure and function. Given that relatively small to medium effect sizes were expected, this thesis paid significant attention to optimising the protocols, addressing methodological issues relating to measurement of frontal lobe function, brain structure and cortisol. Chapters 2, 7 and 8 examined the evidence that some cognitive tests show differential sensitivity to the integrity of frontal sub-regions, and reported how these measures relate to cognitive domains and brain structure in old age. It was hypothesised that our cognitive tests would show associations with the volumes of different frontal lobe sub-regions, based on neuropsychological literature.

### *12.2.1 Neural Substrates of Cognitive Performance*

Relationships between scores on neuropsychological tests and brain structure were not as predicted; rather the integrity of the anterior cingulate cortex (ACC) showed the most consistent relationships with all tests. However, extrapolating from deficits arising from frontal sub-regional lesions may not be appropriate when considering regional brain volume changes due to age. Age-related atrophy in healthy individuals appears to progress at a very slow rate (usually 0.5% per year after 60 years of age; Resnick et al., 2003), and so represents a) different mechanisms and types of structural change to those experienced in clinical lesion groups and b) the opportunity to exploit neural plasticity, by gradually shifting the pattern of recruitment of available neural resources. Moreover, the pattern of structural change

with age is far more diffuse than the relatively circumscribed lesions typical in neuropsychological studies. The ACC has been implicated in numerous cognitive tasks in younger adults, but the finding that variability in this region correlated with most task scores could also reflect the central role of the ACC in integrating information across a more distributed neural network (a role for which it is well-placed in light of its connective and architectural properties).

Indeed, recent functional imaging studies support the idea that the neural correlates of particular tasks differ between old and young, with auxiliary activations in older participants (de Chastelaine et al., 2011; Goh, 2011; Park & Reuter-Lorenz, 2009). However, what this divergent pattern of BOLD activity represents, whether this is common to all tasks and to all individuals, remains to be seen. Nevertheless, selecting established components of the well-characterised network involved in verbal memory ability, Chapter 7 demonstrated that better integrity of the right dorsolateral prefrontal cortex (DLPFC) was positively correlated with immediate verbal memory recall, but only for poor performers. Similarly, the integrity of the anterior and posterior corpus callosum showed significant associations with delayed verbal memory recall, for the high and low groups respectively. This finding is interesting because it seemingly replicates - with structural MRI data – recent findings from fMRI and DTI (de Chastelaine et al., 2011; Duverne et al., 2009). Future work could adopt a similar strategy to examine whether the neurostructural correlates of other tasks vary as a function of ability in old age. Differences in age-related decline in other connective, cortical and subcortical components are also likely to contribute to declines in cognitive performance, but this study only focussed on the frontal lobes and so was unable to account for this. Thus, further studies could

usefully integrate brain-wide information about the cortex, white matter interconnectivity and sub-cortical structures to build a clearer picture of the brain's functional architecture and its age-associated change. This would represent a major challenge, necessitating large datasets, broad tests of cognitive function, and currently even the most recent studies investigating neural substrates of cognitive performance do not combine connectivity analysis with measures of node integrity (e.g. Wen et al., 2011; van den Heuvel & Sporns, 2011). The LBC1936 is well-placed to obtain – and then combine – such measures in order to examine task-relevant networks, the functional impact of their change over time, and identify possible explanatory variables.

However, as discussed in Chapters 3 and 5, the methods for quantifying brain structure are numerous, with different strengths and drawbacks. By systematically reviewing the extant approaches for manually identifying frontal lobe sub-regions in the context of functional, cytoarchitectural and hodological characteristics, a highly reproducible parcellation protocol was developed and implemented. Automated segmentation of the entire frontal lobe was comparatively inaccurate (but showed the potential for future refinement); though sub-regional parcellation using automated methods is attractive for large cohorts, a manual approach is preferred where feasible (Chapter 6). This work suggests several avenues for further research. First, even in large cohorts, there is a need to minimise measurement error – the assumption of equivalence made by popular automatic segmentation tools is clearly flawed (because they use single-atlas approaches that cannot fully account for individual differences in morphology), and some labs have observed problems with such tools in terms of their reproducibility (René Mandl, Neuroimaging Research Group,

University Medical Centre, Utrecht – personal communication; Dr Mark Bastin & Colin Buchanan, Brain Research Imaging Centre, University of Edinburgh – personal communication). In the broader context of connectome and structural network analysis, this work also has implications for the precision with which nodes are identified, and consequently the reliability of between-subject comparisons of the connective pathways themselves. The development of improved brain parcellation methods is desirable; for example, a semi-automated method that allows direct user input to identify relevant landmarks with a fast intuitive interface, or by incorporating meta-data (such as presence of specific variations, degree of atrophy, in order to select the most appropriate atlas) into an automated multi-atlas approach should be a priority in order to address these issues. Secondly, the relationship between cortical morphology and functional-cytoarchitectonic properties is still in need of further study. In particular, the posterior boundaries for the frontal pole and anterior cingulate remain to be clearly elucidated. Thirdly, the practical implications of applying different sub-regional boundaries has not been addressed, but would be a useful exercise to highlight the importance of protocol design and selection. Two projects are currently underway to i) demonstrate the volumetric implications of various manual parcellation methods, and ii) compare the pattern of associations between volumes derived from different parcellation methods and cognitive performance.



### *12.2.2 Cortisol, Brain Structure and Function in Healthy Old Age*

As reviewed in Chapter 4, few studies have combined measures of cortisol, brain structure and cognitive functioning in an elderly cohort. Several have examined cortisol and brain structure, or cortisol and cognitive function, but few have focussed on the frontal lobes or combined indices of cortisol, brain structure and cognition. Moreover, none have formally tested the hypothesis that brain structure mediates the negative relationship between cortisol levels and cognitive performance. In the present study, flatter diurnal slope, and elevated cortisol before or after cognitive testing were generally associated with poorer cognitive performance. Higher cortisol levels in the evening or at the start of cognitive testing were associated with a smaller left medial superior frontal gyrus and higher mean diffusivity of the left uncinate fasciculus. A flatter diurnal slope showed a trend association with lower fractional anisotropy in the splenium of the corpus callosum. Finally, Chapter 10 reported a formal statistical test of the hypothesis that measures of brain structure mediate the relationship between elevated cortisol levels in old age and poorer cognitive functioning. The mean diffusivity of the left uncinate fasciculus significantly mediated the relationship between cortisol levels at the start of the cognitive testing battery and post-error slowing. Fractional anisotropy of the splenium of the corpus callosum significantly mediated the relationship between diurnal cortisol slope and both immediate and delayed verbal memory recall. This latter finding could offer an alternative explanation for the failure of several studies to replicate a negative association between cortisol levels and hippocampal volume, in spite of numerous reports of negative cortisol-memory ability correlations.

Although this could be taken as support for the hypothesis that GCs are a determinant of cognitive ageing via their negative effects on brain structure, there are several reasons to treat these results with caution. As discussed at the outset of this thesis (General Introduction), the corss-sectional design of the research herein does not allow a direct test of the causal relationships amongst cortisol, brain structure and cognition because intra-individual change was not measured. Measures of cortisol over time relative to cognitive decline in the context of actual volumetric change in the same ROIs would be required to provide a clearer picture of these variables' diachronic interplay in ageing. As such, although a causal hypothesis can be tested using cross-sectional data, the reported studies represent a snapshot of a single period in old age, rather than a study of ageing *per se*. The study design necessitated a large number of simultaneous comparisons, only a single correlation (between the Simon Effect and volume of the DLPFC) survived correction procedures. The adoption of False Discovery Rate was based on reports that it is more appropriate (less conservative) in preliminary investigations where replication will be required, such that bias against true positive findings is alleviated with the cost of some increased risk of type I error (Pike, 2011). Although attempts were made to interpret results in the light of both FDR and plausible patterns in the results that may be present at above-chance levels, the fact that even this liberal correction procedure attenuated most results to non-significance is a key point. The cortisol-structure-cognition associations were examined in unprecedented detail, but such detail increases the likelihood of erroneously rejecting null hypotheses. Further work could use bootstrapping techniques to further investigate instances where the pattern of relationships reported herein is plausible, but individual results – even where three-

way associations appear to hold as with the mediation candidates – could represent false discoveries in this comparatively low-powered study. Although chronic exposure to extremely high levels of cortisol are damaging to brain and behaviour (Patil et al., 2007), it could be that cortisol levels in the healthy individuals in the current sample were not sufficient to produce a detectable affected .

Moreover, the data were cross-sectional, limiting our ability to infer cause and effect, and generalisations of these findings to older individuals of different age-ranges to the sample studied herein. Though this study is therefore an observation on the relationship between cortisol, cognitive scores and brain structure *in old age* (rather than *in ageing*), the current data offers an informative test-bed for the hypothesis that elevated cortisol is a determinant of cognitive ageing through its deleterious effects of brain structure. The study was an entirely male sub-sample within a self-selecting cohort who met a strict set of inclusion criteria, and therefore not representative of the general UK population. Also, relatively little work has been conducted regarding GC effects on the brain's white matter, aside from several studies in rodents and one in monkeys (Scheff, Bernardo & Cottman, 1980; Scheff & DeKosky, 1983, 1989; Willette et al., 2011). Rodent models suggest that elevated GCs in old age may impair axonal repair following damage, but it is important to acknowledge that cortisol may not be the only mechanism to affect white matter integrity. These relationships should be examined in light of other potential determinants of brain structural decline in old age, to identify the unique contributions that cortisol might make to brain structure, and also to subsequent cognitive performance. Furthermore, numerous additional factors have been identified which might confer differential sensitivity to lifetime GC exposure.

Variability in the production of another endogenous steroid, dehydroepiandrosterone (DHEA) which is thought to have anti-glucocorticoid effects may confer some neuroprotective effects (Heaney et al., 2011; van Niekerk, Huppert & Hubert, 2001). DHEA is thought to regulate the enzyme 11 $\beta$ -HSD1; an enzyme which converts inert cortisone into active GC (Holmes & Seckl, 2006), thus endogenous levels of this enzyme may also mediate the effects of chronic GC exposure (MacLulich et al., 2012). Other factors could be exercise (Liu et al., 2010), diet (Wilette et al., 2011), blood pressure (MacLulich et al., 2009), genetic status (*APOE*: Gerritsen et al 2009; Lee et al., 2008; *APOE* & *TOMM40*: Bruno et al., 2011, but see Fiocco et al., 2008). A large cohort with longitudinal design and measures of cortisol would be required in order to take account of so many possible covariates.

The temporal stability of the cortisol profile, and also the transience of the effects of cortisol on the brain merit further consideration. Effects seem at least partially reversible in Cushing's syndrome (Toffanin et al., 2011), so it could be that any effects of cortisol on dendrite arbours or axonal sprouting are only concomitant with a period of high cortisol. A recent review suggested that stress-induced remodelling in the PFC can be brought about relatively rapidly, and that reversible effects may also be potentially rapid (Czeh et al., 2008). Similarly, surgical treatment of Cushing's disease leads to at least partial reversal of the structural and cognitive effects (reviewed in Patil et al., 2007). Therefore, the extent of any observed effects could fluctuate with alterations in cortisol profile (and possibly other factors) from year to year. Even if our findings do reflect some direct relationship between cortisol and function, via brain structure, the assumption that this represents the static state of affairs or concrete negative trajectory for each individual may be flawed (note also

that longitudinal studies of brain structures report transient volumetric increases as well as decreases with increasing age, e.g. Raz et al., 2010).

Conversely, a large longitudinal study ( $n=911$ ) reported stable cross-sectional associations between high cortisol and poorer cognitive function (Gerritsen et al., 2009), but elevated levels of cortisol do not seem to confer a faster cognitive decline (but see Beluche et al., 2010, Li et al., 2006). Might elevated lifetime cortisol levels, or at a critical period in the lifecourse reduce the age at which various cognitive abilities begin their downward trajectory? It could be that, although there is less variance in cortisol levels in young humans, certain times in development and young-adulthood are more sensitive to smaller differences in cortisol. As such, an individual exposed to slightly higher cortisol levels in their youth might actually result in poorer cognitive ability throughout the lifecourse and into old age. It may be that there is a critical period of sensitivity to GCs early in the lifecourse, but that cortisol levels of the magnitude found in healthy old age are not sufficiently high to cause accelerated decline beyond a decreased sensitivity threshold. There is some further evidence to support this; children's cognitive function was reported to predict cortisol levels forty-five years later in adulthood (Power, Li & Hertzman, 2008), and a recent review suggests that exposure to stress in early-life may have ramifications for cognitive ability at least into early adulthood (Hedges & Woon, 2011). It is also likely that many of the rodent models examining cortisol, brain structure and cognition use relatively young animals. A recent study reported that dendritic spine loss in response to a behavioural stress paradigm was only present in young rodents, while spines in middle and old-aged animals were remarkably stable (Bloss et al., 2011).

The current dataset allows an extension of the work by Power et al. (2008), who showed associations between childhood cognitive function and cortisol in middle-age. The presence of age 11 intelligence scores for the participants in this study allows a unique examination of how cortisol levels in old age relate to cognitive change from childhood (measured by the Moray House Test taken at age 11), and cognitive change from peak intelligence (as measured by the National Adult Reading Test; both described in Chapter 5). The table in Appendix G shows correlations between the six cortisol metrics and measures of g, speed of processing, immediate and delayed memory recall controlled for participants' IQ at age 11 and peak IQ. The results indicate that higher cortisol in response to a cognitive stressor (at the START and END of the cognitive test battery) is more strongly related to change in intelligence over the lifecourse than simply decline from peak IQ. Assuming that individual differences in cortisol levels are sufficiently stable across the lifespan to allow inferences to be drawn from our current measures of salivary cortisol in old age, this offers support to the idea that early life influences might influence an individual's trajectory towards their cognitive status in old age. Measures of allostatic load experienced in childhood and throughout the lifespan might offer further insights into determinants of old age cognitive ability (Evans & Kim, 2012; Lehman et al., 2005).

In summary, the work contained in this thesis makes valid contributions to cognitive ageing research. Methodological issues such as appropriate measures of brain structure and cognitive function are addressed, in addition to the role of cortisol as a potential determinant of cognitive ability in old age. Further development of methods, exploration of the brain's functional organisation in old age, and

identification of valid allostatic markers throughout the lifecourse in the current cohort will help to characterise the decline of complex cognitive ability with ageing.

## References

- Ahn, R., Lee, Y., Choi, J., Kwon, H.-B., & Chun-S-i. (2007). Salivary cortisol and DHEA levels in the Korean population: age-related differences, diurnal rhythm, and correlations with serum levels. *Yonsei Medical Journal*, 48(3), 379–388. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2628086/>
- Akana, S. F., Chu, a, Soriano, L., & Dallman, M. F. (2001). Corticosterone exerts site-specific and state-dependent effects in prefrontal cortex and amygdala on regulation of adrenocorticotrophic hormone, insulin and fat depots. *Journal of Neuroendocrinology*, 13(7), 625–637. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11442777>
- Allen, J. S., Tranel, D., Bruss, J., & Damasio, H. (2006). Correlations between regional brain volumes and memory performance in anoxia. *Journal of Clinical and Experimental Neuropsychology*, 28(4), 457–476. doi:10.1080/13803390590949287
- Allman, J., Hakeem, a., & Watson, K. (2002). Book Review: Two Phylogenetic Specializations in the Human Brain. *The Neuroscientist*, 8(4), 335–346. doi:10.1177/107385840200800409
- Allman, J. M., Watson, K. K., Tetreault, N. a, & Hakeem, A. Y. (2005). Intuition and autism: a possible role for Von Economo neurons. *Trends in Cognitive Sciences*, 9(8), 367–373. doi:10.1016/j.tics.2005.06.008
- Almeida, D. M., Piazza, J. R., & Stawski, R. S. (2009). Interindividual differences and intraindividual variability in the cortisol awakening response: an examination of age and gender. *Psychology and Aging*, 24(4), 819–827. doi:10.1037/a0017910
- Arnsten, A. F. T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews: Neuroscience*, 10(6), 410–422. doi:10.1038/nrn2648
- Aron, A. R., Robbins, T. W., & Poldrack, R. A. (2004). Inhibition and the right inferior frontal cortex. *Trends in Cognitive Sciences*, 8(4), 170–177. doi:10.1016/j.tics.2004.02.010
- Asami, T., Hayano, F., Nakamura, M., Yamasue, H., Uehara, K., Otsuka, T., Roppongi, T., et al. (2008). Anterior cingulate cortex volume reduction in patients with panic disorder. *Psychiatry and Clinical Neurosciences*, 62(3), 322–330. doi:10.1111/j.1440-1819.2008.01800.x
- Baaré, W. F., Hulshoff Pol, H. E., Hijman, R., Mali, W. P., Viergever, M. A., & Kahn, R. S. (1999). Volumetric analysis of frontal lobe regions in



- schizophrenia: relation to cognitive function and symptomatology. *Biological Psychiatry*, 45(12), 1597–1605. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10376121>
- Baker, S. C., Rogers, R. D., Owen, M., Frith, C. D., Dolan, R. J., Frackowiak, R. S., & Robbins, T. W. (1996). Neural systems engaged by planning: a PET study of the Tower of London task. *Neuropsychologia*, 34(6), 515–526. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8736565>
- Ballmaier, M., Toga, A., Blanton, R., Sowell, E. R., Lavretsky, H., Peterson, B. S., Pham, D., et al. (2004). Anterior cingulate, gyrus rectus, and orbitofrontal abnormalities in elderly depressed patients: an MRI-based parcellation of the prefrontal cortex. *American Journal of Psychiatry*, 161, 99–108. Retrieved from <http://ajp.psychiatryonline.org/cgi/content/abstract/161/1/99>
- Barbey, A.K., Colom, R., Solomon, J., Krueger, F., Forbes, C., & Grafman, J. (2010). An integrative architecture for general intelligence and executive function revealed by lesion mapping. *Brain*, 135(4), 1154–1164.
- Barcelo, F., & Knight, R. T. (2002). Both random and perseverative errors underlie WCST deficits in prefrontal patients. *Neuropsychologia*, 40, 349–356.
- Barch, D. M., Braver, T. S., Akbudak, E., Conturo, T., Ollinger, J., & Snyder, A. (2001). Anterior cingulate cortex and response conflict: effects of response modality and processing domain. *Cerebral Cortex*, 11(9), 837–848. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11532889>
- Barnes, J., Godbolt, A. K., Frost, C., Boyes, R. G., Jones, B. F., Scahill, R. I., Rossor, M. N., et al. (2007). Atrophy rates of the cingulate gyrus and hippocampus in AD and FTLD. *Neurobiology of Aging*, 28(1), 20–28. doi:10.1016/j.neurobiolaging.2005.11.012
- Bastin, M.E., Munoz Maniega, S., Ferguson, K.J., Brown, L.J., Wardlaw, J.M., MacLullich, A.M., Clayden, J.D. (2010). Quantifying the effects of normal ageing on white matter structure using unsupervised tract shape modelling. *NeuroImage* 2010;51:1–10.
- Batty, G. D., Deary, I. J., & Gottfredson, L. S. (2007). Premorbid (early life) IQ and later mortality risk: systematic review. *Annals of Epidemiology*, 17(4), 278–288. doi:10.1016/j.annepidem.2006.07.010
- Batty, G. D., Wennerstad, K. M., Smith, G. D., Gunnell, D., Deary, I. J., Tynelius, P., & Rasmussen, F. (2009). IQ in early adulthood and mortality by middle age: cohort study of 1 million Swedish men. *Epidemiology*, 20(1), 100–109. doi:10.1097/EDE.0b013e31818ba076
- Beauchamp, M., Dagher, A., Aston, J.A., & Doyon, J. (2003). Dynamic functional changes associated with cognitive skill learning of an adapted version of the

Tower of London task. *NeuroImage*, 20(3), 1649–1660.  
doi:10.1016/j.neuroimage.2003.07.003

- Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, 50(1-3), 7–15. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8039375>
- Bechara, A., Damasio, H., Tranel, D., & Anderson, S. W. (1998). Dissociation Of working memory from decision making within the human prefrontal cortex. *The Journal of Neuroscience*, 18(1), 428–437. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9412519>
- Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1997). Deciding advantageously before knowing the advantageous strategy. *Science*, 275(5304), 1293–1295. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9036851>
- Bechara, A., Dolan, S., Denburg, N., Hindes, A., Anderson, S. W., & Nathan, P. E. (2001). Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia*, 39(4), 376–389. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11164876>
- Bechara, A., Tranel, D., Damasio, H., & Damasio, A. R. (1996). Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. *Cerebral Cortex*, 6(2), 215–225. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8670652>
- Beckmann, M., Johansen-Berg, H., & Rushworth, M. F. S. (2009). Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *The Journal of Neuroscience*, 29(4), 1175–1190. doi:10.1523/JNEUROSCI.3328-08.2009
- Beer, J. S., Heerey, E. a, Keltner, D., Scabini, D., & Knight, R. T. (2003). The regulatory function of self-conscious emotion: insights from patients with orbitofrontal damage. *Journal of Personality and Social Psychology*, 85(4), 594–604. doi:10.1037/0022-3514.85.4.594
- Beer, J. S., John, O. P., Scabini, D., & Knight, R. T. (2006). Orbitofrontal cortex and social behavior: integrating self-monitoring and emotion-cognition interactions. *Journal of Cognitive Neuroscience*, 18(6), 871–879. doi:10.1162/jocn.2006.18.6.871
- Beluche, I., Carrière, I., Ritchie, K., & Ancelin, M. L. (2010). A prospective study of diurnal cortisol and cognitive function in community-dwelling elderly people. *Psychological Medicine*, 40(6), 1039–1049. doi:10.1017/S0033291709991103

- Benoit, R. G., Gilbert, S. J., Volle, E., & Burgess, P. W. (2010). When I think about me and simulate you: medial rostral prefrontal cortex and self-referential processes. *NeuroImage*, 50(3), 1340–1349. doi:10.1016/j.neuroimage.2009.12.091
- Berlin, H. A., Rolls, E. T., & Kischka, U. (2004). Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. *Brain*, 127(5), 1108–1126. doi:10.1093/brain/awh135
- Bergman, R.A.; Afifi, A.K. (2005). *Functional neuroanatomy: text and atlas*. New York: McGraw-Hill
- Berman, K. F., Ostrem, J. L., Randolph, C., Gold, J., Goldberg, T. E., Coppola, R., Carson, R. E., et al. (1995). Physiological activation of a cortical network during performance of the Wisconsin Card Sorting Test: a positron emission tomography study. *Neuropsychologia*, 33(8), 1027–1046. Retrieved from <http://linkinghub.elsevier.com/retrieve/pii/0028393295000352>
- Bernal, B. & Ardila, A. (2009). The role of the arcuate fasciculus in conduction aphasia. *Brain*, 132, 2309–2316.
- Berthoz, S., Armony, J. L., Blair, R. J. R., & Dolan, R. J. (2002). An fMRI study of intentional and unintentional (embarrassing) violations of social norms. *Brain*, 125(8), 1696–1708. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12135962>
- Bird, C. M., Castelli, F., Malik, O., Frith, U., & Husain, M. (2004). The impact of extensive medial frontal lobe damage on “Theory of Mind” and cognition. *Brain*, 127(Pt 4), 914–928. doi:10.1093/brain/awh108
- Bjork, J. M., Momenan, R., & Hommer, D. W. (2009). Delay discounting correlates with proportional lateral frontal cortex volumes. *Biological Psychiatry*, 65(8), 710–713. doi:10.1016/j.biopsych.2008.11.023
- Bland JM, Altman DG (1986): Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, 1, 307–310.
- Bloss, E. B., Janssen, W. G., Ohm, D. T., Yuk, F. J., Wadsworth, S., Saardi, K. M., McEwen, B. S., et al. (2011). Evidence for reduced experience-dependent dendritic spine plasticity in the aging prefrontal cortex. *The Journal of Neuroscience*, 31(21), 7831–7839. doi:10.1523/JNEUROSCI.0839-11.2011
- Boghi, A., Rasetti, R., Avidano, F., Manzone, C., Orsi, L., D’Agata, F., Caroppo, P., et al. (2006). The effect of gender on planning: An fMRI study using the Tower of London task. *NeuroImage*, 33(3), 999–1010. doi:10.1016/j.neuroimage.2006.07.022

- Botteron, K. N., Raichle, M. E., Drevets, W. C., Heath, A. C., & Todd, R. D. (2002). Volumetric reduction in left subgenual prefrontal cortex in early onset depression. *Biological Psychiatry*, 51(4), 342–344. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11958786>
- Botvinick, Matthew M. (2007). Conflict monitoring and decision making: reconciling two perspectives on anterior cingulate function. *Cognitive, Affective & Behavioral Neuroscience*, 7(4), 356–366. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18189009>
- Botvinick, Matthew M, Cohen, J. D., & Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: an update. *Trends in Cognitive Sciences*, 8(12), 539–546. doi:10.1016/j.tics.2004.10.003
- Boyle, M.P., Brewer, J.A., Funatsu, M., Wozniak, D.F., Tsien, J.Z., Izumi, Y. & Muglia, L.J. (2005). Acquired deficit of forebrain glucocorticoid receptor produces depression-like changes in adrenal axis regulation and behaviour. *Proceedings of the National Academy of Sciences*, 102(2), 473-478.
- Brambati, S. M., Rankin, K. P., Narvid, J., Seeley, W. W., Dean, D., Rosen, H. J., Miller, B. L., et al. (2009). Atrophy progression in semantic dementia with asymmetric temporal involvement: a tensor-based morphometry study. *Neurobiology of Aging*, 30(1), 103–111. doi:10.1016/j.neurobiolaging.2007.05.014
- Brambilla, P., Nicoletti, M. a, Harenski, K., Sassi, R. B., Mallinger, A. G., Frank, E., Kupfer, D. J., et al. (2002). Anatomical MRI study of subgenual prefrontal cortex in bipolar and unipolar subjects. *Neuropsychopharmacology*, 27(5), 792–799. doi:10.1016/S0893-133X(02)00352-4
- Bremner, J. D., Bronen, R. A., Erasquin, G. D., Vermetten, E., Staib, L. H., Ng, C. K., Soufer, R., et al. (1998). Development and reliability of a method for using magnetic resonance imaging for the definition of regions of interest for Positron Emission Tomography. *Clinical Positron Imaging*, 1(3), 145–159.
- Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles. *Trends in Cognitive Sciences*, 14, 277–290. doi:10.1016/j.tics.2010.04.004
- Brown, W. (1910). Some experimental results in the correlation of mental abilities. *British Journal of Psychology*, 3, 296–322.
- Brown, S.M., Henning, S., & Wellman, C.L. (2005). Mild, short-term stress alters dendrite morphology in rat medial prefrontal cortex. *Cerebral Cortex*, 15(11), 1714-1722. doi: 10.1093/cercor/bhi048
- Brotis, A. G., Kapsalaki, E. Z., Paterakis, K., Smith, J. R., & Fountas, K. N. (2009). Historic evolution of open cingulectomy and stereotactic cingulotomy in the

management of medically intractable psychiatric disorders, pain and drug addiction. *Stereotactic and Functional Neurosurgery*, 87(5), 271–291. doi:10.1159/000226669

- Buchanan, T. W., Kern, S., Allen, J. S., Tranel, D., & Kirschbaum, C. (2004). Circadian regulation of cortisol after hippocampal damage in humans. *Biological Psychiatry*, 56(9), 651–656. doi:10.1016/j.biopsych.2004.08.014
- Buchsbaum, B. R., Greer, S., Chang, W. L., & Berman, K. F. (2005). Meta-analysis of neuroimaging studies of the Wisconsin card-sorting task and component processes. *Human Brain Mapping*, 25(1), 35–45. doi:10.1002/hbm.20128
- Buchsbaum, B. R., Padmanabhan, A., & Berman, K. F. (2011). The neural substrates of recognition memory for verbal information: Spanning the divide between short-and long-term memory. *Journal of Cognitive Neuroscience*, 23(4), 978–991. doi:10.1162/jocn.2010.21496.The
- Buckner, R.L. & Logan, J.M. (2002). Frontal contributions to episodic memory encoding in the young and elderly. In: Parker AE, Wilding EL, Bussey T, editors. *The Cognitive Neuroscience of Memory Encoding and Retrieval*. Philadelphia: Psychology Press. p. 59-81.
- Burgess, P. W., Simons, J. S., Dumontheil, I., & Gilbert, S. J. (2006). The gateway hypothesis of rostral prefrontal cortex (area 10) function. In J. Duncan, L. H. Phillips, & P. McLeod (Eds.), *Measuring the Mind: Speed, Control and Age*. (Vol. 11, pp. 217–248). Oxford University Press, Oxford. doi:10.1016/j.tics.2007.05.004
- Burzynska, A. Z., Nagel, I. E., Preuschhof, C., Gluth, S., Bäckman, L., Li, S.-C., Lindenberger, U., et al. (2012). Cortical thickness is linked to executive functioning in adulthood and aging. *Human Brain Mapping*, 33(7), 1607-1620. doi:10.1002/hbm.21311
- Bush, G., Luu, P., & Posner, M. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, 4(6), 215–222. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10827444>
- Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience*, 12(1), 1–47. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10769304>
- Cabeza, R., Dolcos, F., Graham, R., & Nyberg, L. (2002). Similarities and differences in the neural correlates of episodic memory retrieval and working memory. *NeuroImage*, 16(2), 317–330. doi:10.1006/nimg.2002.1063
- Calvin, C.M., Deary, I.J., Fenton, C., Roberts, B.A., Der, G., Leckenby, N., & Batty, G.D. (2011). Intelligence in youth and all-cause mortality: Systematic review and meta-analysis. *International Journal of Epidemiology*, 40(3), 626-644.

- Cantor-Graae, E., Warkentin, S., Franzen, G., & Risberg, J. (1993). Frontal lobe challenge: A comparison of activation procedures during rCBF measurements in normal subjects. *Neuropsychiatry, Neuropsychology and Behavioral Neurology*, 6(2), 83–92. Retrieved from [http://journals.lww.com/cogbehavneurol/Abstract/1993/04000/Frontal\\_Lobe\\_Challenge\\_\\_A\\_Comparison\\_of\\_Activation.3.aspx](http://journals.lww.com/cogbehavneurol/Abstract/1993/04000/Frontal_Lobe_Challenge__A_Comparison_of_Activation.3.aspx)
- Carper, R. A., & Courchesne, E. (2005). Localized enlargement of the frontal cortex in early autism. *Biological Psychiatry*, 57(2), 126–133. doi:10.1016/j.biopsych.2004.11.005
- Carter, C. S., & van Veen, V. (2007). Anterior cingulate cortex and conflict detection: an update of theory and data. *Cognitive, Affective & Behavioral neuroscience*, 7(4), 367–379. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18189010>
- Catani, M., Dell’acqua, F., Vergani, F., Malik, F., Hodge, H., Roy, P., Valabregue, R., et al. (2012). Short frontal lobe connections of the human brain. *Cortex*, 48(2), 273–391. doi:10.1016/j.cortex.2011.12.001
- Catani, M., & Thiebaut de Schotten, M. (2008). A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*, 44(8), 1105–1132. doi:10.1016/j.cortex.2008.05.004
- Cazalis, F., Valabregue, R., Pelegrini-Issac, M., Asloun, S., Robbins, T. W., & Granon, S. (2003). Individual differences in prefrontal cortical activation on the Tower of London planning task: implication for effortful processing. *European Journal of Neuroscience*, 17(10), 2219–2225. doi:10.1046/j.1460-9568.2003.02633.x
- Cazalis, F., Feydy, A., Valabrègue, R., Pélérini-Issac, M., Pierot, L., & Azouvi, P. (2006). fMRI study of problem-solving after severe traumatic brain injury. *Brain Injury*, 20(10), 1019–1028. doi:10.1080/02699050600664384
- Cerqueira, J. J., Almeida, O. F. X., & Sousa, N. (2008). The stressed prefrontal cortex. Left? Right! *Brain, Behavior, and Immunity*, 22(5), 630–638. doi:10.1016/j.bbi.2008.01.005
- Cerqueira, J. J., Mailliet, F., Almeida, O. F. X., Jay, T. M., & Sousa, N. (2007). The prefrontal cortex as a key target of the maladaptive response to stress. *The Journal of Neuroscience*, 27(11), 2781–2787. doi:10.1523/JNEUROSCI.4372-06.2007
- Cerqueira, J. J., Pêgo, J. M., Taipa, R., Bessa, J. M., Almeida, O. F. X., & Sousa, N. (2005). Morphological correlates of corticosteroid-induced changes in prefrontal cortex-dependent behaviors. *The Journal of Neuroscience*, 25(34), 7792–7800. doi:10.1523/JNEUROSCI.1598-05.2005

- Chaouloff, F., & Groc, L. (2011). Temporal modulation of hippocampal excitatory transmission by corticosteroids and stress. *Frontiers in Neuroendocrinology*, 32(1), 25-42. doi:10.1016/j.yfrne.2010.07.004
- Chiavaras, M. M., LeGoualher, G., Evans, a, & Petrides, M. (2001). Three-dimensional probabilistic atlas of the human orbitofrontal sulci in standardized stereotaxic space. *NeuroImage*, 13(3), 479–496. doi:10.1006/nimg.2000.0641
- Chiavaras, M. M., & Petrides, M. (2000). Orbitofrontal sulci of the human and macaque monkey brain. *The Journal of Comparative Neurology*, 422(1), 35–54. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11170813>
- Ciaramelli, E., Muccioli, M., Làdavas, E., & di Pellegrino, G. (2007). Selective deficit in personal moral judgment following damage to ventromedial prefrontal cortex. *Social Cognitive and Affective Neuroscience*, 2(2), 84–92. doi:10.1093/scan/nsm001
- Cicerone, K., & Tanenbaum, L. (1997). Disturbance of social cognition after traumatic orbitofrontal brain injury. *Archives of Clinical Neuropsychology*, 12(2), 173–188. Retrieved from <http://linkinghub.elsevier.com/retrieve/pii/S0887617796000224>
- Cima, M., Tonnaer, F., & Hauser, M. D. (2010). Psychopaths know right from wrong but don't care. *Social Cognitive and Affective Neuroscience*, 5(1), 59–67. doi:10.1093/scan/nsp051
- Cockrell, J.R. & Folstein, M.F.(1988). Mini-mental state examination (MMSE). *Psychopharmacology Bulletin*, 24:689–692
- Cohen, M. X., Ridderinkhof, K. R., Haupt, S., Elger, C. E., & Fell, J. (2008). Medial frontal cortex and response conflict: evidence from human intracranial EEG and medial frontal cortex lesion. *Brain Research*, 1238, 127–142. doi:10.1016/j.brainres.2008.07.114
- Cohen, R., Kaplan, R., Moser, D., Jenkins, M., & Wilkinson, H. (1999). Impairments of attention after cingulotomy. *Neurology*, 53, 819–824. Retrieved from <http://www.neurology.org/cgi/content/abstract/53/4/819>
- Cole, M. W., Yeung, N., Freiwald, W. a, & Botvinick, M. (2009). Cingulate cortex: diverging data from humans and monkeys. *Trends in Neurosciences*, 32(11), 566–574. doi:10.1016/j.tins.2009.07.001
- Colom, R. (2007). Intelligence? What intelligence? *Behavioral and Brain Sciences*, 30,155–156.
- Colom, R., Haier, R.J., Head, K., Álvarez-Linera, J., Quiroga, M.Á., Shih, P.C., & Jung, R.E. (2009). Gray matter correlates of fluid, crystallized and spatial intelligence: Testing the P-FIT model. *Intelligence*, 37(2), 124-135.

- Coluccia, D., Wolf, O. T., Kollias, S., Roozendaal, B., Forster, A., & de Quervain, D. J.-F. (2008). Glucocorticoid therapy-induced memory deficits: acute versus chronic effects. *The Journal of Neuroscience*, 28(13), 3474–3478. doi:10.1523/JNEUROSCI.4893-07.2008
- Convit, A., Wolf, O. T., de Leon, M. J., Patalinjug, M., Kandil, E., Caraos, C., Scherer, A., et al. (2001). Volumetric analysis of the pre-frontal regions: findings in aging and schizophrenia. *Psychiatry Research: Neuroimaging*, 107(2), 61–73. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11530273>
- Cook, S. C., & Wellman, C. L. (2004). Chronic stress alters dendritic morphology in rat medial prefrontal cortex. *Journal of Neurobiology*, 60(2), 236–248. doi:10.1002/neu.20025
- Cools, R., Stefanova, E., Barker, R., Robbins, T., & Owen, M. (2002). Dopaminergic modulation of high-level cognition in Parkinson's disease: the role of the prefrontal cortex revealed by PET. *Brain*, 125(3), 584–594. doi:10.1093/brain/awf052
- Coryell, W., Nopoulos, P., Drevets, W., Wilson, T., & Andreasen, N. C. (2005). Subgenual prefrontal cortex volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. *The American Journal of Psychiatry*, 162(9), 1706–1712. Retrieved from <http://cat.inist.fr/?aModele=afficheN&cpsidt=17098877>
- Craik, F. I. M., & Rose, N. S. (2012). Memory encoding and aging: A neurocognitive perspective. *Neuroscience and Biobehavioral Reviews*, 36(7), 1729–1739. doi:10.1016/j.neubiorev.2011.11.007
- Crespo-Facorro, B., Kim, J. J., Andreasen, N. C., O'Leary, D. S., Wiser, a K., Bailey, J. M., Harris, G., et al. (1999). Human frontal cortex: an MRI-based parcellation method. *NeuroImage*, 10(5), 500–519. doi:10.1006/nimg.1999.0489
- Crawford, J. R., Mychalkiw, B., Johnson, D. A., & Moore, J. W. (1996). WAIS-R short-forms: Criterion validity in healthy and clinical samples. *British Journal of Clinical Psychology*, 35, 638–640.
- Crawford, J.R., Bryan, J., Luszcz, M.A., Obonsawin, M.C. & Stewart, L. (2000). The executive decline hypothesis of cognitive aging: Do executive deficits qualify as differential deficits and do they mediate age-related memory decline? *Aging, Neuropsychology and Cognition*, 7(1), 9-31.
- Croxson, P. L., Johansen-Berg, H., Behrens, T. E. J., Robson, M. D., Pinski, M. a, Gross, C. G., Richter, W., et al. (2005). Quantitative investigation of connections of the prefrontal cortex in the human and macaque using probabilistic diffusion tractography. *The Journal of Neuroscience*, 25(39), 8854–8866. doi:10.1523/JNEUROSCI.1311-05.2005



- Culang, M. E., Sneed, J. R., Keilp, J. G., Rutherford, B. R., Pelton, G. H., Devanand, D. P., & Roose, S. P. (2009). Change in Cognitive Functioning Following Acute Antidepressant Treatment in Late-Life Depression. *American Journal of Geriatric Psychiatry*, 17(10), 881–888. doi:10.1097/JGP.0b013e3181b4bf4a
- Curtis, C. E., Zald, D. H., & Pardo, J. V. (2000). Organization of working memory within the human prefrontal cortex: a PET study of self-ordered object working memory. *Neuropsychologia*, 38(11), 1503–1510. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10906375>
- Czéh, B., Perez-Cruz, C., Fuchs, E., & Flügge, G. (2008). Chronic stress-induced cellular changes in the medial prefrontal cortex and their potential clinical implications: does hemisphere location matter? *Behavioural Brain Research*, 190(1), 1–13. doi:10.1016/j.bbr.2008.02.031
- Dagher, A., Owen, A. M., Boecker, H., & Brooks, D. J. (1999). Mapping the network for planning: a correlational PET activation study with the Tower of London task. *Brain*, 122 (1), 1973–1987. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10506098>
- Dagher, A. (2001). The role of the striatum and hippocampus in planning: A PET activation study in Parkinson's disease. *Brain*, 124(5), 1020–1032. doi:10.1093/brain/124.5.1020
- Danielmeier, C., Eichele, T., Forstmann, B. U., Tittgemeyer, M., & Ullsperger, M. (2011). Posterior medial frontal cortex activity predicts post-error adaptations in task-related visual and motor areas. *The Journal of Neuroscience*, 31(5), 1780–1789. doi:10.1523/JNEUROSCI.4299-10.2011
- Dapretto, M., Davies, M. S., Pfeifer, J. H., Scott, A. a, Sigman, M., Bookheimer, S. Y., & Iacoboni, M. (2006). Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. *Nature Neuroscience*, 9(1), 28–30. doi:10.1038/nn1611
- Davidson, P. S. R., Gao, F. Q., Mason, W. P., Winocur, G., & Anderson, N. D. (2008). Verbal fluency, trail making, and Wisconsin Card Sorting Test performance following right frontal lobe tumor resection. *Journal of Clinical and Experimental Neuropsychology*, 30(1), 18–32. doi:10.1080/13803390601161166
- Davis, S.W., Dennis, N.A., Daselaar, S.M., Fleck, M.S. & Cabeza, R. (2007). Que PASA? The posterior-anterior shift in aging. *Cerebral Cortex*, 18(5), 1201–1209.
- De Kloet, E. R., Vreugdenhil, E., Oitzl, M. S., & Joëls, M. (1998). Brain corticosteroid receptor balance in health and disease. *Endocrine Reviews*, 19(3), 269–301. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9626555>

- Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., Penke, L., et al. (2009). Age-associated cognitive decline. *British Medical Bulletin*, 92, 135–152. doi:10.1093/bmb/ldp033
- Deary, I. J., Gow, A. J., Taylor, M. D., Corley, J., Brett, C., Wilson, V., Campbell, H., et al. (2007). The Lothian Birth Cohort 1936: a study to examine influences on cognitive ageing from age 11 to age 70 and beyond. *BMC Geriatrics*, 7, 28. doi:10.1186/1471-2318-7-28
- Deary, I. J., Penke, L., & Johnson, W. (2010). The neuroscience of human intelligence differences. *Nature reviews. Neuroscience*, 11(3), 201–211. doi:10.1038/nrn2793
- Deary, I. J., Whalley, L. J., Lemmon, H., Crawford, J. ., & Starr, J. M. (2000). The Stability of Individual Differences in Mental Ability from Childhood to Old Age: Follow-up of the 1932 Scottish Mental Survey. *Intelligence*, 28(1), 49–55. doi:10.1016/S0160-2896(99)00031-8
- Deary, I.J., Whiteman, M.C., Starr, J.M., Whalley, L.J., & Fox, H.C. (2004). The impact of childhood intelligence on later life: Following up the Scottish mental surveys of 1932 and 1947. *Journal of Personality & Social Psychology*, 86(1), 130-147.
- Dedovic, K., Duchesne, A., Andrews, J., Engert, V., & Pruessner, J. C. (2009). The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. *NeuroImage*, 47(3), 864–871. doi:10.1016/j.neuroimage.2009.05.074
- Dedovic, K., D’Aguiar, C., & Pruessner, J. C. (2009). What stress does to your brain: a review of neuroimaging studies. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, 54(1), 6–15. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/19175975>
- Dedovic, K., Engert, V., Duchesne, A., Lue, S. D., Andrews, J., Efanov, S. I., Beaudry, T., et al. (2010). Cortisol Awakening Response and Hippocampal Volume: Vulnerability for Major Depressive Disorder? *Biological Psychiatry*. 68(9), 847-853. doi:10.1016/j.biopsych.2010.07.025
- Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). *Delis Kaplan Executive Function System: Technical manual*. San Antonio, TX: The Psychological Corporation.
- Denburg, N. L., Tranel, D., & Bechara, a. (2005). The ability to decide advantageously declines prematurely in some normal older persons. *Neuropsychologia*, 43(7), 1099–1106. doi:10.1016/j.neuropsychologia.2004.09.012
- Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., et al. (2006). An automated labeling system for subdividing the

- human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, 31(3), 968–980. doi:10.1016/j.neuroimage.2006.01.021
- Deuschle, M., Gotthardt, U., Schweiger, U., Weber, B., Körner, a, Schmider, J., Standhardt, H., et al. (1997). With aging in humans the activity of the hypothalamus-pituitary-adrenal system increases and its diurnal amplitude flattens. *Life Sciences*, 61(22), 2239–2246. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9393943>
- Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain*, 118, 279–306.
- Devlin, J. T., & Poldrack, R. a. (2007). In praise of tedious anatomy. *NeuroImage*, 37(4), 1033–41; discussion 1050–1058. doi:10.1016/j.neuroimage.2006.09.055
- Dias, R., Robbins, T., & Roberts, A. C. (1997). Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin Card Sort Test: restriction to novel situations and independence from“ on-line” processing. *Journal of Neuroscience*, 17(23), 9285–9297. Retrieved from <http://neuro.cjb.net/cgi/content/abstract/17/23/9285>
- Diehl, J., Grimmer, T., Drzezga, A., Riemenschneider, M., Förstl, H., & Kurz, A. (2004). Cerebral metabolic patterns at early stages of frontotemporal dementia and semantic dementia. A PET study. *Neurobiology of Aging*, 25(8), 1051–1056. doi:10.1016/j.neurobiolaging.2003.10.007
- Diorio, D., Viau, V., & Meaney, M. J. (1993). The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. *The Journal of Neuroscience*, 13(9), 3839–3847. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8396170>
- Doraiswamy, P., Krishnan, K., Oxman, T., Jenkyn, L., Coffey, D., Burt, T., & Clary, C. (2003). Does antidepressant therapy improve cognition in elderly depressed patients? *The Journals of Gerontology: Medical Sciences*, 58A(12), 1137–1144. Retrieved from <http://biomedgerontology.oxfordjournals.org/content/58/12/M1137.short>
- Drevets, W., Price, J., Simpson, J., & Todd, R. (1997). Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*, 386, 824–827. Retrieved from <http://dionysus.psych.wisc.edu/lit/articles/DrevetsW1997a.pdf>
- Driscoll, I., Davatzikos, C., An, Y., Wu, X., Shen, D., Kraut, M. & Resnick, S.M. (2009). Longitudinal pattern of regional brain volume change differentiates normal ageing from MCI. *Neurology*, 72(22), 1906-1913.
- Dumontheil, I., Gilbert, S. J., Frith, C. D., & Burgess, P. W. (2010). Recruitment of lateral rostral prefrontal cortex in spontaneous and task-related thoughts. *The*

*Quarterly Journal of Experimental Psychology*, 63(9), 1740–1756. Retrieved from <http://www.tandfonline.com/doi/abs/10.1080/17470210903538114>

- Dumontheil, I., Burgess, P. W., & Blakemore, S.-J. (2008). Development of rostral prefrontal cortex and cognitive and behavioural disorders. *Developmental Medicine and Child Neurology*, 50(3), 168–181. doi:10.1111/j.1469-8749.2008.02026.x
- Duncan, J. (2010). The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends in Cognitive Sciences*, 14(4), 172–179. doi:10.1016/j.tics.2010.01.004
- Duverne, S., Motamedinia, S., & Rugg, M. D. (2009). The relationship between aging, performance, and the neural correlates of successful memory encoding. *Cerebral Cortex*, 19(3), 733–744. doi:10.1093/cercor/bhn122
- D’Esposito, M., & Postle, B. R. (1999). The dependence of span and delayed-response performance on prefrontal cortex. *Neuropsychologia*, 37(11), 1303–1315. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10530730>
- Egner, T. (2007). Congruency sequence effects and cognitive control. *Cognitive, Affective & Behavioural Neuroscience*, 7(4), 380–390.
- Egner, T. (2008). Multiple conflict-driven control mechanisms in the human brain. *Trends in Cognitive Sciences*, 12(10), 374–380. doi:10.1016/j.tics.2008.07.001
- Eisenberger, N. I., Taylor, S. E., Gable, S. L., Hilmert, C. J., & Lieberman, M. D. (2007). Neural pathways link social support to attenuated neuroendocrine stress responses. *NeuroImage*, 35(4), 1601–1612. doi:10.1016/j.neuroimage.2007.01.038
- Elderkin-Thompson, V., Ballmaier, M., Hellemann, G., Pham, D., & Kumar, A. (2008). Executive function and MRI prefrontal volumes among healthy older adults. *Neuropsychology*, 22(5), 626–637. doi:10.1037/0894-4105.22.5.626
- Elderkin-Thompson, V., Hellemann, G., Pham, D., & Kumar, A. (2009). Prefrontal brain morphology and executive function in healthy and depressed elderly. *International Journal of Geriatric Psychiatry*, 24(5), 459–468. doi:10.1002/gps.2137
- Elliott, R., Baker, S. C., Rogers, R. D., O’Leary, D. A., Paykel, E. S., Frith, C. D., Dolan, R. J., et al. (1997). Prefrontal dysfunction in depressed patients performing a complex planning task: a study using positron emission tomography. *Psychological Medicine*, 27(4), 931–942. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9234470>
- Elliott, R., Frith, C. D., & Dolan, R. J. (1997). Differential neural response to positive and negative feedback in planning and guessing tasks.

*Neuropsychologia*, 35(10), 1395–1404. Retrieved from  
<http://www.ncbi.nlm.nih.gov/pubmed/9347486>

- Elst, L. T. V., Hesslinger, B., Thiel, T., Geiger, E., Haeghele, K., Lemieux, L., Lieb, K., et al. (2003). Frontolimbic brain abnormalities in patients with borderline personality disorder: a volumetric magnetic resonance imaging study. *Biological Psychiatry*, 54, 163–171. doi:10.1016/S0006-3223(03)01743-2
- Eriksen, B., & Eriksen, C. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, 16(1), 143–149. Retrieved from <http://www.springerlink.com/index/25N076M6P4X45525.pdf>
- Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., & Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron*, 51(6), 871–882. doi:10.1016/j.neuron.2006.07.029
- Evans, P. D., Fredhoi, C., Loveday, C., Hucklebridge, F., Aitchison, E., Forte, D., & Clow, a. (2011). The diurnal cortisol cycle and cognitive performance in the healthy old. *International Journal of Psychophysiology*, 79(3), 371–377. doi:10.1016/j.ijpsycho.2010.12.006
- Evans, P., Hucklebridge, F., Loveday, C., & Clow, A. (2012). The cortisol awakening response is related to executive function in older age. *International Journal of Psychophysiology*, 84(2), 201–204. doi:10.1016/j.ijpsycho.2012.02.008
- Fellows, L. K., & Farah, M. J. (2005). Different underlying impairments in decision-making following ventromedial and dorsolateral frontal lobe damage in humans. *Cerebral Cortex*, 15(1), 58–63. doi:10.1093/cercor/bhh108
- Fernandes, K.B., Tavares, R.F., Pelosi, G.G., Correa, F.M., (2007). The paraventricular nucleus of hypothalamus mediates the pressor response to noradrenergic stimulation of the medial prefrontal cortex in unanesthetized rats. *Neuroscience Letters*, 426, 101–105
- Ffytche, D. H., & Catani, M. (2005). Beyond localization: from hodology to function. *Philosophical transactions of the Royal Society of London. Series B, Biological Sciences*, 360 (1456), 767–779. doi:10.1098/rstb.2005.1621
- Fincham, J. M., Carter, C. S., van Veen, V., Stenger, V. A., & Anderson, J. R. (2002). Neural mechanisms of planning: a computational analysis using event-related fMRI. *Proceedings of the National Academy of Sciences of the United States of America*, 99(5), 3346–3351. doi:10.1073/pnas.052703399
- Fischl, B., Rajendran, N., Busa, E., Augustinack, J., Hinds, O., Yeo, B. T. T., Mohlberg, H., et al. (2008). Cortical folding patterns and predicting

cytoarchitecture. *Cerebral Cortex*, 18(8), 1973–1980.  
doi:10.1093/cercor/bhm225

Fitzgerald, P. B., Srithiran, A., Benitez, J., Daskalakis, Z. Z., Oxley, T. J., Kulkarni, J., & Egan, G. F. (2008). An fMRI study of prefrontal brain activation during multiple tasks in patients with major depressive disorder. *Human Brain Mapping*, 29(4), 490–501. doi:10.1002/hbm.20414

Fjell, A. M., Westlye, L. T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., Agartz, I., et al. (2009). High consistency of regional cortical thinning in aging across multiple samples. *Cerebral Cortex*, 19(9), 2001–2012.  
doi:10.1093/cercor/bhn232

Fjell, A. M., Westlye, L. T., Amlien, I. K., & Walhovd, K. B. (2012). A multi-modal investigation of behavioral adjustment: post-error slowing is associated with white matter characteristics. *NeuroImage*, 61(1), 195–205.  
doi:10.1016/j.neuroimage.2012.03.007

Flashman, L. A., McAllister, T. W., Johnson, S. C., Rick, J. H., Green, R. L., & Saykin, A. J. (2001). Specific frontal lobe subregions correlated with unawareness of illness in schizophrenia: a preliminary study. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 13(2), 255–257. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11449033>

Floden, D., Vallesi, A., & Stuss, D. T. (2011). Task context and frontal lobe activation in the Stroop task. *Journal of Cognitive Neuroscience*, 23(4), 867–879. doi:10.1162/jocn.2010.21492

Forget, H. (2002). Persistent cognitive impairment following surgical treatment of Cushing's syndrome. *Psychoneuroendocrinology*, 27(3), 367–383.  
doi:10.1016/S0306-4530(01)00059-2

Fornito, A., Yucel, M., Stuart, G. W., Buchanan, J.-A., Proffitt, T., Anderson, V., Velakoulis, D., & Pantelis, C. (2004). Individual Differences in Anterior Cingulate/Paracingulate Morphology Are Related to Executive Functions in Healthy Males. *Cerebral Cortex*, 14(4), 424–431. doi:10.1093/cercor/bhh004

Fornito, A., Whittle, S., Wood, S. J., Velakoulis, D., Pantelis, C., & Yücel, M. (2006). The influence of sulcal variability on morphometry of the human anterior cingulate and paracingulate cortex. *NeuroImage*, 33(3), 843–854.  
doi:10.1016/j.neuroimage.2006.06.061

Fornito, A., Wood, S. J., Whittle, S., Fuller, J., Adamson, C., Saling, M. M., Velakoulis, D., et al. (2008). Variability of the paracingulate sulcus and morphometry of the medial frontal cortex: associations with cortical thickness, surface area, volume, and sulcal depth. *Human Brain Mapping*, 29(2), 222–236.  
doi:10.1002/hbm.20381

- Fornito, A., Yücel, M., Wood, S. J., Bechdolf, A., Carter, S., Adamson, C., Velakoulis, D., et al. (2009). Anterior cingulate cortex abnormalities associated with a first psychotic episode in bipolar disorder. *The British Journal of Psychiatry*, 194(5), 426–433. doi:10.1192/bjp.bp.107.049205
- Förster, C., Silwedel, C., Golenhofen, N., Burek, M., Kietz, S., Makertz, J & Drenckhahn, D. (2005). Occludin as direct target for glucocorticoid-induced improvement of blood-brain barrier properties in a murine in vitro system. *Journal of Physiology*, 565(2), 475-486.
- Friedman, N.P., Miyake, A., Corley, R.P., Young, S.E., DeFries, J.C., & Hewitt, J.K. (2006). Not All Executive Functions Are Related to Intelligence. *Psychological Science*, 17(2), 172-179.
- Frost, M. A. & Goebel, R. (2011). Measuring structural-functional correspondence: Spatial variability of specialised brain regions after macro-anatomical alignment. *NeuroImage*. doi:10.1016/j.neuroimage.2011.08.035
- Fuchs, E., & Flügge, G. (2003). Chronic social stress: effects on limbic brain structures. *Physiology & Behavior*, 79(3), 417–427. doi:10.1016/S0031-9384(03)00161-6
- Fukui, H., Murai, T., Fukuyama, H., Hayashi, T., & Hanakawa, T. (2005). Functional activity related to risk anticipation during performance of the Iowa Gambling Task. *NeuroImage*, 24(1), 253–259. doi:10.1016/j.neuroimage.2004.08.028
- Furay, A.R., Bruestle, A.E. & Herman, J.P. (2008). The role fo the forebrain glucocorticoid receptor in acute and chronic stress. *Endocrinology*, 149(11), 5482-5490. doi: 10.1210/en.2008-0642
- Gallagher, H L, Happé, F., Brunswick, N., Fletcher, P. C., Frith, U., & Frith, C. D. (2000). Reading the mind in cartoons and stories: an fMRI study of “theory of mind” in verbal and nonverbal tasks. *Neuropsychologia*, 38(1), 11–21. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10617288>
- Gallagher, Helen L., & Frith, C. D. (2003). Functional imaging of “theory of mind.” *Trends in Cognitive Sciences*, 7(2), 77–83. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12584026>
- Gallese, V. (2007). Before and below “theory of mind”: embodied simulation and the neural correlates of social cognition. *Philosophical transactions of the Royal Society of London. Series B, Biological Sciences*, 362(1480), 659–669. doi:10.1098/rstb.2006.2002
- Gansler, D. a, McLaughlin, N. C. R., Iguchi, L., Jerram, M., Moore, D. W., Bhadelia, R., & Fulwiler, C. (2009). A multivariate approach to aggression and the orbital frontal cortex in psychiatric patients. *Psychiatry Research*, 171(3), 145–154. doi:10.1016/j.psychres.2008.03.007

- Garrido, P., de Blas, M., Del Arco, A., Segovia, G., & Mora, F. (2012). Aging increases basal but not stress-induced levels of corticosterone in the brain of the awake rat. *Neurobiology of Aging*, 33(2), 375–382. doi:10.1016/j.neurobiolaging.2010.02.015
- Gerritsen, L., Comijs, H. C., Deeg, D. J. H., Penninx, B. W. J. H., & Geerlings, M. I. (2009). Salivary cortisol, APOE-varepsilon4 allele and cognitive decline in a prospective study of older persons. *Neurobiology of Aging*. doi:10.1016/j.neurobiolaging.2009.09.007
- Geschwind, N., & Galaburda, a M. (1985). Cerebral lateralization. Biological mechanisms, associations, and pathology: III. A hypothesis and a program for research. *Archives of Neurology*, 42(7), 634–654. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/3874617>
- Geyer, S., Weiss, M., Reimann, K., Lohmann, G., & Turner, R. (2011). Microstructural Parcellation of the Human Cerebral Cortex – From Brodmann’s Post-Mortem Map to in vivo Mapping with High-Field Magnetic Resonance Imaging. *Frontiers in Human Neuroscience*, 5 (February), 1–7. doi:10.3389/fnhum.2011.00019
- Ghahremani, D. G., Monterosso, J., Jentsch, J. D., Bilder, R. M., & Poldrack, R. A. (2010). Neural components underlying behavioral flexibility in human reversal learning. *Cerebral Cortex*, 20(8), 1843–1852. doi:10.1093/cercor/bhp247
- Ghosh, B. C. P., Calder, A. J., Peers, P. V., Lawrence, A. D., Acosta-Cabronero, J., Pereira, J. M., Hodges, J. R., et al. (2012). Social cognitive deficits and their neural correlates in progressive supranuclear palsy. *Brain*, 135(Pt 7), 2089–2102. doi:10.1093/brain/aws128
- Gilbert, A. R. (2001). Thalamic Volumes in Patients With First-Episode Schizophrenia. *American Journal of Psychiatry*, 158(4), 618–624. doi:10.1176/appi.ajp.158.4.618
- Gilbert, S. J., Spengler, S., Simons, J. S., Steele, J. D., Lawrie, S. M., Frith, C. D., & Burgess, P. W. (2006). Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. *Journal of Cognitive Neuroscience*, 18(6), 932–948. doi:10.1162/jocn.2006.18.6.932
- Glasser, M. F., & Van Essen, D. C. (2011). Mapping Human Cortical Areas In Vivo Based on Myelin Content as Revealed by T1- and T2-Weighted MRI. *Journal of Neuroscience*, 31(32), 11597–11616. doi:10.1523/JNEUROSCI.2180-11.2011
- Glenn, A. L., Raine, A., Schug, R. A., Young, L., & Hauser, M. (2009). Increased DLPFC activity during moral decision-making in psychopathy. *Molecular Psychiatry*, 14(10), 909–911. Retrieved from <http://www.nature.com/mp/journal/vaop/ncurrent/full/mp200976a.html>



- Gläscher, J., Rudrauf, D., Colom, R., Paul, L. K., Tranel, D., Damasio, H., & Adolphs, R. (2010). Distributed neural system for general intelligence revealed by lesion mapping. *Proceedings of the National Academy of Sciences*, 107(10), 4705–4709. doi:10.1073/pnas.0910397107
- Gläscher, J., Hampton, A. N., & O'Doherty, J. P. (2009). Determining a role for ventromedial prefrontal cortex in encoding action-based value signals during reward-related decision making. *Cerebral Cortex*, 19(2), 483–495. doi:10.1093/cercor/bhn098
- Goh, J. O. S. (2011). Functional Dedifferentiation and Altered Connectivity in Older Adults: Neural Accounts of Cognitive Aging. *Aging and Disease*, 2(1), 30–48. Retrieved from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3066008&tool=pmc.ncbi&rendertype=abstract>
- Gold, S. M., Dziobek, I., Rogers, K., Bayoumy, A., McHugh, P. F., & Convit, A. (2005). Hypertension and hypothalamo-pituitary-adrenal axis hyperactivity affect frontal lobe integrity. *The Journal of Clinical Endocrinology and Metabolism*, 90(6), 3262–3267. doi:10.1210/jc.2004-2181
- Gomez-Beldarrain, M., Harries, C., Garcia-Monco, J. C., Ballus, E., & Grafman, J. (2004). Patients with right frontal lesions are unable to assess and use advice to make predictive judgments. *Journal of Cognitive Neuroscience*, 16(1), 74–89. doi:10.1162/089892904322755575
- Gottfredson, L. S. (1997). Why g matters: The complexity of everyday life. *Intelligence*, 24(1), 79–132. doi:10.1016/S0160-2896(97)90014-3
- Gow, A.J., Johnson, W., Pattie, A., Brett, C.E., Roberts, B., Starr, J.M., & Deary, I.J. (2011). Stability and change in intelligence from age 11 to ages 70, 79 and 87: The Lothian Birth Cohorts of 1921 and 1936. *Psychology & Aging*, 26(1), 232–240. doi: 10.1037/a0021072
- Greene, J. D., Sommerville, R. B., Nystrom, L. E., Darley, J. M., & Cohen, J. D. (2001). An fMRI investigation of emotional engagement in moral judgment. *Science*, 293(5537), 2105–2108. doi:10.1126/science.1062872
- Greene, J.D., Morelli, S., Lowenberg, K., Nystrom, L., & Cohen, J. (2008). Cognitive load selectively interferes with utilitarian moral judgement. *Cognition*, 107(3), 1144–1154. doi:10.1016/j.bbi.2008.05.010
- Greene, J. D., Nystrom, L. E., Engell, A. D., Darley, J. M., & Cohen, J. D. (2004). The neural bases of cognitive conflict and control in moral judgment. *Neuron*, 44(2), 389–400. doi:10.1016/j.neuron.2004.09.027
- Gregory, C., Lough, S., Stone, V., Erzincioğlu, S., Martin, L., Baron-Cohen, S., & Hodges, J. (2002). Theory of mind in patients with frontal variant

frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain*, 125(4), 752–764. doi:10.1093/brain/awf079

- Grieve, S. M., Clark, C. R., Williams, L. M., Peduto, A. J., & Gordon, E. (2005). Preservation of limbic and paralimbic structures in aging. *Human Brain Mapping*, 25(4), 391–401. doi:10.1002/hbm.20115
- Grossman, M., Eslinger, P. J., Troiani, V., Anderson, C., Avants, B., Gee, J. C., McMillan, C., et al. (2010). The role of ventral medial prefrontal cortex in social decisions: converging evidence from fMRI and frontotemporal lobar degeneration. *Neuropsychologia*, 48(12), 3505–3512. doi:10.1016/j.neuropsychologia.2010.07.036
- Gur, R. E., Cowell, P. E., Latshaw, a., Turetsky, B. I., Grossman, R. I., Arnold, S. E., Bilker, W. B., et al. (2000). Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Archives of General Psychiatry*, 57(8), 761–768. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10920464>
- Gur, R. C., Gunning-Dixon, F., Bilker, W. B., & Gur, R. E. (2002). Sex differences in temporo-limbic and frontal brain volumes of healthy adults. *Cerebral Cortex*, 12(9), 998–1003. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12183399>
- Gur, Raquel E., Kohler, C., Turetsky, B. I., Siegel, S. J., Kanes, S. J., Bilker, W. B., Brennan, A. R., et al. (2004). A sexually dimorphic ratio of orbitofrontal to amygdala volume is altered in schizophrenia. *Biological Psychiatry*, 55(5), 512–517. doi:10.1016/j.biopsych.2003.10.009
- Haier, R. J., Colom, R., Schroeder, D. H., Condon, C. a., Tang, C., Eaves, E., & Head, K. (2009). Gray matter and intelligence factors: Is there a neuro-g? *Intelligence*, 37(2), 136–144. doi:10.1016/j.intell.2008.10.011
- Happé, F. G., Winner, E., & Brownell, H. (1998). The getting of wisdom: theory of mind in old age. *Developmental Psychology*, 34(2), 358–362. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9541787>
- Happé, F., Malhi, G. S., & Checkley, S. (2001). Acquired mind-blindness following frontal lobe surgery? A single case study of impaired “theory of mind” in a patient treated with stereotactic anterior capsulotomy. *Neuropsychologia*, 39(1), 83–90. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11115657>
- Harenski, C. L., & Hamann, S. (2006). Neural correlates of regulating negative emotions related to moral violations. *NeuroImage*, 30(1), 313–324. doi:10.1016/j.neuroimage.2005.09.034
- Harrison, B. J., Pujol, J., López-Solà, M., Hernández-Ribas, R., Deus, J., Ortiz, H., Soriano-Mas, C., et al. (2008). Consistency and functional specialization in the default mode brain network. *Proceedings of the National Academy of Sciences*

*of the United States of America*, 105(28), 9781–9786.  
doi:10.1073/pnas.0711791105

- Hasan, K.M. (2006). Diffusion tensor eigenvalues or both mean diffusivity and fractional anisotropy are required in quantitative clinical diffusion tensor MR reports: Fractional anisotropy alone is not sufficient. *Radiology*, 239, 611–613.
- Hastings, R. S., Parsey, R. V., Oquendo, M. a, Arango, V., & Mann, J. J. (2004). Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology*, 29(5), 952–959.  
doi:10.1038/sj.npp.1300371
- Head, D., Buckner, R., Shimony, J., Williams, L., Akbudak, E., Conturo, T., McAvoy, M., et al. (2004). Differential Vulnerability of Anterior White Matter in Nondemented Aging with Minimal Acceleration in Dementia of the Alzheimer Type: Evidence from Diffusion Tensor Imaging. *Cerebral Cortex*, 14(4), 410–423. doi:10.1093/cercor/bhh003
- Head, Denise, Raz, N., Gunning-Dixon, F., Williamson, A., & Acker, J. D. (2002). Age-related differences in the course of cognitive skill acquisition: The role of regional cortical shrinkage and cognitive resources. *Psychology and Aging*, 17(1), 72–84. doi:10.1037//0882-7974.17.1.72
- Heaney, J. L. J., Phillips, A. C., & Carroll, D. (2010). Ageing, depression, anxiety, social support and the diurnal rhythm and awakening response of salivary cortisol. *International Journal of Psychophysiology*.78(3), 201–208.  
doi:10.1016/j.ijpsycho.2010.07.009
- Hedges, D.W. & Woon, F.L. (2011). Early-life stress and cognitive outcome. *Psychopharmacology*, 214: 121–130.
- Herbert, J., Goodyer, I. M., Grossman, a B., Hastings, M. H., de Kloet, E. R., Lightman, S. L., Lupien, S. J., et al. (2006). Do corticosteroids damage the brain? *Journal of Neuroendocrinology*, 18(6), 393–411. doi:10.1111/j.1365-2826.2006.01429.x
- Herman, J., Figueiredo, H., Mueller, N., Ulrich-Lai, Y., Ostrander, M., Choi, D., & Cullinan, W. (2003). Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo–pituitary–adrenocortical responsiveness. *Frontiers in Neuroendocrinology*, 24(3), 151–180.  
doi:10.1016/j.yfrne.2003.07.001
- Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Progress in Neuro-psychopharmacology & Biological Psychiatry*, 29(8), 1201–1213. doi:10.1016/j.pnpbp.2005.08.006

- Herold, R., Feldmann, A., Simon, M., Tényi, T., Kövér, F., Nagy, F., Varga, E., et al. (2009). Regional gray matter reduction and theory of mind deficit in the early phase of schizophrenia: a voxel-based morphometric study. *Acta Psychiatrica Scandinavica*, 119(3), 199–208. doi:10.1111/j.1600-0447.2008.01297.x
- Hill, D. E., Yeo, R. a., Campbell, R. a., Hart, B., Vigil, J., & Brooks, W. (2003). Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. *Neuropsychology*, 17(3), 496–506. doi:10.1037/0894-4105.17.3.496
- Hirayasu, Y., Tanaka, S., Shenton, M. E., Salisbury, D. F., DeSantis, M. a, Levitt, J. J., Wible, C., et al. (2001). Prefrontal gray matter volume reduction in first episode schizophrenia. *Cerebral Cortex*, 11(4), 374–381. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11278200>
- Hof, P. R., Mufson, E. J., & Morrison, J. H. (1995). Human orbitofrontal cortex: cytoarchitecture and quantitative immunohistochemical parcellation. *The Journal of Comparative Neurology*, 359(1), 48–68. doi:10.1002/cne.903590105
- Hornak, J., O'Doherty, J., Bramham, J., Rolls, E. T., Morris, R. G., Bullock, P. R., & Polkey, C. E. (2004). Reward-related reversal learning after surgical excisions in orbito-frontal or dorsolateral prefrontal cortex in humans. *Journal of Cognitive Neuroscience*, 16(3), 463–478. doi:10.1162/089892904322926791
- Hornak, J., Rolls, E. T., & Wade, D. (1996). Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. *Neuropsychologia*, 34(4), 247–261. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8657356>
- Houlihan, L. M., Wyatt, N. D., Harris, S. E., Hayward, C., Gow, A. J., Marioni, R. E., Strachan, M. W. J., et al. (2010). Variation in the uric acid transporter gene (SLC2A9) and memory performance. *Human Molecular Genetics*, 19(11), 2321–2330. doi:10.1093/hmg/ddq097
- Huang, C.-W., Lui, C.-C., Chang, W.-N., Lu, C.-H., Wang, Y.-L., & Chang, C.-C. (2009). Elevated basal cortisol level predicts lower hippocampal volume and cognitive decline in Alzheimer's disease. *Journal of Clinical Neuroscience*, 16(10), 1283–1286. doi:10.1016/j.jocn.2008.12.026
- Hynes, C. a, Baird, A. a, & Grafton, S. T. (2006a). Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. *Neuropsychologia*, 44(3), 374–383. doi:10.1016/j.neuropsychologia.2005.06.011
- Hynes, C. A, Baird, A. A., & Grafton, S. T. (2006b). Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. *Neuropsychologia*, 44(3), 374–383. doi:10.1016/j.neuropsychologia.2005.06.011

- Ibach, B., Poljansky, S., Marienhagen, J., Sommer, M., Männer, P., & Hajak, G. (2004). Contrasting metabolic impairment in frontotemporal degeneration and early onset Alzheimer's disease. *NeuroImage*, 23(2), 739–743. doi:10.1016/j.neuroimage.2004.06.041
- Ichihara-Takeda, S., & Funahashi, S. (2006). Reward-period activity in primate dorsolateral prefrontal and orbitofrontal neurons is affected by reward schedules. *Journal of Cognitive Neuroscience*, 18(2), 212–226. doi:10.1162/089892906775783679
- Issa, A.M., Rowe, W., Gauthier, S., & Meaney, M. J. (1990). Hypothalamic-pituitary-adrenal activity in aged, cognitively impaired and cognitively unimpaired rats. *The Journal of Neuroscience*, 10(10), 3247–3254. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/2170594>
- Izquierdo, A., Wellman, C. L., & Holmes, A. (2006). Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice. *The Journal of Neuroscience*, 26(21), 5733–5738. doi:10.1523/JNEUROSCI.0474-06.2006
- Jaillard, A., Casey, O., Vadot, W., Delon-Martin, C., Detante, O., Le Bas, J., & Hommel, M. (2009). Representational role of Superior Temporal Sulcus in Mental State Attribution: Have or have not? A fMRI-study. *NeuroImage*, 47, S181–S181. doi:10.1016/S1053-8119(09)71999-8
- Johansen-Berg, H., Gutman, D. a, Behrens, T. E. J., Matthews, P. M., Rushworth, M. F. S., Katz, E., Lozano, a M., et al. (2008). Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. *Cerebral Cortex*, 18(6), 1374–1383. doi:10.1093/cercor/bhm167
- John, J. P., Wang, L., Moffitt, A. J., Singh, H. K., Gado, M. H., & Csernansky, J. G. (2006). Inter-rater reliability of manual segmentation of the superior, inferior and middle frontal gyri. *Psychiatry Research*, 148(2-3), 151–163. doi:10.1016/j.psychresns.2006.05.006
- Johnson, W., Brett, C.E., & Deary, I.J. (2010a). The pivotal role of education in the association between ability and social class attainment: A look across three generations. *Intelligence*, 38(1), 55-65.
- Johnson, W., Gow, A.J., Corley, J., Starr, J.M., & Deary, I.J. (2010b). Location in cognitive and residential space at age 70 reflects a lifelong trait over parental and environmental circumstances: the Lothian Birth Cohort 1936. *Intelligence*, 38, 402-411.
- Jones, B. F., Barnes, J., Uylings, H. B. M., Fox, N. C., Frost, C., Witter, M. P., & Scheltens, P. (2006). Differential regional atrophy of the cingulate gyrus in

- Alzheimer disease: a volumetric MRI study. *Cerebral Cortex*, 16(12), 1701–1708. doi:10.1093/cercor/bhj105
- Jonides, J., & Nee, D. E. (2004). Resolving Conflict in Mind and Brain. *Attention And Performance*, 18(5), 2–5.
- Joëls, M., & Baram, T. Z. (2009). The neuro-symphony of stress. *Nature Reviews. Neuroscience*, 10(6), 459–466. doi:10.1038/nrn2632
- Jung, R. E., & Haier, R. J. (2007). The Parieto-Frontal Integration Theory (P-FIT) of intelligence: converging neuroimaging evidence. *The Behavioral and Brain Sciences*, 30(2), 135–54; discussion 154–187. doi:10.1017/S0140525X07001185
- Just, M. A., Cherkassky, V. L., Keller, T. A., Kana, R. K., & Minshew, N. J. (2007). Functional and anatomical cortical underconnectivity in autism: evidence from an fMRI study of an executive function task and corpus callosum morphometry. *Cerebral Cortex*, 17(4), 951–961. doi:10.1093/cercor/bhl006
- Kahane, G., & Shackel, N. (2008). Do abnormal responses show utilitarian bias? *Nature*, 452(March), 2007–2008. doi:10.1038/06785
- Kalmijn, S., Launer, L. J., Stolk, R. P., Jong, F. H. D. E., Pols, H. A. P., Hoffman, A., Breteler, M. M. B., et al. (1998). A prospective study on cortisol, dehydroepiandrosterone sulfate, and cognitive function in the elderly. *Journal of Clinical Endocrinology and Metabolism*, 83(10), 3487–3492. Retrieved from <http://jcem.endojournals.org/content/83/10/3487.short>
- Karlamangla, A. S., Singer, B. H., Chodosh, J., McEwen, B. S., & Seeman, T. E. (2005). Urinary cortisol excretion as a predictor of incident cognitive impairment. *Neurobiology of Aging*, 26 Suppl 1, 80–84. doi:10.1016/j.neurobiolaging.2005.09.037
- Kasckow, J., Xiao, C., & Herman, J. P. (2009). Glial glucocorticoid receptors in aged Fisher 344 (F344) and F344/Brown Norway rats. *Experimental Gerontology*, 44(5), 335–343. doi:10.1016/j.exger.2009.02.003
- Kates, W. R., Frederikse, M., Mostofsky, S. H., Folley, B. S., Cooper, K., Mazur-Hopkins, P., Kofman, O., et al. (2002). MRI parcellation of the frontal lobe in boys with attention deficit hyperactivity disorder or Tourette syndrome. *Psychiatry Research*, 116(1-2), 63–81. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12426035>
- Keane, J., Calder, A. J., Hodges, J. R., & Young, A. W. (2002). Face and emotion processing in frontal variant frontotemporal dementia. *Neuropsychologia*, 40(6), 655–665. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11792405>

- Kegeles, L. S., Malone, K. M., Slifstein, M., Ellis, S. P., Xanthopoulos, E., Keilp, J. G., Campbell, C., et al. (2003). Response of cortical metabolic deficits to serotonergic challenge in familial mood disorders. *Psychiatry: Interpersonal and Biological Processes*, 160(1), 76–82. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12505804>
- Keightley, M. L., Winocur, G., Burianova, H., Hongwanishkul, D., & Grady, C. L. (2006). Age effects on social cognition: faces tell a different story. *Psychology and Aging*, 21(3), 558–572. doi:10.1037/0882-7974.21.3.558
- Kemp, J., Després, O., Sellal, F., & Dufour, A. (2012). Theory of Mind in normal ageing and neurodegenerative pathologies. *Ageing Research Reviews*, 11(2), 199–219. doi:10.1016/j.arr.2011.12.001
- Kennedy, K. M., & Raz, N. (2009). Aging white matter and cognition: differential effects of regional variations in diffusion properties on memory, executive functions, and speed. *Neuropsychologia*, 47(3), 916–927. doi:10.1016/j.neuropsychologia.2009.01.001
- Kern, S., Oakes, T. R., Stone, C. K., McAuliff, E. M., Kirschbaum, C., & Davidson, R. J. (2008). Glucose metabolic changes in the prefrontal cortex are associated with HPA axis response to a psychosocial stressor. *Psychoneuroendocrinology*, 33(4), 517–529. doi:10.1016/j.psyneuen.2008.01.010
- Kerns, J. G. (2006). Anterior cingulate and prefrontal cortex activity in an fMRI study of trial-to-trial adjustments on the Simon task. *NeuroImage*, 33(1), 399–405. doi:10.1016/j.neuroimage.2006.06.012
- Kerns, J. G., Cohen, J. D., MacDonald, A. W., Cho, R. Y., Stenger, V. A., & Carter, C. S. (2004). Anterior cingulate conflict monitoring and adjustments in control. *Science*, 303(5660), 1023–1026. doi:10.1126/science.1089910
- Kikinis, R., Shenton, M. E., Iosifescu, D. V., McCarley, R. W., Saiviroonporn, P., Hokama, H. H., Robatino, a., et al. (1996). A digital brain atlas for surgical planning, model-driven segmentation, and teaching. *IEEE Transactions on Visualization and Computer Graphics*, 2(3), 232–241. doi:10.1109/2945.537306
- Kirschbaum, C., Pirke, K.-M., & Hellhammer, D. H. (1993). The “Trier Social Stress Test”—a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*, 28, 76–81. Retrieved from <http://p113367.typo3server.info/uploads/media/lit9304.pdf>
- Klein, J. C., Rushworth, M. F. S., Behrens, T. E. J., Mackay, C. E., de Crespigny, A. J., D’Arceuil, H., & Johansen-Berg, H. (2010). Topography of connections between human prefrontal cortex and mediodorsal thalamus studied with diffusion tractography. *NeuroImage*, 51(2), 555–64. doi:10.1016/j.neuroimage.2010.02.062

- Klein, J., Rushworth, M., Behrens, T., Mackay, C., de Crespigny, A., D'Arceuil, H., & Johansen-Berg, H. (2010). Topography of connections between human prefrontal cortex and mediodorsal thalamus studied with diffusion tractography. *Neuroimage*, 51(2), 555–564. Retrieved from [http://www.sciencedirect.com/science/article/pii/S1053-8119\(10\)00249-1](http://www.sciencedirect.com/science/article/pii/S1053-8119(10)00249-1)
- Kochunov, P., Thompson, P.M., Lancaster, J.L., Bartzokis, G., Smith, S., Coyle, T., Royall, D.R., Laird, A. & Fox, P.T. (2007). Relationship between white matter fractional anisotropy and other indices of cerebral health in normal aging: tract-based spatial statistics study of aging. *Neuroimage*. 35:478-487.
- Koenigs, M., & Tranel, D. (2007). Irrational economic decision-making after ventromedial prefrontal damage: evidence from the Ultimatum Game. *The Journal of Neuroscience*, 27(4), 951–956. doi:10.1523/JNEUROSCI.4606-06.2007
- Korten, A.E., Jorm, A.F., Jiao, Z., Letenneur, L., Jacomb, P.A, Henderson, A.S., Christensen, H., et al. (1999). Health, cognitive, and psychosocial factors as predictors of mortality in an elderly community sample. *Journal of Epidemiology and Community Health*, 53(2), 83–88. Retrieved from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1756829&tool=pmc-entrez&rendertype=abstract>
- Kraemer, H. C., Giese-Davis, J., Yutsis, M., O'Hara, R., Neri, E., Gallagher-Thompson, D., Taylor, C. B., et al. (2006). Design decisions to optimize reliability of daytime cortisol slopes in an older population. *The American Journal of Geriatric Psychiatry*, 14(4), 325–333. doi:10.1097/01.JGP.0000201816.26786.5b
- Kremen, W. S., O'Brien, R. C., Panizzon, M. S., Prom-Wormley, E., Eaves, L. J., Eisen, S. A., Eyler, L. T., et al. (2010a). Salivary cortisol and prefrontal cortical thickness in middle-aged men: A twin study. *NeuroImage*, 1–10. doi:10.1016/j.neuroimage.2010.02.026
- Kremen, W. S., Panizzon, M. S., Lyons, M. J., & Franz, C. E. (2010b). Cortisol and Brain: Beyond the Hippocampus. *Biological Psychiatry*, (1), 22381. doi:10.1016/j.biopsych.2010.08.035
- Kringelbach, M. (2005). The human orbitofrontal cortex: linking reward to hedonic experience. *Nature Reviews Neuroscience*, 6, 691–702. doi:10.1038/nrn1748
- Kringelbach, M., & Rolls, E.T. (2003). Neural correlates of rapid reversal learning in a simple model of human social interaction. *NeuroImage*, 20; 1371-1383. doi: 10.1016/S1053-8119(03)00393-8
- Kringelbach, M. L., & Rolls, E. T. (2004). The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology.



*Progress in Neurobiology*, 72(5), 341–372.  
doi:10.1016/j.pneurobio.2004.03.006

- Krueger, F., Barbey, A. K., McCabe, K., Strenziok, M., Zamboni, G., Solomon, J., Raymont, V., et al. (2009). The neural bases of key competencies of emotional intelligence. *Proceedings of the National Academy of Sciences of the United States of America*, 106(52), 22486–22491. doi:10.1073/pnas.0912568106
- Kuningas, M., de Rijk, R. H., Westendorp, R. G. J., Jolles, J., Slagboom, P. E., & van Heemst, D. (2007). Mental performance in old age dependent on cortisol and genetic variance in the mineralocorticoid and glucocorticoid receptors. *Neuropsychopharmacology*, 32(6), 1295–1301. doi:10.1038/sj.npp.1301260
- Lacerda, A. L. ., Hardan, A. Y., Yorbik, O., & Keshavan, M. S. (2003). Measurement of the orbitofrontal cortex: a validation study of a new method. *NeuroImage*, 19(3), 665–673. doi:10.1016/S1053-8119(03)00137-X
- Lai, T. J., Payne, M. E., Byrum, C. E., Steffens, D. C., & Krishnan, K. R. R. (2000). Reduction of orbital frontal cortex volume in geriatric depression. *Biological Psychiatry*, 48(10), 971–975. Retrieved from <http://www.sciencedirect.com/science/article/pii/S0006322300010428>
- Lamar, M., & Resnick, S. M. (2004). Aging and prefrontal functions: dissociating orbitofrontal and dorsolateral abilities. *Neurobiology of Aging*, 25(4), 553–558. doi:10.1016/j.neurobiolaging.2003.06.005
- Landfield, P. W., Blalock, E. M., Chen, K.-C., & Porter, N. M. (2007). A New Glucocorticoid Hypothesis of Brain Aging: Implications for Alzheimer's Disease. *Current Alzheimer Research*, 4(2), 205–212. doi:10.2174/156720507780362083
- Larsson, E.-M., Englund, E., Sjöbeck, M., Lätt, J., & Brockstedt, S. (2004). MRI with diffusion tensor imaging post-mortem at 3.0 T in a patient with frontotemporal dementia. *Dementia and Geriatric Cognitive Disorders*, 17(4), 316–319. doi:10.1159/000077162
- Larsson, C. a, Gullberg, B., Råstam, L., & Lindblad, U. (2009). Salivary cortisol differs with age and sex and shows inverse associations with WHR in Swedish women: a cross-sectional study. *BMC Endocrine Disorders*, 9, 16. doi:10.1186/1472-6823-9-16
- Lazeron, R. H. C., Rombouts, S. a R. B., Scheltens, P., Polman, C. H., & Barkhof, F. (2004). An fMRI study of planning-related brain activity in patients with moderately advanced multiple sclerosis. *Multiple Sclerosis*, 10(5), 549–55. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/15471372>
- Lazeron, R. H., Rombouts, S. a, Machielsen, W. C., Scheltens, P., Witter, M. P., Uylings, H. B., & Barkhof, F. (2000). Visualizing brain activation during

- planning: the tower of London test adapted for functional MR imaging. *AJNR. American Journal of Neuroradiology*, 21(8), 1407–1414. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11003272>
- Lee, B. K., Glass, T. A., McAtee, M. J., Wand, G. S., Bandeen-Roche, K., Bolla, K. I., & Schwartz, B. S. (2007). Associations of salivary cortisol with cognitive function in the Baltimore memory study. *Archives of General Psychiatry*, 64(7), 810–818. doi:10.1001/archpsyc.64.7.810
- Lee, T. M. C., Ip, A. K. Y., Wang, K., Xi, C.-H., Hu, P.-P., Mak, H. K. F., Han, S.-H., et al. (2010). Faux pas deficits in people with medial frontal lesions as related to impaired understanding of a speaker's mental state. *Neuropsychologia*, 48(6), 1670–1676. doi:10.1016/j.neuropsychologia.2010.02.012
- Li, S.C., Brehmer, Y., Shing, Y.L., Werkle-Bergner, M. & Lindenberger, U. (2006). Neuromodulation of associative and organizational plasticity across the life span: empirical evidence and neurocomputational modeling. *Neuroscience and Biobehavioural Reviews*, 30:775--790.
- Li, G., Cherrier, M. M., Tsuang, D. W., Petrie, E. C., Colasurdo, E. A., Craft, S., Schellenberg, G. D., et al. (2006). Salivary cortisol and memory function in human aging. *Neurobiology of Aging*, 27(11), 1705–1714. doi:10.1016/j.neurobiolaging.2005.09.031
- Lindberg, O., Ostberg, P., Zandbelt, B. B., Oberg, J., Zhang, Y., Andersen, C., Looi, J. C. L., et al. (2009). Cortical morphometric subclassification of frontotemporal lobar degeneration. *AJNR. American Journal of Neuroradiology*, 30(6), 1233–1239. doi:10.3174/ajnr.A1545
- Linke, J., Kirsch, P., King, A. V., Gass, A., Hennerici, M. G., Bongers, A., & Wessa, M. (2010). Motivational orientation modulates the neural response to reward. *NeuroImage*, 49(3), 2618–2625. doi:10.1016/j.neuroimage.2009.09.013
- Liston, C., Miller, M. M., Goldwater, D. S., Radley, J. J., Rocher, A. B., Hof, P. R., Morrison, J. H., et al. (2006). Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. *The Journal of Neuroscience*, 26(30), 7870–7874. doi:10.1523/JNEUROSCI.1184-06.2006
- Logan, J. M., Sanders, A. L., Snyder, A. Z., Morris, J. C., & Buckner, R. L. (2002). Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. *Neuron*, 33(5), 827–840. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11879658>
- Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature*, 453(7197), 869–878. doi:10.1038/nature06976

- Lough, S., Gregory, C., & Hodges, J. R. (2001). Dissociation of social cognition and executive function in frontal variant frontotemporal dementia. *Neurocase*, 7(2), 123–130. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11320160>
- Lough, S., & Hodges, J. R. (2002). Measuring and modifying abnormal social cognition in frontal variant frontotemporal dementia. *Journal of Psychosomatic Research*, 53(2), 639–646. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12169338>
- Lubrich, B., Spleiss, O., Gebicke-Haerter, P.J. & van Calker, D. (2000). Differential expression, activity and regulation of the sodium/myo-inositol cotransporter in astrocyte cultures from different regions of the rat brain. *Neuropharmacology*, 39(4), 680-690.
- Luciano, M., Gow, A. J., Harris, S. E., Hayward, C., Allerhand, M., Starr, J. M., Visscher, P. M., et al. (2009). Cognitive ability at age 11 and 70 years, information processing speed, and APOE variation: the Lothian Birth Cohort 1936 study. *Psychology and Aging*, 24(1), 129–138. doi:10.1037/a0014780
- Lueken, U., Leisse, M., Mattes, K., Naumann, D., Wittling, W. & Schweiger, E. (2009). Altered tonic and phasic cortisol secretion following unilateral stroke. *Psychoneuroendocrinology*, 34(3), 402–412. doi:10.1016/j.psyneuen.2008.10.002
- Lupien, S J, Gaudreau, S., Tchiteya, B. M., Maheu, F., Sharma, S., Nair, N. P., Hauger, R. L., et al. (1997). Stress-induced declarative memory impairment in healthy elderly subjects: relationship to cortisol reactivity. *The Journal of Clinical Endocrinology and Metabolism*, 82(7), 2070–2075. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9215274>
- Lupien, S J, de Leon, M., de Santi, S., Convit, a, Tarshish, C., Nair, N. P., Thakur, M., et al. (1998). Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neuroscience*, 1(1), 69–73. doi:10.1038/271
- Lupien, S., Lecours, a R., Lussier, I., Schwartz, G., Nair, N. P., & Meaney, M. J. (1994). Basal cortisol levels and cognitive deficits in human aging. *The Journal of Neuroscience*, 14(5 Pt 1), 2893–2903. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8182446>
- Lupien, S., Lecours, a R., Schwartz, G., Sharma, S., Hauger, R. L., Meaney, M. J., & Nair, N. P. (1996). Longitudinal study of basal cortisol levels in healthy elderly subjects: evidence for subgroups. *Neurobiology of Aging*, 17(1), 95–105. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8786810>
- Lupien, Sonia J, Wilkinson, C. W., Brière, S., Ménard, C., Ng Ying Kin, N. M. K., & Nair, N. P. V. (2002). The modulatory effects of corticosteroids on cognition:

- studies in young human populations. *Psychoneuroendocrinology*, 27(3), 401–416. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11818174>
- Luz, C., Dornelles, F., Preissler, T., Collaziol, D., da Cruz, I., & Bauer, M. (2003). Impact of psychological and endocrine factors on cytokine production of healthy elderly people. *Mechanisms of Ageing and Development*, 124, 887–895. doi:10.1016/S0047-6374(03)00148-9
- MacLulich, A.M.J., Ferguson, K.J., Reid, L.M., Deary, I.J., Starr, J.M., Seckl, J.R., Bastin, M.E. & Wardlaw, J.M. (2009). Higher systolic blood pressure is associated with increased water diffusivity in normal-appearing white matter. *Stroke*, 40(12), 3869–3871.
- MacLulich, A. M. J., Deary, I. J., Starr, J. M., Ferguson, K. J., Wardlaw, J. M., & Seckl, J. R. (2005). Plasma cortisol levels, brain volumes and cognition in healthy elderly men. *Psychoneuroendocrinology*, 30(5), 505–515. doi:10.1016/j.psyneuen.2004.12.005
- MacLulich, A. M. J., Ferguson, K. J., Reid, L. M., Deary, I. J., Starr, J. M., Wardlaw, J. M., Walker, B. R., et al. (2012). 11B-Hydroxysteroid Dehydrogenase Type 1, Brain Atrophy and Cognitive Decline. *Neurobiology of Aging*, 33(1), 207.e1–8. doi:10.1016/j.neurobiolaging.2010.09.010
- MacLulich, A. M. J., Ferguson, K. J., Wardlaw, J. M., Starr, J. M., Deary, I. J., & Seckl, J. R. (2006). Smaller left anterior cingulate cortex volumes are associated with impaired hypothalamic-pituitary-adrenal axis regulation in healthy elderly men. *The Journal of Clinical Endocrinology and Metabolism*, 91(4), 1591–1594. doi:10.1210/jc.2005-2610
- MacPherson, S. E., Phillips, L. H., & Della Sala, S. (2002). Age, executive function and social decision making: A dorsolateral prefrontal theory of cognitive aging. *Psychology and Aging*, 17(4), 598–609. doi:10.1037//0882-7974.17.4.598
- MacPherson, S. E., Phillips, L. H., Della Sala, S., & Cantagallo, A. (2009). Iowa Gambling task impairment is not specific to ventromedial prefrontal lesions. *The Clinical Neuropsychologist*, 23(3), 510–522. doi:10.1080/13854040802396586
- Madden, D. J., Spaniol, J., Costello, M. C., Bucur, B., White, L. E., Cabeza, R., Davis, S. W., et al. (2009). Cerebral white matter integrity mediates adult age differences in cognitive performance. *Journal of Cognitive Neuroscience*, 21(2), 289–302. doi:10.1162/jocn.2009.21047
- Madsen, K. S., Jernigan, T. L., Iversen, P., Frokjaer, V. G., Mortensen, E. L., Knudsen, G. M., & Baaré, W. F. C. (2012). Cortisol awakening response and negative emotionality linked to asymmetry in major limbic fibre bundle architecture. *Psychiatry Research: Neuroimaging*, 201(1), 63–72. doi:10.1016/j.psychesns.2011.07.015

- Maia, T. V., & McClelland, J. L. (2004). A reexamination of the evidence for the somatic marker hypothesis: what participants really know in the Iowa gambling task. *Proceedings of the National Academy of Sciences of the United States of America*, 101(45), 16075–16080. doi:10.1073/pnas.0406666101
- Mamah, D., Conturo, T. E., Harms, M. P., Akbudak, E., Wang, L., McMichael, A. R., Gado, M. H., et al. (2010). Anterior thalamic radiation integrity in schizophrenia: a diffusion-tensor imaging study. *Psychiatry Research*, 183(2), 144–150. doi:10.1016/j.psychres.2010.04.013
- Manes, F., Sahakian, B., Clark, L., Rogers, R., Antoun, N., Aitken, M., & Robbins, T. (2002). Decision-making processes following damage to the prefrontal cortex. *Brain*, 125(Pt 3), 624–639. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11872618>
- Mansouri, F. A., Tanaka, K., & Buckley, M. J. (2009). Conflict-induced behavioural adjustment: a clue to the executive functions of the prefrontal cortex. *Nature Reviews. Neuroscience*, 10(2), 141–152. doi:10.1038/nrn2538
- Marenco, S., Coppola, R., Daniel, D. G., Zigun, J. R., & Weinberger, D. R. (1993). Regional cerebral blood flow during the Wisconsin Card Sorting Test in normal subjects studied by Xenon-133 Dynamic SPECT: comparison of absolute values, percent distribution values and covariance analysis. *Psychiatry Research: Neuroimaging*, 50(3), 177–192. Retrieved from <http://linkinghub.elsevier.com/retrieve/pii/092549279390029H>
- Marschner, a, Mell, T., Wartenburger, I., Villringer, a, Reischies, F. M., & Heekeren, H. R. (2005). Reward-based decision-making and aging. *Brain Research Bulletin*, 67(5), 382–390. doi:10.1016/j.brainresbull.2005.06.010
- Matsui, M., Suzuki, M., Zhou, S.-Y., Takahashi, T., Kawasaki, Y., Yuuki, H., Kato, K., et al. (2008). The relationship between prefrontal brain volume and characteristics of memory strategy in schizophrenia spectrum disorders. *Progress in Neuro-psychopharmacology & Biological Psychiatry*, 32(8), 1854–1862. doi:10.1016/j.pnpbp.2008.08.018
- Mattsson, C., Reynolds, R. M., Simonyte, K., Olsson, T., & Walker, B. R. (2009). Combined receptor antagonist stimulation of the hypothalamic-pituitary-adrenal axis test identifies impaired negative feedback sensitivity to cortisol in obese men. *The Journal of Clinical Endocrinology and Metabolism*, 94(4), 1347–1352. doi:10.1210/jc.2008-2054
- Mavaddat, N., Sahakian, B. J., Hutchinson, P. J., & Kirkpatrick, P. J. (1999). Cognition following subarachnoid hemorrhage from anterior communicating artery aneurysm: relation to timing of surgery. *Journal of Neurosurgery*, 91(3), 402–407. doi:10.3171/jns.1999.91.3.0402

- Maylor, E. a, Moulson, J. M., Muncer, A.-M., & Taylor, L. a. (2002). Does performance on theory of mind tasks decline in old age? *British Journal of Psychology (London, England : 1953)*, 93(Pt 4), 465–485. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12519529>
- Mazza, M., Costagliola, C., Di Michele, V., Magliani, V., Pollice, R., Ricci, A., Di Giovanbattista, E., et al. (2007). Deficit of social cognition in subjects with surgically treated frontal lobe lesions and in subjects affected by schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, 257(1), 12–22. doi:10.1007/s00406-006-0676-0
- McCormick, L. M., Ziebell, S., Nopoulos, P., Cassell, M., Andreasen, N. C., & Brumm, M. (2006). Anterior cingulate cortex: an MRI-based parcellation method. *NeuroImage*, 32(3), 1167–1175. doi:10.1016/j.neuroimage.2006.04.227
- McDonald, C. R., Swartz, B. E., Halgren, E., Patell, A., Daimes, R., & Mandelkern, M. (2006). The relationship of regional frontal hypometabolism to executive function: a resting fluorodeoxyglucose PET study of patients with epilepsy and healthy controls. *Epilepsy & Behavior*, 9(1), 58–67. doi:10.1016/j.yebeh.2006.04.007
- McEwen, B S. (1999). Stress and hippocampal plasticity. *Annual Review of Neuroscience*, 22, 105–122. doi:10.1146/annurev.neuro.22.1.105
- McEwen, B.S., & Gianaros, P. J. (2010). Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. *Annals of the New York Academy of Sciences*, 1186, 190–222. doi:10.1111/j.1749-6632.2009.05331.x
- McGuire, J., Langdon, R., Coltheart, M., & Mackenzie, C. (2009). A reanalysis of the personal/impersonal distinction in moral psychology research. *Journal of Experimental Social Psychology*, 45(3), 577–580. doi:10.1016/j.jesp.2009.01.002
- McLaughlin, N., Moore, D. W., Fulwiler, C., Bhadelia, R., & Gansler, D. a. (2009). Differential Contributions of Lateral Prefrontal Cortex Regions to Visual Memory Processes. *Brain Imaging and Behavior*, 3(2), 202–211. doi:10.1007/s11682-009-9062-7
- Medalla, M., & Barbas, H. (2009). Synapses with inhibitory neurons differentiate anterior cingulate from dorsolateral prefrontal pathways associated with cognitive control. *Neuron*, 61(4), 609–620. doi:10.1016/j.neuron.2009.01.006
- Medina, K. L., McQueeny, T., Nagel, B. J., Hanson, K. L., Schweinsburg, A. D., & Tapert, S. F. (2008). Prefrontal cortex volumes in adolescents with alcohol use disorders: unique gender effects. *Alcoholism, Clinical and Experimental Research*, 32(3), 386–394. doi:10.1111/j.1530-0277.2007.00602.x

- Medina, K., McQueeny, T., Nagel, B., Hanson, K. L., Yang, T., & Tapert, S. F. (2009). Prefrontal cortex morphometry in abstinent adolescent marijuana users: subtle gender effects. *Addiction Biology*, 14(4), 457–468. doi:10.1111/j.1369-1600.2009.00166.x.Prefrontal
- Mell, T., Heekeren, H. R., Marschner, a, Wartenburger, I., Villringer, a, & Reischies, F. M. (2005). Effect of aging on stimulus-reward association learning. *Neuropsychologia*, 43(4), 554–563. doi:10.1016/j.neuropsychologia.2004.07.010
- Mesulam, M.-M. (1990). Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Annals of Neurology*, 28, 597–613. Retrieved from <http://onlinelibrary.wiley.com/doi/10.1002/ana.410280502/abstract>
- Michaud, K., Forget, H., & Cohen, H. (2009). Chronic glucocorticoid hypersecretion in Cushing's syndrome exacerbates cognitive aging. *Brain and Cognition*, 71(1), 1–8. doi:10.1016/j.bandc.2009.02.013
- Milner, B. (1963). Effects of different brain lesions on card sorting: The role of the frontal lobes. *Archives of Neurology*, 9(1), 90–100. Retrieved from <http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Effects+of+different+brain+lesions+on+card+sorting:+the+role+of+the+frontal+lobes#0>
- Mitchell, J. P., Macrae, C. N., & Banaji, M. R. (2006). Dissociable medial prefrontal contributions to judgments of similar and dissimilar others. *Neuron*, 50(4), 655–663. doi:10.1016/j.neuron.2006.03.040
- Moberg, P. J., Doty, R. L., Turetsky, B. I., Arnold, S. E., Mahr, R. N., Gur, R. C., Bilker, W., et al. (1997). Olfactory identification deficits in schizophrenia: correlation with duration of illness. *The American journal of psychiatry*, 154(7), 1016–1018. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9210756>
- Mohlman, J., Price, R. B., Eldreth, D. a, Chazin, D., Glover, D. M., & Kates, W. R. (2009). The relation of worry to prefrontal cortex volume in older adults with and without generalized anxiety disorder. *Psychiatry Research*, 173(2), 121–127. doi:10.1016/j.psychres.2008.09.010
- Moll, J., de Oliveira-Souza, R., Bramati, I., & Grafman, J. (2002). Functional Networks in Emotional Moral and Nonmoral Social Judgments. *NeuroImage*, 16(3), 696–703. doi:10.1006/nimg.2002.1118
- Moll, Jorge, Zahn, R., Oliveira-Souza, R. D., Krueger, F., & Grafman, J. (2005). The neural basis of human moral cognition. *Nature Reviews*, 6, 799–809. Retrieved from <http://www.nature.com/nrn/journal/v6/n10/abs/nrn1768.html>
- Moll, Jorge, de Oliveira-Souza, R., Eslinger, P. J., Bramati, I. E., Mourão-Miranda, J., Andreiulo, P. A., & Pessoa, L. (2002). The neural correlates of moral

- sensitivity: a functional magnetic resonance imaging investigation of basic and moral emotions. *The Journal of Neuroscience*, 22(7), 2730–2736. doi:20026214
- Montaron, M. F., Drapeau, E., Dupret, D., Kitchener, P., Aurousseau, C., Le Moal, M., Piazza, P. V., et al. (2006). Lifelong corticosterone level determines age-related decline in neurogenesis and memory. *Neurobiology of Aging*, 27(4), 645–654. doi:10.1016/j.neurobiolaging.2005.02.014
- Morcom, A. M., Good, C. D., Frackowiak, R. S. J., & Rugg, M. D. (2003). Age effects on the neural correlates of successful memory encoding. *Brain*, 126(1), 213–229. doi:10.1093/brain/awg020
- Moretto, G., Làdavas, E., Mattioli, F., & di Pellegrino, G. (2010). A psychophysiological investigation of moral judgment after ventromedial prefrontal damage. *Journal of Cognitive Neuroscience*, 22(8), 1888–1899. Retrieved from <http://www.mitpressjournals.org/doi/full/10.1162/jocn.2009.21367>
- Morris, R. G., Ahmed, S., Syed, G. M., & Toone, B. K. (1993). Neural correlates of planning ability: frontal lobe activation during the Tower of London test. *Neuropsychologia*, 31(12), 1367–1378. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8127433>
- Moscovitch, M., & Winocur, G. (1995). Frontal lobes, memory, and aging. *Annals of the New York Academy of Sciences*, 769, 119–150. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8595020>
- Mujica-Parodi, L. R., Renelique, R., & Taylor, M. K. (2009). Higher body fat percentage is associated with increased cortisol reactivity and impaired cognitive resilience in response to acute emotional stress. *International Journal of Obesity (2005)*, 33(1), 157–165. doi:10.1038/ijo.2008.218
- Nagahama, Y., Okina, T., Suzuki, N., Nabatame, H., & Matsuda, M. (2005). The cerebral correlates of different types of perseveration in the Wisconsin Card Sorting Test. *Journal of Neurology, Neurosurgery & Psychiatry*, 76(2), 169–175. doi:10.1136/jnnp.2004.039818
- Nagel, B., Medina, K., Yoshii, J., Schweinsburg, A. D., Moadab, I., & Tapert, S. F. (2006). Age-related changes in prefrontal white matter volume across adolescence. *Neuroreport*, 17(13), 1427–1431. doi:10.1016/j.bbi.2008.05.010
- Najt, P., Nicoletti, M., Chen, H. H., Hatch, J. P., Caetano, S. C., Sassi, R. B., Axelson, D., et al. (2007). Anatomical measurements of the orbitofrontal cortex in child and adolescent patients with bipolar disorder. *Neuroscience Letters*, 413(3), 183–186. doi:10.1016/j.neulet.2006.10.016



- Nakamura, M., Nestor, P. G., Levitt, J. J., Cohen, A. S., Kawashima, T., Shenton, M. E., & McCarley, R. W. (2008). Orbitofrontal volume deficit in schizophrenia and thought disorder. *Brain*, *131*(Pt 1), 180–195. doi:10.1093/brain/awm265
- Narr, K. L., Woods, R. P., Thompson, P. M., Szeszko, P., Robinson, D., Dimtcheva, T., Gurbani, M., et al. (2007). Relationships between IQ and regional cortical gray matter thickness in healthy adults. *Cerebral Cortex*, *17*(9), 2163–2171. doi:10.1093/cercor/bhl125
- Nee, D. E., Wager, T. D., & Jonides, J. (2007). Interference resolution: insights from a meta-analysis of neuroimaging tasks. *Cognitive, Affective & Behavioral Neuroscience*, *7*(1), 1–17. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/17598730>
- Newcomer, J., Craft, S., Hershey, T., Askins, K., & Bardgett, M. (1994). Glucocorticoid-induced impairment in declarative memory performance in adult humans. *Journal of Neuroscience*, *14*(April), 2047–2053. Retrieved from <http://www.jneurosci.org/cgi/content/abstract/14/4/2047>
- Newman, S., Carpenter, P., Varma, S., & Just, M.A. (2003). Frontal and parietal participation in problem solving in the Tower of London: fMRI and computational modeling of planning and high-level perception. *Neuropsychologia*, *41*(12), 1668–1682. doi:10.1016/S0028-3932(03)00091-5
- Newman, S. D., Greco, J. A., & Lee, D. (2009). An fMRI study of the Tower of London: a look at problem structure differences. *Brain Research*, *1286*, 123–132. doi:10.1016/j.brainres.2009.06.031
- Nifosi, F., Toffanin, T., Follador, H., Zonta, F., Padovan, G., Pigato, G., Carollo, C., et al. (2010). Reduced right posterior hippocampal volume in women with recurrent familial pure depressive disorder. *Psychiatry Research*, *184*(1), 23–28. doi:10.1016/j.psychresns.2010.05.012
- Nolte, J., & Angevine, J. B. (1995). *The human brain in photographs and diagrams*, Mosby, St.
- Nyholt, D.R. (2001). Genetic case-control association studies - correcting for multiple testing. *Human Genetics* *109*, 564–567.
- Nyhus, E., & Barceló, F. (2009). The Wisconsin Card Sorting Test and the cognitive assessment of prefrontal executive functions: A critical update. *Brain and Cognition*, *71*(3), 437–451. doi:10.1016/j.bandc.2009.03.005
- Ochsner, K. N., Kosslyn, S. M., Cosgrove, G. R., Cassem, E. H., Price, B. H., Nierenberg, a a, & Rauch, S. L. (2001). Deficits in visual cognition and attention following bilateral anterior cingulotomy. *Neuropsychologia*, *39*(3), 219–230. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11163601>

- Ongür, D., & Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex*, 10(3), 206–219. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10731217>
- Ongür, Dost, Ferry, A. T., & Price, J. L. (2003). Architectonic subdivision of the human orbital and medial prefrontal cortex. *The Journal of comparative neurology*, 460(3), 425–449. doi:10.1002/cne.10609
- Ott, J. (1999). *Analysis of human genetic linkage*, 3<sup>rd</sup> Ed. Johns Hopkins University Press, Baltimore.
- Otte, C., Hart, S., Neylan, T. C., Marmar, C. R., Yaffe, K., & Mohr, D. C. (2005). A meta-analysis of cortisol response to challenge in human aging: importance of gender. *Psychoneuroendocrinology*, 30(1), 80–91. doi:10.1016/j.psyneuen.2004.06.002
- Owen, A. M., Doyon, J., Petrides, M., & Evans, A. C. (1996). Planning and spatial working memory: a positron emission tomography study in humans. *The European Journal of Neuroscience*, 8(2), 353–364. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8714706>
- Owen, A. M., Stern, C. E., Look, R. B., Tracey, I., Rosen, B. R., & Petrides, M. (1998). Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 95(13), 7721–7726. Retrieved from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=22736&tool=pmcentrez&rendertype=abstract>
- Owen, A.M., Downes, J., Sahakian, B., Polkey, C., & Robbins, T. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia*, 28(10), 1021–1034. Retrieved from <http://linkinghub.elsevier.com/retrieve/pii/002839329090137D>
- O'Brien, J.T., Schweitzer, I., Ames, D., Tuckwell, V., & Mastwyk, M. (1994). Cortisol suppression by dexamethasone in the healthy elderly: effects of age, dexamethasone levels, and cognitive function. *Biological Psychiatry*, 36(6), 389–394. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7803600>
- O'Brien, J.T., Lloyd, A., McKeith, I., Gholkar, A., & Ferrier, N. (2004). A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. *The American Journal of Psychiatry*, 161(11), 2081–2090. doi:10.1176/appi.ajp.161.11.2081
- O'Doherty, J., Kringelbach, M. L., Rolls, E. T., Hornak, J., & Andrews, C. (2001). Abstract reward and punishment representations in the human orbitofrontal cortex. *Nature Neuroscience*, 4(1), 95–102. doi:10.1038/82959

- O'Sullivan, M., Jones, D. K., Summers, P. E., Morris, R. G., Williams, S. C. R., & Markus, H. S. (2001). Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology*, 57(4), 632–638. doi:10.1212/WNL.57.4.632
- Padoa-Schioppa, C., & Assad, J. A. (2006). Neurons in the orbitofrontal cortex encode economic value. *Nature*, 441(7090), 223–226. doi:10.1038/nature04676
- Palomero-Gallagher, N., Vogt, B. A., Schleicher, A., Mayberg, H. S., & Zilles, K. (2009). Receptor architecture of human cingulate cortex: evaluation of the four-region neurobiological model. *Human Brain Mapping*, 30(8), 2336–2355. doi:10.1002/hbm.20667
- Pariante, C., Thomas, S., Lovestone, S., Makoff, A., & Kerwin, R. (2004). Do antidepressants regulate how cortisol affects the brain? *Psychoneuroendocrinology*, 29(4), 423–447. doi:10.1016/j.psyneuen.2003.10.009
- Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annual Review of Psychology*, 60, 173–196. doi:10.1146/annurev.psych.59.103006.093656
- Patel, P. D., Lopez, J. F., Lyons, D. M., Burke, S., Wallace, M., & Schatzberg, a F. (2001). Glucocorticoid and mineralocorticoid receptor mRNA expression in squirrel monkey brain. *Journal of Psychiatric Research*, 34(6), 383–392. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11165305>
- Patel, P., Katz, M., Karssen, A., & Lyons, D. (2008). Stress-induced changes in corticosteroid receptor expression in primate hippocampus and prefrontal cortex. *Psychoneuroendocrinology*, 33(3), 360–367. doi:10.1016/j.bbi.2008.05.010
- Patil, C., Lad, S., Katznelson, L., & Laws, E. (2007). Brain atrophy and cognitive deficits in Cushing's disease. *Neurosurgical Focus*, 23(3), 11–14. doi:10.3171/FOC-07/09/E11
- Paus, T., Tomaiuolo, F., Otaky, N., Petrides, M., Atlas, J., Morris, R., & Evans, A. C. (1996). Human cingulate and paracingulate sulci: Pattern, variability, asymmetry, and probabilistic map. *Cerebral Cortex*, 6, 207–214.
- Pengas, G., Hodges, J. R., Watson, P., & Nestor, P. J. (2010). Focal posterior cingulate atrophy in incipient Alzheimer's disease. *Neurobiology of Aging*, 31(1), 25–33. doi:10.1016/j.neurobiolaging.2008.03.014
- Penke, L., Maniega, S. M., Bastin, M. E., Valdés Hernández, M. C., Murray, C., Royle, N. a, Starr, J. M., et al. (2012). Brain white matter tract integrity as a neural foundation for general intelligence. *Molecular Psychiatry*, 17(10), 1026–1030. doi:10.1038/mp.2012.66

- Perez-Alvarez, F., Timoneda, C., & Reixach, J. (2007). An fMRI study of emotional engagement in decision-making. *Transaction Advanced Research*, 2, 45–51.
- Perez-Cruz, C., Simon, M., Czéh, B., Flügge, G., & Fuchs, E. (2009). Hemispheric differences in basilar dendrites and spines of pyramidal neurons in the rat prelimbic cortex: activity- and stress-induced changes. *The European Journal of Neuroscience*, 29(4), 738–747. doi:10.1111/j.1460-9568.2009.06622.x
- Perret E. (1974). The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. *Neuropsychologia* 12(3), 323–330.
- Persson, J., Nyberg, L., Lind, J., Larsson, A., Nilsson, L.-G., Ingvar, M., & Buckner, R. L. (2006). Structure-function correlates of cognitive decline in aging. *Cerebral Cortex*, 16(7), 907–915. doi:10.1093/cercor/bhj036
- Peters, S., Cleare, A. J., Papadopoulos, A., & Fu, C. H. Y. (2011). Cortisol responses to serial MRI scans in healthy adults and in depression. *Psychoneuroendocrinology*, 36(5), 737–741. doi:10.1016/j.psyneuen.2010.10.009
- Peterson, B. S., Kane, M. J., Alexander, G. M., Lacadie, C., Skudlarski, P., Leung, H. C., May, J., et al. (2002). An event-related functional MRI study comparing interference effects in the Simon and Stroop tasks. *Brain Research*, 13(3), 427–440. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11919006>
- Petrides, M. (2000). The role of the mid-dorsolateral prefrontal cortex in working memory. *Experimental brain research*, 133(1), 44–54. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10933209>
- Petrides, M., Alivisatos, B., Evans, A.C., & Meyer, E. (1993). Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proceedings of the National Academy of Sciences*, 90(3), 873–877. Retrieved from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=45772&tool=pmcentrez&rendertype=abstract>
- Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal-and temporal-lobe lesions in man. *Neuropsychologia*, 20(3), 249–262. Retrieved from <http://linkinghub.elsevier.com/retrieve/pii/0028393282901002>
- Petrides, M., Tomaiuolo, F., Yeterian, E. H., & Pandya, D. N. (2012). The Prefrontal Cortex: Comparative Architectonic Organization in the Human and the Macaque Monkey Brains. *Cortex*, 48, 46–57. doi:10.1016/j.cortex.2011.07.002
- Phillips, L. H., & Della Sala, S. (1998). Aging, intelligence, and anatomical segregation in the frontal lobes. *Learning and Individual Differences*, 10(3), 217–243. Retrieved from <http://linkinghub.elsevier.com/retrieve/pii/S1041608099801319>

- Phillips, L. H., Wynn, V. E., MacPherson, S., & Gilhooly, K. J. (2001). Mental planning and the Tower of London task. *The Quarterly Journal of Experimental Psychology A*, 54(2), 579–597. doi:10.1080/02724980042000237
- Phillips, L., MacPherson, S. E., & Della Sala, S. (2002). Age, cognition and emotion: the role of anatomical segregation in the frontal lobes. In J. Grafman (Ed.), *Handbook of Neuropsychology* (2nd ed., Vol. 7, pp. 73–97). Elsevier Science. Retrieved from <http://www.uth.tmc.edu/clinicalneuro/institute/2004/Philips.pdf>
- Pike, N. (2011). Using false discovery rates for multiple comparisons in ecology and evolution. *Methods in Ecology and Evolution*, 2, 278–282.
- Poletti, C. E., & Creswell, G. (1977). Fornix system efferent projections in the squirrel monkey: an experimental degeneration study. *The Journal of Comparative Neurology*, 175(1), 101–128. doi:10.1002/cne.901750107
- Porter, R. J., Barnett, N. a., Idey, a., McGuckin, E. a., & O'Brien, J. T. (2002). Effects of hydrocortisone administration on cognitive function in the elderly. *Journal of Psychopharmacology*, 16(1), 65–71. doi:10.1177/026988110201600106
- Power, C., Li, L., & Hertzman, C. (2008). Cognitive development and cortisol patterns in mid-life: Findings from a British birth cohort. *Psychoneuroendocrinology*, 33, 530–539. doi:10.1016/j.psyneuen.2008.01.017.
- Prasad, K. M. R., Sahni, S. D., Rohm, B. R., & Keshavan, M. S. (2005). Dorsolateral prefrontal cortex morphology and short-term outcome in first-episode schizophrenia. *Psychiatry Research*, 140(2), 147–155. doi:10.1016/j.psychresns.2004.05.009
- Preacher, K. J., & Hayes, A. F. (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior research methods, instruments, & computers : a journal of the Psychonomic Society, Inc*, 36(4), 717–731. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/15641418>
- Prehn, K., Wartenburger, I., Mériaux, K., Scheibe, C., Goodenough, O. R., Villringer, A., van der Meer, E., et al. (2008). Individual differences in moral judgment competence influence neural correlates of socio-normative judgments. *Social cognitive and affective neuroscience*, 3(1), 33–46. doi:10.1093/scan/nsm037
- Provost, J.-S., Petrides, M., Simard, F., & Monchi, O. (2012). Investigating the Long-Lasting Residual Effect of a Set Shift on Frontostriatal Activity. *Cerebral Cortex*, 22(12), 2811–2819.. doi:10.1093/cercor/bhr358
- Pruessner, J. C., Baldwin, M. W., Dedovic, K., Renwick, R., Mahani, N. K., Lord, C., Meaney, M., et al. (2005). Self-esteem, locus of control, hippocampal volume, and cortisol regulation in young and old adulthood. *NeuroImage*, 28(4), 815–826. doi:10.1016/j.neuroimage.2005.06.014

- Pruessner, J. C., Dedovic, K., Khalili-Mahani, N., Engert, V., Pruessner, M., Buss, C., Renwick, R., et al. (2008). Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biological Psychiatry*, 63(2), 234–240. doi:10.1016/j.biopsych.2007.04.041
- Pruessner, J. C., Dedovic, K., Pruessner, M., Lord, C., Buss, C., Collins, L., Dagher, A., et al. (2010). Stress regulation in the central nervous system: evidence from structural and functional neuroimaging studies in human populations - 2008 Curt Richter Award Winner. *Psychoneuroendocrinology*, 35(1), 179–191. doi:10.1016/j.psyneuen.2009.02.016
- Pujol, J., Vendrell, P., Deus, J., Junqué, C., Bello, J., Martí-Vilalta, J. L., & Capdevila, A. (2001). The effect of medial frontal and posterior parietal demyelinating lesions on stroop interference. *NeuroImage*, 13(1), 68–75. doi:10.1006/nimg.2000.0662
- Pujol, Jesus, Reixach, J., Harrison, B. J., Timoneda-Gallart, C., Vilanova, J. C., & Pérez-Alvarez, F. (2008). Posterior cingulate activation during moral dilemma in adolescents. *Human brain mapping*, 29(8), 910–921. doi:10.1002/hbm.20436
- Putnam, K. M., Pizzagalli, D. A., Gooding, D. C., Kalin, N. H., & Davidson, R. J. (2008). Neural activity and diurnal variation of cortisol: evidence from brain electrical tomography analysis and relevance to anhedonia. *Psychophysiology*, 45(6), 886–895. doi:10.1111/j.1469-8986.2008.00697.x
- Pérez-Iglesias, R., Tordesillas-Gutiérrez, D., McGuire, P. K., Barker, G. J., Roiz-Santiañez, R., Mata, I., de Lucas, E. M., et al. (2010). White matter integrity and cognitive impairment in first-episode psychosis. *The American Journal of Psychiatry*, 167(4), 451–458. doi:10.1176/appi.ajp.2009.09050716
- Rademacher, J., Caviness, V. S., Steinmetz, H., & Galaburda, a M. (1993). Topographical variation of the human primary cortices: implications for neuroimaging, brain mapping, and neurobiology. *Cerebral Cortex*, 3(4), 313–329. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8400809>
- Radley, J J, Sisti, H. M., Hao, J., Rocher, a B., McCall, T., Hof, P. R., McEwen, B. S., et al. (2004). Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. *Neuroscience*, 125(1), 1–6. doi:10.1016/j.neuroscience.2004.01.006
- Radley, J.J., Arias, C. M., & Sawchenko, P. E. (2006). Regional differentiation of the medial prefrontal cortex in regulating adaptive responses to acute emotional stress. *The Journal of Neuroscience*, 26(50), 12967–12976. doi:10.1523/JNEUROSCI.4297-06.2006
- Radley, J.J., Rocher, A. B., Rodriguez, A., Ehlenberger, D. B., Dammann, M., McEwen, B. S., Morrison, J. H., et al. (2008). Repeated stress alters dendritic

spine morphology in the rat medial prefrontal cortex. *The Journal of Comparative Neurology*, 507(1), 1141–1150. doi:10.1002/cne.21588

- Rajkowska, G., & Goldman-Rakic, P. S. (1995). Cytoarchitectonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the Talairach Coordinate System. *Cerebral Cortex*, 5(4), 323–337. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7580125>
- Ranta, M. E., Crocetti, D., Clauss, J. a, Kraut, M. a, Mostofsky, S. H., & Kaufmann, W. E. (2009). Manual MRI parcellation of the frontal lobe. *Psychiatry Research*, 172(2), 147–154. doi:10.1016/j.psychresns.2009.01.006
- Rasser, P. E., Johnston, P., Lagopoulos, J., Ward, P. B., Schall, U., Thienel, R., Bender, S., et al. (2005). Functional MRI BOLD response to Tower of London performance of first-episode schizophrenia patients using cortical pattern matching. *NeuroImage*, 26(3), 941–951. doi:10.1016/j.neuroimage.2004.11.054
- Ratnanather, J. T., Botteron, K. N., Nishino, T., Massie, a B., Lal, R. M., Patel, S. G., Peddi, S., et al. (2001). Validating cortical surface analysis of medial prefrontal cortex. *NeuroImage*, 14(5), 1058–1069. doi:10.1006/nimg.2001.0906
- Rauch, S. L., Shin, L. M., Segal, E., Pitman, R. K., Carson, M. A., McMullin, K., Whalen, P. J., et al. (2003). Selectively reduced regional cortical volumes in post-traumatic stress disorder. *Neuroreport*, 14(7), 913–916. doi:10.1097/01.wnr.0000071767
- Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., Loken, W. J., et al. (1997). Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cerebral Cortex*, 7(3), 268–282. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9143446>
- Raz, N., Torres, I. J., Briggs, S. D., Spencer, W. D., Thornton, A. E., Loken, W. J., Gunning, F. M., et al. (1995). Selective neuroanatomic abnormalities in Down's syndrome and their cognitive correlates: Evidence from MRI morphometry. *Neurology*, 45, 356–366.
- Raz, N., Ghisletta, P., Rodrigue, K. M., Kennedy, K. M., & Lindenberger, U. (2010). Trajectories of brain aging in middle-aged and older adults: regional and individual differences. *NeuroImage*, 51(2), 501–511. doi:10.1016/j.neuroimage.2010.03.020
- Raz, N., Gunning-Dixon, F., Head, D., Rodrigue, K. M., Williamson, A., & Acker, J. D. (2004). Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. *Neurobiology of Aging*, 25(3), 377–396. doi:10.1016/S0197-4580(03)00118-0
- Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., Dahle, C., et al. (2005). Regional brain changes in aging healthy adults:

- general trends, individual differences and modifiers. *Cerebral cortex*, 15(11), 1676–1689. doi:10.1093/cercor/bhi044
- Raz, N., Rodrigue, K. M., Kennedy, K. M., & Acker, J. D. (2007). Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. *Neuropsychology*, 21(2), 149–157. doi:10.1037/0894-4105.21.2.149
- Remijne, P. L., Nielen, M. M. a, Uylings, H. B. M., & Veltman, D. J. (2005). Neural correlates of a reversal learning task with an affectively neutral baseline: an event-related fMRI study. *NeuroImage*, 26(2), 609–618. doi:10.1016/j.neuroimage.2005.02.009
- Resnick, S. M., Lamar, M., & Driscoll, I. (2007). Vulnerability of the orbitofrontal cortex to age-associated structural and functional brain changes. *Annals of the New York Academy of Sciences*, 1121, 562–575. doi:10.1196/annals.1401.027
- Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B., & Davatzikos, C. (2003). Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *The Journal of Neuroscience*, 23(8), 3295–3301. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12716936>
- Robbins, T.W., James, M., Owen, A.M., Sahakian, B.J., Lawrence, A.D., McInnes, L., & Rabbitt, P.M.A. (1998). A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: Implications for theories of executive functioning and cognitive ageing. *Journal of the International Neuropsychological Society*, 4, 474-490.
- Roberts, K. L., & Hall, D. a. (2008). Examining a supramodal network for conflict processing: a systematic review and novel functional magnetic resonance imaging data for related visual and auditory stroop tasks. *Journal of Cognitive Neuroscience*, 20(6), 1063–1078. doi:10.1162/jocn.2008.20074
- Roca, M., Parr, A. Thompson, R., Woolgar, A., Torralva, T., Antoun, N., Manes, F., & Duncan, J. (2010). Executive function and fluid intelligence after frontal lobe lesions. *Brain*, 133 (1), 234-247.
- Rolls, E T, Hornak, J., Wade, D., & McGrath, J. (1994). Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *Journal of Neurology, Neurosurgery & Psychiatry*, 57(12), 1518–1524. doi:10.1136/jnnp.57.12.1518
- Rolls, E.T., & Grabenhorst, F. (2008). The orbitofrontal cortex and beyond: from affect to decision-making. *Progress in Neurobiology*, 86(3), 216–244. doi:10.1016/j.pneurobio.2008.09.001
- Rosen, H. J., Gorno-Tempini, M. L., Goldman, W. P., Perry, R. J., Schuff, N., Weiner, M., Feiwell, R., et al. (2002). Patterns of brain atrophy in



frontotemporal dementia and semantic dementia. *Neurology*, 58(2), 198–208.  
doi:10.1212/WNL.58.2.198

Rossi, S., Miniussi, C., Pasqualetti, P., Babiloni, C., Rossini, P.M., Cappa, S.F. (2004). Age-related functional changes of prefrontal cortex in long-term memory: a repetitive transcranial magnetic stimulation study. *Journal of Neuroscience*, 24:7939–7944.

Rosso, I. M., Makris, N., Thermenos, H. W., Hodge, S. M., Brown, A., Kennedy, D., Caviness, V. S., et al. (2010). Regional prefrontal cortex gray matter volumes in youth at familial risk for schizophrenia from the Harvard Adolescent High Risk Study. *Schizophrenia Research*, 123(1), 15–21.  
doi:10.1016/j.schres.2010.06.015

Rowe, J. B., Owen, A. M., Johnsrude, I. S., & Passingham, R. E. (2001). Imaging the mental components of a planning task. *Neuropsychologia*, 39(3), 315–327.  
Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11163609>

Rudebeck, P. H., Bannerman, D. M., & Rushworth, M. F. S. (2008). The contribution of distinct subregions of the ventromedial frontal cortex to emotion, social behavior, and decision making. *Cognitive, Affective & Behavioral Neuroscience*, 8(4), 485–497. doi:10.3758/CABN.8.4.485

Rupp, C. I., Fleischhacker, W. W., Kemmler, G., Oberbauer, H., Scholtz, A. W., Wanko, C., & Hinterhuber, H. (2005). Various bilateral olfactory deficits in male patients with schizophrenia. *Schizophrenia Bulletin*, 31(1), 155–165.  
doi:10.1093/schbul/sbi018

Rushworth, M. F. S., & Behrens, T. E. J. (2008). Choice, uncertainty and value in prefrontal and cingulate cortex. *Nature Neuroscience*, 11(4), 389–397.  
doi:10.1038/nn2066

Sabb, F. W., Bilder, R. M., Chou, M., & Bookheimer, S. Y. (2007). Working memory effects on semantic processing: priming differences in pars orbitalis. *NeuroImage*, 37(1), 311–322. doi:10.1016/j.neuroimage.2007.04.050

Salat, D H, Kaye, J. a, & Janowsky, J. S. (2001). Selective preservation and degeneration within the prefrontal cortex in aging and Alzheimer disease. *Archives of Neurology*, 58(9), 1403–1408. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11559311>

Salat, David H, Kaye, J. a, & Janowsky, J. S. (2002). Greater orbital prefrontal volume selectively predicts worse working memory performance in older adults. *Cerebral Cortex*, 12(5), 494–505. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11950767>

Salmon, E., Garraux, G., Delbeuck, X., Collette, F., Kalbe, E., Zuendorf, G., Perani, D., et al. (2003). Predominant ventromedial frontopolar metabolic impairment

in frontotemporal dementia. *NeuroImage*, 20(1), 435–440. doi:10.1016/S1053-8119(03)00346-X

- Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, 103, 403–428.
- Salthouse, T. A. (2004). What and when of cognitive aging. *Current Directions in Psychological Science*, 13(4), 140–144.
- Salthouse, T.A. (2005). Relations between cognitive abilities and measures of executive functioning. *Neuropsychology*, 19(4), 532–545.
- Salthouse, T. A. (2011). Neuroanatomical substrates of age-related cognitive decline. *Psychological Bulletin*, 137(5), 753–784. doi:10.1037/a0023262
- Sanches, M., Caetano, S., Nicoletti, M., Monkul, E. S., Chen, H. H., Hatch, J. P., Yeh, P.-H., et al. (2009). An MRI-based approach for the measurement of the dorsolateral prefrontal cortex in humans. *Psychiatry Research*, 173(2), 150–154. doi:10.1016/j.psychres.2009.02.007
- Sanfilipo, M., Lafargue, T., Rusinek, H., Arena, L., Loneragan, C., Lautin, a, Feiner, D., et al. (2000). Volumetric measure of the frontal and temporal lobe regions in schizophrenia: relationship to negative symptoms. *Archives of General Psychiatry*, 57(5), 471–480. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10807487>
- Sapolsky, R., Krey, L., & McEwen, B. (1986). The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocrine Reviews*, 7(3), 284–301. Retrieved from <http://sageke.highwire.org/cgi/content/abstract/2002/38/cp21>
- Sapolsky, R., Romero, L., & Munck, A. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews*, 21(1), 55– 89. Retrieved from <http://edrv.endojournals.org/cgi/content/abstract/edrv;21/1/55>
- Sapolsky, R., Uno, H., Rebert, C., & Finch, C.E. (1990). Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *Journal of Neuroscience*, 10(9), 2897–2902. Retrieved from <http://www.jneurosci.org/cgi/content/abstract/10/9/2897>
- Sarazin, M., Pillon, B., Giannakopoulos, P., Rancurel, G., Samson, Y., & Dubois, B. (1998). Clinicometabolic dissociation of cognitive functions and social behavior in frontal lobe lesions. *Neurology*, 51(1), 142–148. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9674793>
- Sasson, E., Doniger, G. M., Pasternak, O., Tarrasch, R., & Assaf, Y. (2012). Structural correlates of cognitive domains in normal aging with diffusion tensor

imaging. *Brain Structure & Function*, 217(2), 503–515. doi:10.1007/s00429-011-0344-7

- Schaich Borg, J., Hynes, C., Van Horn, J., Grafton, S., & Sinnott-Armstrong, W. (2006). Consequences, action, and intention as factors in moral judgments: an fMRI investigation. *Journal of Cognitive Neuroscience*, 18(5), 803–817. doi:10.1162/jocn.2006.18.5.803
- Schall, U., Johnston, P., Lagopoulos, J., Jüptner, M., Jentzen, W., Thienel, R., Dittmann-Balçar, A., et al. (2003). Functional brain maps of Tower of London performance: a positron emission tomography and functional magnetic resonance imaging study. *NeuroImage*, 20(2), 1154–1161. doi:10.1016/S1053-8119(03)00338-0
- Scheff, S., Benardo, L., & Cotman, C. (1980). Decline in reactive fiber growth in the dentate gyrus of aged rats compared to young adult rats following entorhinal cortex removal. *Brain Research*, 199, 21–38. Retrieved from <http://www.sciencedirect.com/science/article/pii/0006899380902279>
- Scheff, S. W., & Cotman, C. W. (1982). Chronic glucocorticoid therapy alters axon sprouting in the hippocampal dentate gyrus. *Experimental Neurology*, 76(3), 644–654. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7084379>
- Scheff, S. W., & DeKosky, S. T. (1983). Steroid suppression of axon sprouting in the hippocampal dentate gyrus of the adult rat: dose-response relationship. *Experimental Neurology*, 82(1), 183–191. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/6628607>
- Scheff, S. W., & Dekosky, S. T. (1989). Glucocorticoid suppression of lesion-induced synaptogenesis: effect of temporal manipulation of steroid treatment. *Experimental Neurology*, 105(3), 260–264. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/2767199>
- Schenker, N. M., Desgouttes, A.-M., & Semendeferi, K. (2005). Neural connectivity and cortical substrates of cognition in hominoids. *Journal of Human Evolution*, 49(5), 547–569. doi:10.1016/j.jhevol.2005.06.004
- Schlaepfer, T. E., Harris, G. J., Tien, A. Y., Peng, L., Lee, S., & Pearlson, G. D. (1995). Structural differences in the cerebral cortex of healthy female and male subjects: a magnetic resonance imaging study. *Psychiatry Research*, 61(3), 129–135. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8545497>
- Schlaepfer, T. E., Harris, G. J., Tien, A. Y., Peng, L. W., Lee, S., Federman, E. B., Chase, G. A., et al. (1994). Decreased regional cortical gray matter volume in schizophrenia. *American Journal of Psychiatry*, 151(June), 842–848. Retrieved from <http://homepage.mac.com/thomas.schlaepfer/CV/page4/files/A7.pdf>

- Schmierer, K., Wheeler-Kingshott, C.A.M., Boulby, P.A., Scaravilli, F., Altmann, D.R., Barker, G.J., Tofts, P.S. & Miller, D.H. (2007). Diffusion tensor imaging of post-mortem multiple sclerosis brain. *NeuroImage*, 35(2), 467-477.
- Seckl, J., & Olsson, T. (1995). Glucocorticoid hypersecretion and the age-impaired hippocampus: cause or effect? *Journal of Endocrinology*, 145, 201–211. Retrieved from <http://joe.endocrinology-journals.org/cgi/content/abstract/145/2/201>
- Seeley, W. W., Merkle, F. T., Gaus, S. E., Craig, a D. B., Allman, J. M., Hof, P. R., & Economo, C. V. (2012). Distinctive neurons of the anterior cingulate and frontoinsular cortex: a historical perspective. *Cerebral Cortex*, 22(2), 245–250. doi:10.1093/cercor/bhr005
- Seeman, T. E., McEwen, B. S., Singer, B. H., Albert, M. S., & Rowe, J. W. (1997). Increase in urinary cortisol excretion and memory declines: MacArthur studies of successful aging. *The Journal of Clinical Endocrinology and Metabolism*, 82(8), 2458–2465. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9253318>
- Segar, T. M., Kasckow, J. W., Welge, J. A., & Herman, J. P. (2009). Heterogeneity of neuroendocrine stress responses in aging rat strains. *Physiology & Behavior*, 96(1), 6–11. doi:10.1016/j.physbeh.2008.07.024
- Seidman, L J, Yurgelun-Todd, D., Kremen, W. S., Woods, B. T., Goldstein, J. M., Faraone, S. V., & Tsuang, M. T. (1994). Relationship of prefrontal and temporal lobe MRI measures to neuropsychological performance in chronic schizophrenia. *Biological Psychiatry*, 35(4), 235–246. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8186328>
- Seidman, Larry J, Valera, E. M., Makris, N., Monuteaux, M. C., Boriell, D. L., Kelkar, K., Kennedy, D. N., et al. (2006). Dorsolateral prefrontal and anterior cingulate cortex volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging. *Biological Psychiatry*, 60(10), 1071–1080. doi:10.1016/j.biopsych.2006.04.031
- Semendeferi, K., Armstrong, E., Schleicher, a, Zilles, K., & Van Hoesen, G. W. (2001). Prefrontal cortex in humans and apes: a comparative study of area 10. *American Journal of Physical Anthropology*, 114(3), 224–241. doi:10.1002/1096-8644(200103)114:3<224::AID-AJPA1022>3.0.CO;2-I
- Semendeferi, K., Damasio, H., Frank, R., & Van Hoesen, G. W. (1997). The evolution of the frontal lobes: a volumetric analysis based on three-dimensional reconstructions of magnetic resonance scans of human and ape brains. *Journal of Human Evolution*, 32(4), 375–388. doi:10.1006/jhev.1996.0099

- Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London*, 298(1089), 199–209. Retrieved from <http://www.jstor.org/stable/2395870>
- Shallice, Tim, Stuss, D. T., Picton, T. W., Alexander, M. P., & Gillingham, S. (2008). Mapping task switching in frontal cortex through neuropsychological group studies. *Frontiers in Neuroscience*, 2(1), 79–85. doi:10.3389/neuro.01.013.2008
- Shamay-Tsoory, S G, Tomer, R., & Aharon-Peretz, J. (2005). The neuroanatomical basis of understanding sarcasm and its relationship to social cognition. *Neuropsychology*, 19(3), 288–300. doi:10.1037/0894-4105.19.3.288
- Shamay-Tsoory, S G, Tomer, R., Berger, B. D., & Aharon-Peretz, J. (2003). Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. *Journal of Cognitive Neuroscience*, 15(3), 324–337. doi:10.1162/089892903321593063
- Shamay-Tsoory, S G, Tomer, R., Berger, B. D., Goldsher, D., & Aharon-Peretz, J. (2005). Impaired “affective theory of mind” is associated with right ventromedial prefrontal damage. *Cognitive and Behavioral Neurology*, 18(1), 55–67. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/15761277>
- Shamay-Tsoory, Simone G, Aharon-Peretz, J., & Perry, D. (2009). Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain*, 132(Pt 3), 617–627. doi:10.1093/brain/awn279
- Shamay-Tsoory, Simone G, Harari, H., Aharon-Peretz, J., & Levkovitz, Y. (2010). The role of the orbitofrontal cortex in affective theory of mind deficits in criminal offenders with psychopathic tendencies. *Cortex*, 46(5), 668–677. doi:10.1016/j.cortex.2009.04.008
- Shenhav, A., & Greene, J. D. (2010). Moral Judgments Recruit Domain-General Valuation Mechanisms to Integrate Representations of Probability and Magnitude. *Neuron*, 67(4), 667–677. doi:10.1016/j.neuron.2010.07.020
- Shrout, P.E., Fleiss, J.L., 1979. Intraclass correlations: uses in assessing rater reliability. *Psychological Bulletin* 2, 420–428.
- Simon, J., & Berbaum, K. (1990). Effect of conflicting cues on information processing: The “Stroop Effect” vs. the “Simon effect.” *Acta psychologica*, 73, 159–170. Retrieved from <http://linkinghub.elsevier.com/retrieve/pii/000169189090077S>
- Smith, G. E. (1907). A new topographical survey of the human cerebral cortex, being an account of the distribution of the anatomically distinct cortical areas and their relationship to the cerebral sulci. *Journal of Anatomy and Physiology*, 41(Pt 4),

237–254. Retrieved from  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1289123/>

- Snaith, R. (2003). The hospital anxiety and depression scale. *Health and Quality of Life Outcomes*, 1(29). Retrieved from  
<http://www3.interscience.wiley.com/journal/119537678/abstract>
- Sowell, E. R., Trauner, D. a, Gamst, A., & Jernigan, T. L. (2002). Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. *Developmental Medicine and Child Neurology*, 44(1), 4–16. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11811649>
- Spearman, Charles, C. (1910). Correlation calculated from faulty data. *British Journal of Psychology*, 3, 271–295.
- Squire, L. R. (2009). Memory and brain systems: 1969-2009. *The Journal of Neuroscience*, 29(41), 12711–12716. doi:10.1523/JNEUROSCI.3575-09.2009
- Steele, J. D., & Lawrie, S. M. (2004). Segregation of cognitive and emotional function in the prefrontal cortex: a stereotactic meta-analysis. *NeuroImage*, 21(3), 868–875. doi:10.1016/j.neuroimage.2003.09.066
- Stone, V. E., Baron-Cohen, S., & Knight, R. T. (1998). Frontal lobe contributions to theory of mind. *Journal of Cognitive Neuroscience*, 10(5), 640–656. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/15701227>
- Strelzyk, F., Hermes, M., Naumann, E., Oitzl, M., Walter, C., Busch, H.-P., Richter, S., et al. (2012). Tune it down to live it up? Rapid, nongenomic effects of cortisol on the human brain. *The Journal of Neuroscience*, 32(2), 616–625. doi:10.1523/JNEUROSCI.2384-11.2012
- Stroop, J. R. (1992). Studies of interference in verbal reactions. *Journal of Experimental Psychology: General*, (121), 15–23.
- Stuss, D. T. (2011). Functions of the frontal lobes: Relation to executive functions. *Journal of the International Neuropsychological Society*, 17, 759–765.
- Stuss, D.T., & Alexander, M. (2007). Is there a dysexecutive syndrome? *Philosophical Transactions B: Biological Sciences*, 362(1481), 901–915
- Stuss, D.T., Floden, D., Alexander, M. P., Levine, B., & Katz, D. (2001). Stroop performance in focal lesion patients: dissociation of processes and frontal lobe lesion location. *Neuropsychologia*, 39(8), 771–786. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11369401>
- Stuss, D.T., Shallice, T., Alexander, M. P., & Picton, T. W. (1995). A multidisciplinary approach to anterior attentional functions. *Annals of the New*

*York Academy of Sciences*, 769, 191–211. Retrieved from  
<http://www.ncbi.nlm.nih.gov/pubmed/8595026>

- Stuss, D. (2000). Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: effects of lesion location and test structure on separable cognitive processes. *Neuropsychologia*, 38(4), 388–402. doi:10.1016/S0028-3932(99)00093-7
- Stuss, Donald T., & Levine, B. (2002). Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annual Review of Psychology*, 53, 401–433. doi:10.1146/annurev.psych.53.100901.135220
- Sullivan, E. V., & Pfefferbaum, A. (2007). Neuroradiological characterization of normal adult ageing. *The British Journal of Radiology*, 80, S99–S108. doi:10.1259/bjr/22893432
- Sullivan, R. M., & Gratton, a. (1999). Lateralized effects of medial prefrontal cortex lesions on neuroendocrine and autonomic stress responses in rats. *The Journal of Neuroscience*, 19(7), 2834–2840. Retrieved from  
<http://www.ncbi.nlm.nih.gov/pubmed/10087094>
- Suzuki, M., Zhou, S.-Y., Takahashi, T., Hagino, H., Kawasaki, Y., Niu, L., Matsui, M., et al. (2005). Differential contributions of prefrontal and temporolimbic pathology to mechanisms of psychosis. *Brain*, 128(Pt 9), 2109–2122. doi:10.1093/brain/awh554
- Swick, D., & Jovanovic, J. (2002). Anterior cingulate cortex and the Stroop task: neuropsychological evidence for topographic specificity. *Neuropsychologia*, 40(8), 1240–1253. Retrieved from  
<http://www.ncbi.nlm.nih.gov/pubmed/11931927>
- Swick, D., & Turken, A. U. (2002). Dissociation between conflict detection and error monitoring in the human anterior cingulate cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 99(25), 16354–16359. doi:10.1073/pnas.252521499
- Szeszko, P. R., Bilder, R. M., Lencz, T., Ashtari, M., Goldman, R. S., Reiter, G., Wu, H., et al. (2000). Reduced anterior cingulate gyrus volume correlates with executive dysfunction in men with first-episode schizophrenia. *Schizophrenia Research*, 43(2-3), 97–108. Retrieved from  
<http://www.ncbi.nlm.nih.gov/pubmed/10858628>
- Szeszko, P. R., Bilder, R. M., Lencz, T., Pollack, S., Alvir, J. M., Ashtari, M., Wu, H., et al. (1999). Investigation of frontal lobe subregions in first-episode schizophrenia. *Psychiatry Research*, 90(1), 1–15. Retrieved from  
<http://www.ncbi.nlm.nih.gov/pubmed/10320207>

- Szeszko, P. R., Robinson, D., Alvir, J. M., Bilder, R. M., Lencz, T., Ashtari, M., Wu, H., et al. (1999). Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder. *Archives of General Psychiatry*, 56(10), 913–919. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10530633>
- Sánchez, M. M., Young, L. J., Plotsky, P. M., & Insel, T. R. (2000). Distribution of corticosteroid receptors in the rhesus brain: relative absence of glucocorticoid receptors in the hippocampal formation. *The Journal of Neuroscience*, 20(12), 4657–4668. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10844035>
- Takahashi, T., Kawasaki, Y., Kurokawa, K., Hagino, H., Nohara, S., Yamashita, I., Nakamura, K., et al. (2002). Lack of normal structural asymmetry of the anterior cingulate gyrus in female patients with schizophrenia: a volumetric magnetic resonance imaging study. *Schizophrenia Research*, 55(1-2), 69–81. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11955965>
- Takahashi, T., Suzuki, M., Kawasaki, Y., Hagino, H., Yamashita, I., Nohara, S., Nakamura, K., et al. (2003). Perigenual Cingulate Gyrus Volume in Patients with Schizophrenia : A Magnetic Resonance Imaging Study. *Biological Psychiatry*, 53, 593–600. doi:10.1016/S0006-3223(03)01483-X
- Takahashi, T., Suzuki, M., Kawasaki, Y., Kurokawa, K., Hagino, H., Yamashita, I., Zhou, S.-Y., et al. (2002). Volumetric magnetic resonance imaging study of the anterior cingulate gyrus in schizotypal disorder. *European Archives of Psychiatry and Clinical Neuroscience*, 252(6), 268–277. doi:10.1007/s00406-002-0392-3
- Taylor, S. E., Burklund, L. J., Eisenberger, N. I., Lehman, B. J., Hilmert, C. J., & Lieberman, M. D. (2008). Neural bases of moderation of cortisol stress responses by psychosocial resources. *Journal of Personality and Social Psychology*, 95(1), 197–211. doi:10.1037/0022-3514.95.1.197
- Tchiteya, B. M., Lecours, A. R., Elie, R., & Lupien, S. J. (2003). Impact of a unilateral brain lesion on cortisol secretion and emotional state: anterior/posterior dissociation in humans. *Psychoneuroendocrinology*, 28(5), 674–686. doi:10.1016/S0306-4530(02)00050-1
- Tessner, K. D., Walker, E. F., Dhruv, S. H., Hochman, K., & Hamann, S. (2007). The relation of cortisol levels with hippocampus volumes under baseline and challenge conditions. *Brain Research*, 1179, 70–78. doi:10.1016/j.brainres.2007.05.027
- Thiebaut de Schotten, M., Dell’Acqua, F., Valabregue, R., & Catani, M. (2012). Monkey to human comparative anatomy of the frontal lobe association tracts. *Cortex*, 48(1), 82–96. doi:10.1016/j.cortex.2011.10.001
- Tisserand, D. J., Pruessner, J. C., Arigita, E. J. S., Boxtel, M. P. J. V., Evans, A. C., Jolles, J., & Uylings, H. B. M. (2002). Regional Frontal Cortical Volumes



Decrease Differentially in Aging : An MRI Study to Compare Volumetric Approaches and Voxel-Based Morphometry. *NeuroImage*, 17(2), 657– 669. doi:10.1006/nimg.2002.1173

- Toffanin, T., Nifosi, F., Follador, H., Passamani, A., Zonta, F., Ferri, G., Scanarini, M., et al. (2011). Volumetric MRI analysis of hippocampal subregions in Cushing's disease: a model for glucocorticoid neural modulation. *European Psychiatry*, 26(1), 64–67. doi:10.1016/j.eurpsy.2010.09.003
- Tomaszewski Farias, S., Cahn-Weiner, D. A., Harvey, D. J., Reed, B. R., Mungas, D., Kramer, J. H., & Chui, H. (2009). Longitudinal changes in memory and executive functioning are associated with longitudinal change in instrumental activities of daily living in older adults. *The Clinical Neuropsychologist*, 23(3), 446–461. doi:10.1080/13854040802360558
- Torralva, T., Kipps, C. M., Hodges, J. R., Clark, L., Bekinschtein, T., Roca, M., Calcagno, M. L., et al. (2007). The relationship between affective decision-making and theory of mind in the frontal variant of fronto-temporal dementia. *Neuropsychologia*, 45(2), 342–349. doi:10.1016/j.neuropsychologia.2006.05.031
- Turken, U., & Swick, D. (1999). Response selection in the human anterior cingulate cortex. *Nature Neuroscience*, 2(10), 920–924. doi:10.1038/13224
- Turken, A. U., & Swick, D. (2008). The effect of orbitofrontal lesions on the error-related negativity. *Neuroscience Letters*, 441(1), 7–10. doi:10.1016/j.neulet.2008.05.115
- Tzourio, N., Petit, L., Mellet, E., Orssaud, C., Crivello, F., Benali, K., Salamon, G., et al. (1997). Use of anatomical parcellation to catalog and study structure-function relationships in the human brain. *Human Brain Mapping*, 5(4), 228–232. doi:10.1002/(SICI)1097-0193(1997)5:4<228::AID-HBM4>3.0.CO;2-5
- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, 15(1), 273–289. doi:10.1006/nimg.2001.0978
- Ullsperger, M., & Von Cramon, D. Y. (2001). Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage*, 14(6), 1387–1401. doi:10.1006/nimg.2001.0935
- Ullsperger, M., & Von Cramon, D. Y. (2004). Neuroimaging of performance monitoring: Error detection and beyond. *Cortex*, 40, 593–604.

- Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews. Neuroscience*, 10(6), 397–409. doi:10.1038/nrn2647
- Unterrainer, J M, Rahm, B., Kaller, C. P., Ruff, C. C., Spreer, J., Krause, B. J., Schwarzwald, R., et al. (2004). When planning fails: individual differences and error-related brain activity in problem solving. *Cerebral Cortex*, 14(12), 1390–1397. doi:10.1093/cercor/bhh100
- Unterrainer, J M, Ruff, C. C., Rahm, B., Kaller, C. P., Spreer, J., Schwarzwald, R., & Halsband, U. (2005). The influence of sex differences and individual task performance on brain activation during planning. *NeuroImage*, 24(2), 586–590. doi:10.1016/j.neuroimage.2004.09.020
- Unterrainer, Josef M, & Owen, A. M. (2006). Planning and problem solving: from neuropsychology to functional neuroimaging. *Journal of Physiology*, 99(4-6), 308–317. doi:10.1016/j.jphysparis.2006.03.014
- Uylings, H B M, Rajkowska, G., Sanz-Arigita, E., Amunts, K., & Zilles, K. (2005). Consequences of large interindividual variability for human brain atlases: converging macroscopical imaging and microscopical neuroanatomy. *Anatomy and Embryology*, 210(5-6), 423–431. doi:10.1007/s00429-005-0042-4
- Uylings, Harry B M, Sanz-Arigita, E. J., de Vos, K., Pool, C. W., Evers, P., & Rajkowska, G. (2010). 3-D cytoarchitectonic parcellation of human orbitofrontal cortex correlation with postmortem MRI. *Psychiatry Research*, 183(1), 1–20. doi:10.1016/j.psychresns.2010.04.012
- Vallar, G., & Baddeley, A. D. (1984). Fractionation of working memory: Neuropsychological evidence for a phonological short-term store. *Journal of Verbal Learning and Verbal Behavior*, 23(2), 151–161. doi:10.1016/S0022-5371(84)90104-X
- Vallesi, A. (2012). Organisation of executive functions: Hemispheric asymmetries. *Journal of Cognitive Psychology*, 24(4), 367–386.
- Van Overwalle, F. (2009). Social cognition and the brain: a meta-analysis. *Human Brain Mapping*, 30(3), 829–858. doi:10.1002/hbm.20547
- Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia*, 42(10), 1394–1413. doi:10.1016/j.neuropsychologia.2004.04.006
- Van Veen, V., & Carter, C. S. (2002). The timing of action-monitoring processes in the anterior cingulate cortex. *Journal of Cognitive Neuroscience*, 14(4), 593–602. doi:10.1162/08989290260045837

- Van Veen, V., Cohen, J.D., Botvinick, M.M., Stenger, V.A., & Carter, C.S. (2001). Anterior cingulate cortex, conflict monitoring and levels of processing. *NeuroImage*, 14(6), 1302-1308.
- Vendrell, P., Junqué, C., Pujol, J., Jurado, M., Molet, J., & Grafman, J. (1995). The role of prefrontal regions in the Stroop task. *Neuropsychologia*, 33(3), 341-352.
- Vogt, B. A., Nimchinsky, E. a, Vogt, L. J., & Hof, P. R. (1995). Human cingulate cortex: surface features, flat maps, and cytoarchitecture. *The Journal of Comparative Neurology*, 359(3), 490–506. doi:10.1002/cne.903590310
- Volle, E., Gilbert, S. J., Benoit, R. G., & Burgess, P. W. (2010). Specialization of the rostral prefrontal cortex for distinct analogy processes. *Cerebral Cortex*, 20(11), 2647–2659. doi:10.1093/cercor/bhq012
- Vyas, A., Mitra, R., Rao, B.S.S. & Chattarji, S. (2002). Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *Journal of Neuroscience*, 22:6810-6818.
- Wagner, G., Koch, K., Reichenbach, J. R., Sauer, H., & Schlösser, R. G. M. (2006). The special involvement of the rostrolateral prefrontal cortex in planning abilities: an event-related fMRI study with the Tower of London paradigm. *Neuropsychologia*, 44(12), 2337–2347. doi:10.1016/j.neuropsychologia.2006.05.014
- Wakana, S., Jiang, H., Nagae-Poetscher, L., van Zijl, P., & Mori, S. (2004). Fiber Tract-based Atlas of Human White Matter Anatomy. *Radiology*, 230(1), 77–87. Retrieved from <http://radiology.rsna.org/content/230/1/77.short>
- Wang, J., Korczykowski, M., Rao, H., Fan, Y., Pluta, J., Gur, R. C., McEwen, B. S., et al. (2007). Gender difference in neural response to psychological stress. *Social Cognitive and Affective Neuroscience*, 2(3), 227–239. doi:10.1093/scan/nsm018
- Wang, J., Rao, H., Wetmore, G. S., Furlan, P. M., Korczykowski, M., Dinges, D. F., & Detre, J. (2005). Perfusion functional MRI reveals cerebral blood flow pattern under psychological stress. *Proceedings of the National Academy of Sciences of the United States of America*, 102(49), 17804–17809. doi:10.1073/pnas.0503082102
- Wardlaw, J. M., Bastin, M. E., Valdés Hernández, M. C., Maniega, S. M., Royle, N. a, Morris, Z., Clayden, J. D., et al. (2011). Brain aging, cognition in youth and old age and vascular disease in the Lothian Birth Cohort 1936: rationale, design and methodology of the imaging protocol. *International Journal of Stroke*, 6(6), 547–559. doi:10.1111/j.1747-4949.2011.00683.x
- Wechsler, D. (1998). *WMS-IIIUK Administration and Scoring Manual*. London, UK, Psychological Corporation.

- Wechsler, D. (1998). *WAIS-IIIUK Administration and Scoring Manual*. London, UK, Psychological Corporation.
- Weiler, J. A., Bellebaum, C., & Daum, I. (2008). Aging affects acquisition and reversal of reward-based associative learning. *Learning & Memory*, *15*(4), 190–197. doi:10.1101/lm.890408
- Wellman, C. L. (2001). Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. *Journal of Neurobiology*, *49*(3), 245–253. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11745662>
- Westlye, L. T., Walhovd, K. B., Bjørnerud, A., Due-Tønnessen, P., & Fjell, A. M. (2009). Error-related negativity is mediated by fractional anisotropy in the posterior cingulate gyrus—a study combining diffusion tensor imaging and electrophysiology in healthy adults. *Cerebral Cortex*, *19*(2), 293–304. doi:10.1093/cercor/bhn084
- Westlye, L. T., Walhovd, K. B., Dale, A. M., Bjørnerud, A., Due-Tønnessen, P., Engvig, A., Grydeland, H., et al. (2010). Life-span changes of the human brain white matter: diffusion tensor imaging (DTI) and volumetry. *Cerebral Cortex*, *20*(9), 2055–2068. doi:10.1093/cercor/bhp280
- Wheeler, E. Z., & Fellows, L. K. (2008). The human ventromedial frontal lobe is critical for learning from negative feedback. *Brain*, *131*(Pt 5), 1323–1331. doi:10.1093/brain/awn041
- Whiting, P., Rutjes, A. W. S., Reitsma, J. B., Bossuyt, P. M. M., & Kleijnen, J. (2003). The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, *3*, 25. doi:10.1186/1471-2288-3-25
- Wible, C. G., Shenton, M. E., Hokama, H., Kikinis, R., Jolesz, F. A., Metcalf, D., & Mccarley, R. W. (1995). Prefrontal cortex and schizophrenia. *Archives of General Psychiatry*, *52*, 279–288.
- Willette, A.A., Coe, C. L., Colman, R. J., Bendlin, B. B., Kastman, E. K., Field, A. S., Alexander, A. L., et al. (2012). Calorie restriction reduces psychological stress reactivity and its association with brain volume and microstructure in aged rhesus monkeys. *Psychoneuroendocrinology*, *37*(7), 903–916. doi:10.1016/j.psyneuen.2011.10.006
- Williams, Z. M., Bush, G., Rauch, S. L., Cosgrove, G. R., & Eskandar, E. N. (2004). Human anterior cingulate neurons and the integration of monetary reward with motor responses. *Nature Neuroscience*, *7*(12), 1370–1375. doi:10.1038/nn1354
- Wilmsmeier, A., Ohrmann, P., Suslow, T., Siegmund, A., Koelkebeck, K., Rothermundt, M., Kugel, H., et al. (2010). Neural correlates of set-shifting:

- decomposing executive functions in schizophrenia. *Journal of Psychiatry & Neuroscience*, 35(5), 321–329. doi:10.1503/jpn.090181
- Wittfoth, M., Küstermann, E., Fahle, M., & Herrmann, M. (2008). The influence of response conflict on error processing: evidence from event-related fMRI. *Brain Research*, 1194, 118–129. doi:10.1016/j.brainres.2007.11.067
- Wolf, O. T., Convit, A., McHugh, P. F., Kandil, E., Thorn, E. L., De Santi, S., & McEwen, B. S. (2001). Cortisol differentially affects memory in young and elderly men. *Behavioural Neuroscience*, 115(5), 1002–1011.
- Woodward, S. H., Kaloupek, D. G., Streeter, C. C., Martinez, C., Schaer, M., & Eliez, S. (2006). Decreased anterior cingulate volume in combat-related PTSD. *Biological Psychiatry*, 59(7), 582–587. doi:10.1016/j.biopsych.2005.07.033
- Xue, G., Ghahremani, D. G., & Poldrack, R. a. (2008). Neural substrates for reversing stimulus-outcome and stimulus-response associations. *The Journal of Neuroscience*, 28(44), 11196–11204. doi:10.1523/JNEUROSCI.4001-08.2008
- Yamasue, H., Iwanami, A., Hirayasu, Y., Yamada, H., Abe, O., Kuroki, N., Fukuda, R., et al. (2004). Localized volume reduction in prefrontal, temporolimbic, and paralimbic regions in schizophrenia: an MRI parcellation study. *Psychiatry Research*, 131(3), 195–207. doi:10.1016/j.psychresns.2004.05.004
- Yau, J. L. W., McNair, K. M., Noble, J., Brownstein, D., Hibberd, C., Morton, N., Mullins, J. J., et al. (2007). Enhanced hippocampal long-term potentiation and spatial learning in aged 11beta-hydroxysteroid dehydrogenase type 1 knock-out mice. *The Journal of Neuroscience*, 27(39), 10487–10496. doi:10.1523/JNEUROSCI.2190-07.2007
- Yen, C.-P., Kuan, C.-Y., Sheehan, J., Kung, S.-S., Wang, C.-C., Liu, C.-K., & Kwan, A. L. (2009). Impact of bilateral anterior cingulotomy on neurocognitive function in patients with intractable pain. *Journal of Clinical Neuroscience*, 16(2), 214–219. doi:10.1016/j.jocn.2008.04.008
- Yen, S. S., & Laughlin, G. a. (1998). Aging and the adrenal cortex. *Experimental Gerontology*, 33(7-8), 897–910. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/17073162>
- Yeterian, E. H., Pandya, D. N., Tomaiuolo, F., & Petrides, M. (2012). The cortical connectivity of the prefrontal cortex in the monkey brain. *Cortex*, 48(1), 58–81. doi:10.1016/j.cortex.2011.03.004
- Yochim, B. P., Baldo, J. V., Kane, K. D., & Delis, D. C. (2009). D-KEFS Tower Test performance in patients with lateral prefrontal cortex lesions: the importance of error monitoring. *Journal of Clinical and Experimental Neuropsychology*, 31(6), 658–663. doi:10.1080/13803390802448669

- Young, L., & Saxe, R. (2008). The neural basis of belief encoding and integration in moral judgment. *NeuroImage*, 40(4), 1912–1920. doi:10.1016/j.neuroimage.2008.01.057
- Young, L., & Saxe, R. (2009). An fMRI investigation of spontaneous mental state inference for moral judgment. *Journal of Cognitive Neuroscience*, 21(7), 1396–1405. doi:10.1162/jocn.2009.21137
- Yücel, M., Stuart, G. W., Maruff, P., Velakoulis, D., Crowe, S. F., Savage, G., & Pantelis, C. (2001). Hemispheric and gender-related differences in the gross morphology of the anterior cingulate/paracingulate cortex in normal volunteers: an MRI morphometric study. *Cerebral Cortex*, 11(1), 17–25. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11113032>
- Zahr, N. M., Rohlfsing, T., Pfefferbaum, A., & Sullivan, E. V. (2009). Problem solving, working memory, and motor correlates of association and commissural fiber bundles in normal aging: a quantitative fiber tracking study. *NeuroImage*, 44(3), 1050–1062. doi:10.1016/j.neuroimage.2008.09.046
- Zald, D. H. (2007). Orbital versus dorsolateral prefrontal cortex: anatomical insights into content versus process differentiation models of the prefrontal cortex. *Annals of the New York Academy of Sciences*, 1121, 395–406. doi:10.1196/annals.1401.012
- de Chastelaine, M., Wang, T. H., Minton, B., Muftuler, L. T., & Rugg, M. D. (2011). The Effects of Age, Memory Performance, and Callosal Integrity on the Neural Correlates of Successful Associative Encoding. *Cerebral Cortex*, 21(9), 2166–2176. doi:10.1093/cercor/bhq294
- de Ruiter, M. B., Veltman, D. J., Goudriaan, A. E., Oosterlaan, J., Sjoerds, Z., & van den Brink, W. (2009). Response perseveration and ventral prefrontal sensitivity to reward and punishment in male problem gamblers and smokers. *Neuropsychopharmacology*, 34(4), 1027–1038. doi:10.1038/npp.2008.175
- de Zubicaray, G. I., Chalk, J. B., Rose, S. E., Semple, J., & Smith. (1997). Deficits on self ordered tasks associated with hyperostosis frontalis interna. *Journal of Neurology, Neurosurgery, and Psychiatry*, 63(3), 309–314. Retrieved from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2169696&tool=pmc&entrez&rendertype=abstract>
- den Braber, A., Ent, D. V., 'T, Blokland, G. a M., van Grootheest, D. S., Cath, D. C., Veltman, D. J., de Ruiter, M. B., et al. (2008). An fMRI study in monozygotic twins discordant for obsessive-compulsive symptoms. *Biological Psychology*, 79(1), 91–102. doi:10.1016/j.biopsycho.2008.01.010
- di Pellegrino, G., Ciaramelli, E., & Làdavas, E. (2007). The regulation of cognitive control following rostral anterior cingulate cortex lesion in humans. *Journal of Cognitive Neuroscience*, 19(2), 275–286. doi:10.1162/jocn.2007.19.2.275

- van Veen, V., Cohen, J. D., Botvinick, M. M., Stenger, V. A., & Carter, C. S. (2001). Anterior cingulate cortex, conflict monitoring, and levels of processing. *Neuroimage*, 14(6), 1302–1308. doi:10.1006/nimg.2001.0923
- van den Heuvel, O. a, Groenewegen, H. J., Barkhof, F., Lazon, R. H. C., van Dyck, R., & Veltman, D. J. (2003). Frontostriatal system in planning complexity: a parametric functional magnetic resonance version of Tower of London task. *NeuroImage*, 18(2), 367–374. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12595190>
- van den Heuvel, O. A., Veltman, D. J., Groenewegen, H. J., Cath, D. C., van Balkom, A. J. L. M., van Hartkamp, J., Barkhof, F., et al. (2005). Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. *Archives of General Psychiatry*, 62(3), 301–309. doi:10.1001/archpsyc.62.3.301

## Appendices

### ***Appendix A: Reviewed Frontal Lobe Parcellation Protocols***

The following table lists the parcellation protocols identified during the systematic literature review in Chapter 3. The number and type of participant group are also provided. The protocols are grouped broadly by method; the paper to have first reported a particular method is shown in bold face, and subsequent paper to have directly cited this technique and applied it to a different sample and listed directly below it. A list of abbreviations used to denote participant groups are given here, and also at the end of this section for ease of reference. Full references for these protocols can be found in Appendix B, and details of the sub-regional boundary definitions and quality scoring reported in Chapter 3 can be found in the supplementary excel spreadsheet, submitted in electronic format.

AAMI - Age-associated Memory Impairment; AD - Alzheimer's Disease; ADHD - Attention Defecit Hyperactivity Disorder; ALI - Autistic with language impairment; ALN - Autistic with normal language ability; hfASD - High Functioning Austism Spectrum Disorder; BPD - Borderline Personality Disorder; CHI - Closed Head Injury; FHR Schiz - Familial High Risk of Schizophrenia; FPDD - Familial Pure Depressive Disorder; FTD - Frontotemporal Dementia; tvFTD - temporal variant of frontotemporal dementia; GAD - Generalized Anxiety Disorder; HA - Healthy Adult; HC - Healthy Control; LBD - Lewy Body Dementia; MDD - Major Depressive Disorder; OCD - Obsessive Compulsive Disorder; PNFA - Progressive Non-Fluent Aphasia; PPA - Primary Progressive Aphasia; PTSD - Post Traumatic Stress Disorder; SD - Semantic Dementia; SLI - Specific Language Impairment; VCFS - Velo-cardio-facial Syndrome.



Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Author & Year	Sample type	<i>n</i>
Almeida et al (2003)	EOD	24
	LOD	27
	HC	39
Kohler et al (2010)	Depression	25
	HC	29
Aylward <i>et al.</i> , (1997)	HA	10
Schretlen <i>et al.</i> , (2000)	HA	112
Baaré <i>et al.</i> , (1999)	Schizophrenia	14
	HC	14
Staal et al., (2000)	Schizophrenia	16
	Healthy Siblings	16
	HC	32
Ballmaier <i>et al.</i> (2004)	Depressed	24
	HC	19
Blanton et al (2004)	Children	46
Elderkin-Thompson <i>et al.</i> , (2008)	HA	23
Elderkin-Thompson <i>et al.</i> , (2009)	Depressed	26
	HC	23
Bartzokis et al (1993)	Healthy males	70
Berryhill et al (1995)	Severe CHI children	14
	Mild CHI children	14
Beyer et al (2009)	Bipolar	56
	HC	43
Bjork et al (2009)	HA	29

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Authors & Year	Sample type	<i>n</i>
<b>Bokde et al (2002)</b>	HCs	5
	AD	3
	Vascular Dementia	1
	FTD	1
Bokde et al (2005)	HA	10
<b>Convit <i>et al.</i>, (2001)</b>	Schizophrenia	9
	HC – middle aged	9
	HC – old	9
Gold <i>et al.</i> , (2005)	Hypertensive	27
	HC	27
<b>Bremner <i>et al.</i>, (1998)</b>	HA	11
Bremner et al (2000)	MDD	16
	HC	16
Bremner <i>et al.</i> , (2002)	MDD	15
	HC	20
<b>Carper &amp; Courchesne (2000)</b>	Autism	42
	HC	29
Carper & Courchesne (2005)	Autism	25
	HC	18
Castellanos et al (1996)	ADHD	55
	HC	57
Coffey et al (1991)	Depressed	35
Coffey et al (1998)	HA	330

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Author & Year	Sample type	<i>n</i>
<b>Colchester et al 2001</b>	Korsakoff	11
	Herpes E	9
	Focal frontal Lesion	6
	HC	10
Kopelman et al., (2001)	Amnestic	40
	HC	10
<b>Crespo-Facorro et al., (1999)</b>	HC	NR
	Schizophrenia	NR
	Schizophreniform	NR
	Autism	NR
	Schizoaffective	NR
Crespo-Facorro et al., (2000)	HC	34
	Schizophrenia	26
Chemerinski et al (2002)	Schizophrenia	45
	HC	45
Coryell et al (2005)	MDD	10
	Schizophrenia	10
	HCS	10
Antonucci et al (2006)	Psychiatric (various)	15
Gansler et al (2009)	Psychiatric (various)	41
	HC	19
Szendi et al (2006)	Schizophrenia	13
	HC	13

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Author & Year	Sample type	<i>n</i>
Boes et al (2007)	Cleft Palate	30
	HC	43
Wood et al (2007) - adults	HA	60
Wood et al (2008) children	HA	74
Lindberg et al (2009)	FTD	12
	SD	13
	PNFA	9
	HC	27
Croxson et al (2005)	HA	10
De Bellis et al (2005)	Alcohol Use Disorder	14
	HC	28
<b>Drevets et al (1997)</b>	Bipolar	21
	Unipolar	17
	HC	21
Hirayasu et al (1999)	Schizophrenia	17
	Affective disorder	24
	HC	20
Hastings et al (2004)	Depression	18
	HC	18
Nifosi et al (2010)	FPDD	15
	HC	15

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

<b>Author &amp; Year</b>	<b>Sample type</b>	<b><i>n</i></b>
<b>Botterton et al (2002)</b>	Depression (young)	30
	Depression (old)	18
	HC (young)	8
	HC (old)	9
Kegeles et al (2003)	MDD/Bipolar	19
	HC	10
Brambilla et al (2002)	Unipolar	18
	Bipolar	27
	HC	38
Egan et al (1994)	Schizophrenia	16
	HC	16
<b>Exner et al (2002)</b>	Basal Ganglia lesion	20
	HC	20
Exner et al (2006)	Schizophrenia	15
	HC	15
<b>Filipek et al (1997)</b>	ADHD	15
	HC	15
<b>Flashman et al (2001)</b>	Schizophrenia	15
Fornito <i>et al.</i> , (2006)	HA	24

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

<b>Author &amp; Year</b>	<b>Sample type</b>	<b><i>n</i></b>
<b>Foundas et al (2001)</b>	HA	12
Knaus et al (2006)	HA	48
Knaus et al (2007)	HA	60
Knaus et al (2009)	ASD	40
	HC	40
Fukui et al (2000)	PPA	17
	FTD	11
	AD	24
<b>Giedd et al (1996)</b>	HA	104
Casey et al (1997)	ADHD	26
	HC	26
Kumra et al (2000)	Schizophrenia	44
	HC	64
	Psychotic Disorder	27
	HC	42
Geroldi et al 1999	AD	28
	HC	30
<b>Ginovart et al (1997)</b>	Huntington's Disease	5
	HC	5
Backman et al (1997)	Huntington's Disease	5
	HC	5

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Author & Year	Sample type	<i>n</i>
<b>Gur et al (2000)</b>	Schizophrenia	70
	HC	81
Cowell et al (1994)	HA - mid	96
	- old	34
Turetsky et al (1995)	Schizophrenia	<b>71</b>
	HC	77
Kumar et al (1997)	Minor Depression	18
	HC	31
Kumar et al (2000)	MDD	51
	HC	30
Matsui et al (2000)	18-42yrs(59)	
Gur et al (2002)	HA	116
Gur et al (2004)	Schizophrenia	31
	HC	80
Mohlman et al (2009)	GAD	15
	HC	15
Hanninen et al (1997)	AAMI	43
	HC	47
<b>Harris et al (1994)</b>	HA	57
Schlaepfer et al (1994)	Schizophrenia	46
	HC	60
	Bipolar	27
Schlaepfer et al (1995)	HA	60

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

<b>Author &amp; Year</b>	<b>Sample type</b>	<b><i>n</i></b>
Hasan et al (2011)	HA MZ Twins	12
	DZ Twins	12
<b>Haznedaar et al (1997)</b>	ASD	7
	HC	7
Haznedaar et al (2004)	Schizophrenia	27
	Schizotypy	13
	HC	32
Hill et al (2003)	ADHD	23
	HC	24
Howard et al (1995)	Delusional Disorder	19
	Schizophrenia	31
	HC	35
Iordanova <i>et al.</i> , (2006)	LBD	8
	AD	8
	HC	9
James et al., (2004)	Schizophrenia	16
	HC	16
<b>Jernigan et al (1991)</b>	HA	55
Jernigan et al (2001)	HA	78
Sowell et al (2002)	HA	35
<b>John <i>et al.</i>, (2006)</b>	Schizophrenia	5
	HC	5
John <i>et al.</i> , (2007)	HA	20



Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

<b>Author &amp; Year</b>	<b>Sample type</b>	<b><i>n</i></b>
John et al., (2009)	Schizophrenia	23
	HC	23
Kates et al (2002)	Tourettes Syndrome	13
	ADHD	13
	HC	13
Kelsoe et al (1988)	Schizophrenia	27
	HC	14
<b>Lacerda et al (2003)</b>	HA	20
Riffkin <i>et al.</i> , (2005)	OCD	18
	Schizophrenia	18
	HC	18
Najt et al (2007)	Bipolar	14
	HCS	20
Girgis et al (2007)	ASD	11
	HC	18
Monkul et al (2007)	Unipolar	17
	HC	17
Chanen et al (2007)	BPD	20
	HC	20
Nery et al (2009)	Bipolar	28
	HC	28
Atmaca et al (2010)	Body dysmorphic	12
	HC	12
Lai et al (2000)	Depressed	20

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Author & Year	Sample type	<i>n</i>
Lyoo et al (1998)	BPD	25
	HC	25
<b>MacLulich et al (2002)</b>	HA - males	100
MacLulich et al (2006)	HA	20
<b>McCormick <i>et al.</i>, (2006)</b> ACC only	Random selection of Schizophrenia and HC	14
Asami et al (2008)	Panic Disorder	26
	HC	26
McLaughlin et al. (2009)	Affective disorder	20
Mueller et al (1998)	HA - young-old	11
	HA - middle-old	15
	HA - old-old	20
<b>Murphy et al (1993)</b>	Turner's syndrome	18
	HC	19
Murphy et al (1996)	HA - M	35
	- F	34
van Amelsvoort et al (2001)	VCFS	10
	HC	13
McAlonan et al (2002)	Asperger	21
	HC	24
Nakamura et al (2008)	Schizophrenia	24
	HC	25

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Author & Year	Sample type	<i>n</i>
<b>Nagel et al (2006)</b>	Healthy teens	65
Medina et al (2008)	Alcohol Use Disorder	14
	HC	17
Medina et al (2009)	Marijuana Users	16
	HC	16
<b>Noga et al (1995)</b>	Schizophrenia	14
	HC	14
Kaur et al (2005)	Bipolar	16
	HC	21
Nolan et al (2002)	MDD	22
	HC	22
Pantel et al (1997)	Depressed	19
	AD	27
	HC	13
Paus et al (1996)	HA	105
<b>Rademacher et al., (1992)</b>	N/A	N/A
Caviness et al., (1996)	HA	15
Grachev et al (1997)	Trichotillomania	10
	HCs	10
<b>Tzourio et al., (1997)</b>	N/A	N/A
Kennedy et al (1998)	HA M	10
	F	10
Goldstein et al (1999)	Schizophrenia	29
	HC	26

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Author & Year	Sample type	n
Szeszko et al (1999a)	Schizophrenia	19
	HC	26
Szeszko et al (1999b)	OCD	26
	HC	26
Szeszko et al (2000)	Schizophrenia	35
Allen et al (2002)	HA M	23
	F	23
Rauch et al (2003)	PTSD	9
	Controls	9
Takeoka et al (2003)	Ramsussen Encaphalitis	1
Fossé et al (2004)	ALI	16
	ALN	6
	SLI	9
	HC	18
Allen et al (2005)	HA M	43
	F	44
Frazier et al (2005)	Bipolar Disorder	32
	HC	15
Rupp et al (2005)	Schizophrenia	33
	HC	40
Allen et al (2006)	Anoxic	13
	HC M	43
	F	44
Seidman et al (2006)	ADHD	24
	HC	18

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Author & Year	Sample type	<i>n</i>
Rosso et al (2010)	FHR Schizophrenia	27
	HC	48
Betjemann et al (2010)	HA MZ twins	41
	DZ twins	30
Raine et al (1991)	HA	17
Rankin et al (2004)	FTD	27
<b>Ranta et al., (2009)</b>	ADHD	15
	HC	15
Ratnanather et al (2001)	HC	5
Raz <i>et al.</i> , (1995)	Down's Syndrome	13
	HA	12
Raz et al (1997)	HA	148
Head et al (2002)	HA	68
Hesslinger et al (2002)	ADHD	8
	HC	17
Raz et al (2003)	Hypertensive	40
	HC	40
van Elst et al (2003)	BPD	8
	HC	8
Raz et al (2004)	HC	200
Raz 2005	HA	72
Raz et al (2007)	Vascular Risk	23
	HC	23
Raz et al (2010)	HA	40

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Author & Year	Sample type	<i>n</i>
Rosen et al (2002)	tvFTD	9
	HC	10
<b>Salat et al (1999a)</b>	AD	22
	HC - old	22
	HC - young	26
Salat et al (1999b)	AD	30
	HC	17
Salat et al (2001)	AD	22
	HC - old	22
	HC - young	26
Salat et al (2002)	HA - young	20
	- old	31
Sanches et al., (2009)	HA	10
<b>Sanfilipo et al (2000)</b>	Schizophrenia	53
	HC	29
Sanfilipo et al (2002)	Schizophrenia	62
	HC	27
Seidman et al (1994)	Schizophrenia	19
Gilbert et al (2001)	Schizophrenia	16
	HC	25
Prasad et al (2005)	Schizophrenia	25

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Author & Year	Sample type	<i>n</i>
<b>Semendeferi et al (1997)</b>	HA	4
Semendeferi & Damasio (2000)	HA	10
Semendeferi et al (2002)	HA	10
Schenker et al (2005)	HA	10
Sherwood et al (2011)	HA	87
<b>Soininen et al (1995)</b>	AAMI	16
	HC	16
Laakso et al (1995)	AD	32
	HC	16
Suga et al (2010)	Schizophrenia	29
	HC	29
	HC	
Yamasaki et al (2010)	hfASD	13
	HC	11
<b>Suzuki et al. (2005)</b>	Schizotypal disorder	25
	Schizophrenia	53
	HC	59
Matsui et al (2008)	Schizotypal disorder	25
	Schizophrenia	35
	HC	19

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Author & Year	Sample type	<i>n</i>
<b>Takahashi <i>et al.</i>, (2002a)</b>	Schizophrenia	40
	HC	40
Takahashi <i>et al.</i> , (2002b)	Schizotypal disorder	24
	Schizophrenia	40
	HC	48
Takahashi <i>et al.</i> , (2003)	Schizophrenia	40
	HC	40
<b>Tisserand <i>et al.</i>, (2002)</b>	HA	57
Tomaiuolo <i>et al</i> (1999)	HA	50
Uylings <i>et al</i> (2010)	Post-mortem	32
van Petten <i>et al.</i> (2004)	HA	48
<b>Wible <i>et al</i> (1995)</b>	Schizophrenia	15
	HC	15
Wible <i>et al.</i> , (1997)	HA	15
Rosenberg <i>et al</i> (1997)	OCD	19
	HC	19
Hirayasu <i>et al</i> (2001)	Shizophrenia	17
	Affective disorder	17
	HC	17
Wible <i>et al</i> (2001)	Schizophrenia	17
Wible <i>et al</i> (2001)	HC	17
Yamasue <i>et al.</i> (2004)	Schizophrenia	27
	HC	27



Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Author & Year	Sample type	<i>n</i>
Wilde et al (2005)	TBI	16
	HC	16
<b>Woods et al., (1996)</b>	Schizophrenia	19
	HC	19
Maher et al (1998)	Schizophrenia	16
Woodward et al (2005)	Gulf War Veterans	36
	Vietnam Veterans	63
Yucel et al (2008)	MDD	65
	HC	93
<b>Zipursky et al (1992)</b>	Schizophrenia	22
	HC	20
Sullivan et al (1996)	Schizophrenia	34
	HC	47
Pfefferbaum et al (1997)	HC - young	65
	HC - old	27
	Alcoholic - young	33
	Alcoholic - old	29
Fama et al (1997)	AD	50
	HC	136
Mathalon et al (2001)	Schizophrenia	24
	HC	25
Fama et al (2004)	AD	50
Greenwood et al (2005)	Neurofibromatosis I	36
	Relatives	36

Table A. Systematically-reviewed manual frontal lobe parcellation protocols.

Author & Year	Sample type	<i>n</i>
Zhou et al (2005)	Schizophrenia	59
	HC	58
Zuffante et al (2001)	Schizophrenia	23
	HC	23

Sample type abbreviations: AAMI - Age-associated Memory Impairment; AD - Alzheimer's Disease; ADHD - Attention Defecit Hyperactivity Disorder; ALI - Autistic with language impairment; ALN - Autistic with normal language ability; hfASD - High Functioning Austism Spectrum Disorder; BPD - Borderline Personality Disorder; CHI - Closed Head Injury; FHR Schiz - Familial High Risk of Schizophrenia; FPDD - Familial Pure Depressive Disorder; FTD - Frontotemporal Dementia; tvFTD - temporal variant of frontotemporal dementia; GAD - Generalized Anxiety Disorder; HA - Healthy Adult; HC - Healthy Control; LBD - Lewy Body Dementia; MDD - Major Depressive Disorder; OCD - Obsessive Compulsive Disorder; PNFA - Progressive Non-Fluent Aphasia; PPA - Primary Progressive Aphasia; PTSD - Post Traumatic Stress Disorder; SD - Semantic Dementia; SLI - Specific Language Impairment; VCFS - Velo-cardio-facial Syndrome

## **Appendix B: Frontal Lobe Parcellation Review References:**

- Allen JS, Bruss J, Brown CK and Damasio H. Normal neuroanatomical variation due to age: the major lobes and a parcellation of the temporal region. *Neurobiology of Aging*, 26(9): 1245-1260, 2005.
- Allen JS, Damasio H and Grabowski TJ. Normal neuroanatomical variation in the human brain: an MRI-volumetric study. *American Journal of Physical Anthropology*, 118(4), 341-58, 2002.
- Allen JS, Damasio H, Grabowski TJ, Bruss J and Zhang W. Sexual dimorphism and asymmetries in the gray-white composition of the human cerebrum. *NeuroImage*, 18:880-894, 2003.
- Allen JS, Tranel D, Bruss J and Damasio H. Correlations between regional brain volumes and memory performance in anoxia. *Journal of Clinical and Experimental Neuropsychology*, 28(4), 457-76, 2006.
- Almeida OP, Burton EK, Ferrier N, McKeith IG and O'Brien JT. Depression with late onset is associated with right frontal lobe atrophy. *Psychological Medicine*, 33(4): 675-681, 2003.
- Amelsvoort TV. Structural brain abnormalities associated with deletion at chromosome 22q11: Quantitative neuroimaging study of adults with velo-cardio-facial syndrome. *The British Journal of Psychiatry*, 178(5), 412-419, 2001.
- Aron AR, Robbins TW and Poldrack RA. Inhibition and the right inferior frontal cortex. *Trends in Cognitive Sciences*, 8(4): 170-177, 2004.
- Asami T, Hayano F, Nakamura M, Yamasue H, Uehara K, Otsuka T, Roppongi T, Nihashi N, Inoue T and Hirayasu Y. Anterior cingulate cortex volume reduction in patients with panic disorder. *Psychiatry and Clinical Neurosciences*, 62(3): 322-330, 2008.
- Atmaca M, Bingol I, Aydin A, Yildirim H, Okur I, Yildirim MA, Mermi O and Gurok MG. Brain morphology of patients with body dysmorphic disorder. *Journal of Affective Disorders*, 123(1-3): 258-263, 2010.
- Aylward, Elizabeth H, Augustine, A., Li, Q., & Barta, P. E. (1997). Measurement of frontal lobe volume on magnetic resonance imaging scans. *Psychiatry research: Neuroimaging*, 75, 23-30.

- Baaré WF, Hulshoff PHE, Hijman R, Mali WP, Viergever MA, and Kahn RS. Volumetric analysis of frontal lobe regions in schizophrenia: relation to cognitive function and symptomatology. *Biological Psychiatry*, 45(12): 1597-605, 1999.
- Bäckman L, Robins-Wahlin TB, Lundin A, Ginovart N and Farde L. Cognitive deficits in Huntington's disease are predicted by dopaminergic PET markers and brain volumes. *Brain*, 120(12), 2207-2217, 1997.
- Ballmaier M, Toga A, Blanton R, Sowell ER, Lavretsky H, Peterson BS, Pham D and Kumar A. Anterior cingulate, gyrus rectus, and orbitofrontal abnormalities in elderly depressed patients: an MRI-based parcellation of the prefrontal cortex. *American Journal of Psychiatry*, 161: 99-108, 2004.
- Bartzokis G, Mintz J, Marx P, Osborn D, Gutkind D, Chiang F, Phelan CK and Marder SR. Reliability of in vivo volume measures of hippocampus and other brain structures using MRI. *Magnetic resonance imaging*, 11: 993-1006, 1993.
- Beckmann M, Johansen-Berg H, and Rushworth MFS. Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *The Journal of Neuroscience*, 29(4): 1175-1190, 2009.
- Bellis MD, Narasimhan A, Thatcher DL, Keshavan MS, Soloff P and Clark DB. Prefrontal cortex, thalamus, and cerebellar volumes in adolescents and young adults with adolescent-onset alcohol use disorders and comorbid mental disorders. *Alcoholism: Clinical and Experimental Research*, 29(9), 1590-1600, 2005.
- Benoit RG, Gilbert SJ, Volle E and Burgess PW. When I think about me and simulate you: medial rostral prefrontal cortex and self-referential processes. *NeuroImage*, 50(3): 1340-1349, 2010.
- Berryhill P, Lilly MA, Levin HS, Hillman GR, Mendelsohn D, Brunder DG, Fletcher JM, Kufera J, Kent TA, Yeakley J, Bruce D and Eisenberg HM. Frontal Lobe Changes after Severe Diffuse Closed Head Injury in Children: A Volumetric Study of Magnetic Resonance Imaging. *Neurosurgery*, 37(3): 392-400, 1995.
- Betjemann RS, Johnson EP, Barnard H, Boada R, Filley CM, Filipek PA, Willcutt EG, DeFries JC and Pennington BF. Genetic covariation between brain volumes and IQ, reading performance, and processing speed. *Behavior Genetics*, 40(2), 135-45, 2010.
- Beyer JL, Kuchibhatla M, Payne ME, Macfall J, Cassidy F and Krishnan KRR. Gray and white matter brain volumes in older adults with bipolar disorder. *International Journal of Geriatric Psychiatry*, 24:1445-1452, 2009.

- Bjork JM, Momenan R and Hommer DW. Delay discounting correlates with proportional lateral frontal cortex volumes. *Biological Psychiatry*, 65(8): 710-713, 2009.
- Blatter DD, Bigler ED, Gale SD, Johnson SC, Anderson C, Burnett BM, Parker N, Kurth S and Horn S. Quantitative volumetric analysis of brain MRI: normative database spanning five decades of life. *American Journal of Neuroradiology*, 16:241–245, 1995.
- Blumberg HP, Stern E, Ricketts S, Martinez D, de Asis J, White T, Epstein J, Isenberg N, McBride PA, Kemperman I, Emmerich S, Dhawan V, Eidelberg D, Kocsis J and Silbersweig D. Rostral and orbital prefrontal dysfunction in the manic state of bipolar disorder. *American Journal of Psychiatry*, 156, 1986–1988, 1999.
- Bohland JW, Bokil H, Allen CB and Mitra PP. The brain atlas concordance problem: Quantitative comparison of anatomical parcellations. *Public Library of Science ONE*, 4(9): e7200, 2009.
- Bokde AL, Teipel SJ, Zebuhr Y, Leinsinger G, Gootjes L, Schwarz R, Buerger K, Scheltens P, Moeller HJ and Hampel H. A new rapid landmark-based regional MRI segmentation method of the brain. *Journal of Neurological Science*, 194: 35-40, 2002.
- Bokde ALW, Teipel SJ, Schwarz R, Leinsinger G, Buerger K, Moeller T, Möller H-J and Hampel H. Reliable manual segmentation of the frontal, parietal, temporal, and occipital lobes on magnetic resonance images of healthy subjects. *Brain Research Protocols*, 14(3), 135-145, 2005.
- Bookheimer S. Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annual Review of Neuroscience*, 25:151–188, 2002.
- Botteron KN, Raichle ME, Drevets WC, Heath AC and Todd RD. Volumetric reduction in left subgenual prefrontal cortex in early onset depression. *Biological Psychiatry*, 51(4): 342-344, 2002.
- Brambilla P, Nicoletti MA, Harenski K, Sassi RB, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS and Soares JC. Anatomical MRI study of subgenual prefrontal cortex in bipolar and unipolar subjects. *Neuropsychopharmacology*, 27(5): 792-799, 2002.
- Brammer M, Bullmore E, Simmons A, Williams S, Grasby P, Howard R, Woodruff P and Rabe-Hesketh S. Generic brain activation mapping in functional magnetic resonance imaging: A non-parametric approach. *Magnetic Resonance Imaging*, 15(7), 763-770, 1997.

- Bremner JD, Bronen RA, Erasquin GD, Vermetten E, Staib LH, Ng CK, Soufer R, Charney DS and Innis RB. Development and reliability of a method for using magnetic resonance imaging for the definition of regions of interest for Positron Emission Tomography. *Clinical Positron Imaging*, 1(3): 145-159, 1998.
- Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL and Charney DS. Hippocampal volume reduction in major depression. *American Journal of Psychiatry*, 157:115-117, 2000.
- Bremner JD, Vythilingam M, Vermetten E, Nazeer A, Adil J, Khan S, Staib LH and Charney DS. Reduced volume of orbitofrontal cortex in major depression. *Biological Psychiatry*, 51(4): 273-279, 2002.
- Brodmann, K. *Vergleichende Lokalisationslehre der Großhirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*. Barth, Leipzig, 1909; English translation available in Garey, L. J. *Brodmann's Localization in the Cerebral Cortex*. Smith Gordon, London, 1994.
- Burgess PW, Simons JS, Dumontheil I and Gilbert SJ. The gateway hypothesis of rostral prefrontal cortex (area 10) function. In Duncan J, Phillips LH, and McLeod P(Eds.), *Measuring the Mind: Speed, Control and Age Vol. 3*. Oxford University Press, Oxford, 2006:217-248.
- Bush G, Luu P and Posner M. Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, 4(6): 215-222, 2000.
- Cabeza R and Nyberg L. Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience*, 12(1): 1-47, 2000.
- Campbell, A. W. *Histological Studies on the Localisation of Cerebral Function*. Cambridge University Press, Cambridge, UK, 1905.
- Carper RA and Courchesne E. Inverse correlation between frontal lobe and cerebellum sizes in children with autism. *Brain*, 123(4): 836-44, 2000.
- Carper RA and Courchesne E. Localized enlargement of the frontal cortex in early autism. *Biological Psychiatry*, 57(2): 126-133, 2005.
- Casey BJ, Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Schubert AB, Vauss YC, Vaituzis AC, Dickstein DP, Sarfatti SE and Rapoport JL. Implication of right frontostriatal circuitry in response inhibition and attention deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 36(3):374-383, 1997.

- Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, Sarfatti SE, Vauss YC, Snell JW, Rajapakse JC and Rapoport JL. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Archives of General Psychiatry*, 53: 607-616, 1996.
- Caviness VS, Meyer J, Makris N and Kennedy DN. MRI-Based Topographic Parcellation of Human Neocortex: An Anatomically Specified Method with Estimate of Reliability. *Journal of Cognitive Neuroscience*, 8(6): 566-587, 1996.
- Chi JG, Dooling EC and Gilles FH. Gyral development of the human brain. *Annals of Neurology* 11, 86–93. 1977.
- Chiavaras MM and Petrides M.. Orbitofrontal sulci of the human and macaque monkey brain. *The Journal of Comparative Neurology*, 422(1): 35-54, 2000.
- Chiavaras MM, LeGoualher G, Evans A and Petrides M. Three-dimensional probabilistic atlas of the human orbitofrontal sulci in standardized stereotaxic space. *NeuroImage*, 13(3): 479-496, 2001.
- Coffey CE, Weiner RD, Djang W, Figiel G, Soady S, Patterson L, Holt PD, Spritzer CE and Wilkinson WE. Brain anatomic effects of electroconvulsive therapy. *Archives of General Psychiatry*, 48: 1013-1021, 1991.
- Coffey CE, Lucke JF, Saxton JA, Ratcliff G, Unitas LJ, Billig B and Bryan RN. Sex differences in brain aging: a quantitative magnetic resonance imaging study. *Archives of Neurology*, 55(2): 169-79, 1998.
- Colchester A, Kingsley D, Lasserson D, Kendall B, Bello F, Rush C, Stevens TG, Goodman G, Heilpern G, Stanhope N and Kopelman MD. Structural MRI volumetric analysis in patients with organic amnesia, 1: methods and comparative findings across diagnostic groups. *Journal of Neurology, Neurosurgery, and Psychiatry*, 71(1): 13-22, 2001.
- Convit A, Wolf OT, de Leon MJ, Patalinjug M, Kandil E, Caraos C, Scherer A, Saint Louis LA and Cancro, R. Volumetric analysis of the pre-frontal regions: findings in aging and schizophrenia. *Psychiatry Research: Neuroimaging*, 107(2): 61-73, 2001.
- Coryell W, Nopoulos P, Drevets W, Wilson T and Andreasen NC. Subgenual prefrontal cortex volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. *The American Journal of Psychiatry*, 162(9): 1706–1712, 2005.

- Costafreda SG, Fu CHY, Lee L, Everitt B, Brammer MJ and David AS. A systematic review and quantitative appraisal of fMRI studies of verbal fluency: Role of the left inferior frontal gyrus. *Human Brain Mapping* 27(10): 799-810, 2006.
- Cotter, D., Hudson, L. and Landau, S. (2005). Evidence for orbitofrontal pathology in bipolar disorder and major depression, but not in schizophrenia. *Bipolar Disorders* 7, 358–369.
- Cowell PE, Turetsky BI, Gur RC, Grossman RI, Shtasel DL and Gur RE. Sex differences in aging of the human frontal and temporal lobes. *The Journal of Neuroscience*, 14(8): 4748-55, 1994.
- Crespo-Facorro B, Kim JJ, Andreasen NC, O’Leary DS, Wiser AK, Bailey JM, Harris, G and Magnotta VA. Human frontal cortex: an MRI-based parcellation method. *NeuroImage*, 10(5): 500-519, 1999.
- Crespo-Facorro B, Kim J, Andreasen NC, O’Leary DS and Magnotta V. Regional frontal abnormalities in schizophrenia: a quantitative gray matter volume and cortical surface size study. *Biological Psychiatry*, 48(2): 110-119, 2000a.
- Crespo-Facorro B, Kim J, Andreasen NC, Spinks R, O’Leary DS, Bockholt HJ, Harris G and Magnotta VA. Cerebral cortex: a topographic segmentation method using magnetic resonance imaging. *Psychiatry Research*, 100(2): 97-126, 2000b.
- Croxson PL, Johansen-Berg H, Behrens TEJ, Robson MD, Pinski MA, Gross CG, Richter W, Kastner S and Rushworth MFS. Quantitative investigation of connections of the prefrontal cortex in the human and macaque using probabilistic diffusion tractography. *The Journal of Neuroscience*, 25(39): 8854-8866, 2005.
- Deary IJ, Penke L and Johnson W. The neuroscience of human intelligence differences. *Nature reviews: Neuroscience*, 11(3): 201-211, 2010.
- Desikan, RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS and Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, 31(3): 968-980, 2006.
- Devinsky O, Morrell MJ and Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain*, 118: 279-306, 1995.
- Devlin JT and Poldrack RA. In praise of tedious anatomy. *NeuroImage*, 37(4): 1033-1041; discussion 1050-1058, 2007.



- Drevets WC, Price J, Simpson J and Todd R. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*, 386: 824-827, 1997.
- Dumontheil I, Burgess PW and Blakemore, S-J. Development of rostral prefrontal cortex and cognitive and behavioural disorders. *Developmental Medicine and Child Neurology*, 50(3): 168-181, 2008.
- Dumontheil I, Gilbert SJ, Frith CD and Burgess PW. Recruitment of lateral rostral prefrontal cortex in spontaneous and task-related thoughts. *The Quarterly Journal of Experimental Psychology*, 63(9): 1740–1756, 2010.
- Duvernoy HM. The human brain: Surface, blood supply, and three-dimensional sectional anatomy, 2<sup>nd</sup> Edition. Springer, Wien New York, 1999.
- Egan MF, Duncan CC, Suddath RL, Kirch DG, Mirsky AF and Wyatt RJ. Event-related potential abnormalities correlate with structural brain alterations and clinical features in patients with chronic schizophrenia. *Schizophrenia Research*, 11(3): 259-271, 1994.
- Elderkin-Thompson V, Ballmaier M, Hellemann G, Pham D and Kumar A. Executive function and MRI prefrontal volumes among healthy older adults. *Neuropsychology*, 22(5): 626-637, 2008.
- Elderkin-Thompson V, Hellemann G, Pham D and Kumar A. Prefrontal brain morphology and executive function in healthy and depressed elderly. *International Journal of Geriatric Psychiatry*, 24(5): 459-468, 2009.
- Exner C, Koshack J and Irle E. The differential role of premotor frontal cortex and basal ganglia in motor sequence learning: Evidence from focal basal ganglia lesions. *Learning and Memory*, 9:376-386, 2002.
- Exner C, Weniger G, Schmidt-Samoa C and Irle E. Reduced size of the pre-supplementary motor cortex and impaired motor sequence learning in first-episode schizophrenia. *Schizophrenia Research*, 84(2-3): 386-96, 2006.
- Fama R, Sullivan EV, Shear PK, Marsh L, Yesavage JA, Tinklenberg JR, Lim KO and Pfefferbaum A.. Selective cortical and hippocampal volume correlates of Mattis Dementia Rating Scale in Alzheimer disease. *Archives of Neurology*, 54(6): 719-28, 1997.
- Fama R, Marsh L and Sullivan EV. Dissociation of remote and anterograde memory impairment and neural correlates in alcoholic Korsakoff syndrome. *Journal of the International Neuropsychological Society*, 10(3): 427-41, 2004.

- Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN and Biederman J. Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. *Neurology*, 48(3): 589-601, 1997.
- Fischl B, Rajendran N, Busa E, Augustinack J, Hinds O, Yeo BTT, Mohlberg H, Amunts K and Zilles K. Cortical folding patterns and predicting cytoarchitecture. *Cerebral Cortex*, 18(8): 1973-1980, 2008.
- Flashman LA, McAllister TW, Johnson SC, Rick JH, Green RL and Saykin AJ. Specific frontal lobe subregions correlated with unawareness of illness in schizophrenia: a preliminary study. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 13(2): 255-257, 2001.
- Fornito, A. Individual Differences in Anterior Cingulate/Paracingulate Morphology Are Related to Executive Functions in Healthy Males. *Cerebral Cortex*, 14(4): 424-431, 2004.
- Fornito A, Whittle S, Wood SJ, Velakoulis D, Pantelis C and Yücel M. The influence of sulcal variability on morphometry of the human anterior cingulate and paracingulate cortex. *NeuroImage*, 33(3): 843-854, 2006.
- Foundas AL, Weisberg A, Browning CA and Weinberger DR. Morphology of the frontal operculum: A volumetric magnetic resonance imaging study of the pars triangularis. *Journal of Neuroimaging*, 11:153-159, 2001.
- Frazier J, Breeze J, Makris N, Giuliano A, Herbert M, Seidman L, Biederman J, Hodge SM, Dieterich ME, Gerstein ED, Kennedy DN, Rauch SL, Cohen BM and Caviness VS. Cortical gray matter differences identified by structural magnetic resonance imaging in pediatric bipolar disorder. *Bipolar Disorders*, 7(6): 555-569, 2005.
- Frost MA and Goebel R. Measuring structural-functional correspondence: Spatial variability of specialised brain regions after macro-anatomical alignment. *NeuroImage*, 59(2): 1369-1381, 2012.
- Fukui T. Volumetric study of lobar atrophy in Pick complex and Alzheimer's disease. *Journal of the Neurological Sciences*, 174(2): 111-121, 2000.
- Gansler DA, McLaughlin NCR, Iguchi L, Jerram M, Moore DW, Bhadelia R and Fulwiler C. A multivariate approach to aggression and the orbital frontal cortex in psychiatric patients. *Psychiatry Research*, 171(3): 145-154, 2009.
- Geroldi C, Pihlajamaki M, Laakso MP, DeCarli C, Beltramelli A, Bianchetti A, Soininen H, Trabacchi M and Frisoni GB. APOE-4 is associated with less frontal and more temporal lobe atrophy in Alzheimer's Disease. *Neurology*, 53(8): 1825-1832, 1999.

- Geyer S, Weiss M, Reimann K, Lohmann G and Turner R. Microstructural Parcellation of the Human Cerebral Cortex – From Brodmann’s Post-Mortem Map to in vivo Mapping with High-Field Magnetic Resonance Imaging. *Frontiers in Human Neuroscience*, 5: 1-7, 2011.
- Giedd JN, Snell JW, Lange N, Rajapakse JC, Casey BJ, Kozuch PL, Vaituzis AC, Vauss YC, Hamburger SD, Kaysen D and Rapoport JL. Quantitative magnetic resonance imaging of human brain development: ages 4-18. *Cerebral Cortex*, 6(4): 551-60, 1996.
- Gilbert AR. Thalamic Volumes in Patients With First-Episode Schizophrenia. *American Journal of Psychiatry*, 158(4), 618-624, 2001.
- Gilbert SJ, Spengler S, Simons JS, Steele JD, Lawrie SM, Frith CD and Burgess PW. Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. *Journal of Cognitive Neuroscience*, 18(6): 932-948, 2006.
- Ginovart N, Lundin A, Farde L, Halldin C, Backman L, Swahn CG, Pauli S and Sedvall G. PET study of the pre- and post-synaptic dopaminergic markers for the neurodegenerative process in Huntington's disease. *Brain*, 120: 503-514, 1997.
- Glasser MF and Van Essen DC. Mapping Human Cortical Areas In Vivo Based on Myelin Content as Revealed by T1- and T2-Weighted MRI. *Journal of Neuroscience*, 31(32), 11597-11616, 2011.
- Gläscher J, Rudrauf D, Colom R, Paul LK, Tranel D, Damasio H and Adolphs R. Distributed neural system for general intelligence revealed by lesion mapping. *Proceedings of the National Academy of Sciences*, 107(10): 4705-4709, 2010.
- Gold SM, Dziobek I, Rogers K, Bayoumy A, McHugh PF and Convit A. Hypertension and hypothalamo-pituitary-adrenal axis hyperactivity affect frontal lobe integrity. *The Journal of Clinical Endocrinology and Metabolism*, 90(6): 3262-3267, 2005.
- Goldstein JM, Goodman JM, Seidman LJ, Kennedy DN, Makris N, Lee H, Tourville J, Caviness VS, Faraone SV and Tsuang MT. Cortical abnormalities in schizophrenia identified by structural magnetic resonance imaging. *Archives of General Psychiatry*, 56(6): 537-547, 1999.
- Grachev ID. MRI-based morphometric topographic parcellation of human neocortex in trichotillomania. *Psychiatry and Clinical Neurosciences*, 51(5): 315–321, 1997.
- Greenwood RS, Tupler LA, Whitt JK, Buu A, Dombeck CB, Harp AG, Payne ME, Eastwood JD, Krishnan KRR and MacFall JR.. Brain morphometry, T2-weighted

- hyperintensities, and IQ in children with neurofibromatosis type 1. *Archives of Neurology*, 62(12): 1904-8, 2005.
- Gur RE, Cowell PE, Latshaw A, Turetsky BI, Grossman RI, Arnold SE, Bilker WB and Gur RC. Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Archives of General Psychiatry*, 57(8): 761-768, 2000.
- Gur RE, Kohler C, Turetsky BI, Siegel SJ, Kanes SJ, Bilker WB, Brennan AR and Gur RC. A sexually dimorphic ratio of orbitofrontal to amygdala volume is altered in schizophrenia. *Biological Psychiatry*, 55(5): 512-517, 2004.
- Gur, RC, Gunning-Dixon F, Bilker WB and Gur, RE. Sex differences in temporo-limbic and frontal brain volumes of healthy adults. *Cerebral Cortex*, 12(9), 998-1003, 2002.
- Hänninen T, Hallikainen M, Koivisto K, Partanen K, Laakso MP, Riekkinen P and Soininen H. Decline of frontal lobe functions in subjects with age-associated memory impairment. *Neurology*, 48(1): 148-53, 1997.
- Harris, GJ, Barta PE, Peng LW, Lee S, Brettschneider PD, Shah A, Henderer JD, Schlaepfer TE and Pearlson GD. MR gray and white matter segmentation using manual thresholding: Dependence on image brightness. *American Journal of Neuroradiology*, 15:225-230, 1994.
- Hasan A, McIntosh AM, Droese U-A, Schneider-Axmann T, Lawrie SM, Moorhead TW, Tepest R, Maier W, Falkai R and Wobrock T. Prefrontal cortex gyrification index in twins: an MRI study. *European Archives of Psychiatry and Clinical Neuroscience*, 261(7): 459-65, 2011.
- Hastings RS, Parsey RV, Oquendo MA, Arango V and Mann JJ. Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology*, 29(5): 952-959, 2004.
- Haznedar MM, Buchsbaum MS, Metzger M, Solimando A, Spiegel-Cohen J and Hollander E. Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. *American Journal of Psychiatry*, 154:1047-1050, 1997.
- Head D, Raz N, Gunning-Dixon F, Williamson A and Acker JD. Age-related differences in the course of cognitive skill acquisition: The role of regional cortical shrinkage and cognitive resources. *Psychology and Aging*, 17(1): 72-84, 2002.
- Hill DE, Yeo RA, Campbell RA, Hart B, Vigil J and Brooks W. Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. *Neuropsychology*, 17(3): 496-506, 2003.

- Hirayasu Y, Shenton ME, Salisbury DF, Kwon JS, Wible CG, Fischer IA, Yurgelun-Todd D, Zarate C, Kikinis R, Jolesz FA and McCarley RW. Subgenual cingulate cortex volume in first-episode psychosis. *American Journal of Psychiatry*, 156: 1091-1093, 1999.
- Hirayasu Y, Tanaka S, Shenton ME, Salisbury DF, DeSantis MA, Levitt JJ, Wible C, Yurgelun, Todd D, Kikinis R, Jolesz FA and McCarley RW. Prefrontal gray matter volume reduction in first episode schizophrenia. *Cerebral Cortex*, 11(4): 374-381, 2001.
- Hof PR, Mufson EJ and Morrison JH. Human orbitofrontal cortex: cytoarchitecture and quantitative immunohistochemical parcellation. *The Journal of Comparative Neurology*, 359(1): 48-68, 1995.
- Howard R, Mellers J, Petty R, Bonner D, Menon R, Almeida O, Graves M, Renshaw C and Levy R. Magnetic resonance imaging volumetric measurements of the superior temporal gyrus, hippocampus, parahippocampal gyrus, frontal and temporal lobes in late paraphrenia. *Psychological medicine*, 25(3): 495-503, 1995.
- Iordanova B, Rosenbaum D, Norman D, Weiner M and Studholme C. MR imaging anatomy in neurodegeneration: A robust volumetric parcellations method of frontal lobe gyri with quantitative validation in patients with dementia. *American Journal of Neuroradiology*, 27:1747-1754, 2006.
- James A, James S, Smith D and Javaloyes A. Cerebellar, prefrontal cortex, and thalamic volumes over two time points in adolescent-onset schizophrenia. *American Journal of Psychiatry*, 161: 1023-1029, 2004.
- Jernigan TL, Archibald SL, Berhow MT, Sowell ER, Foster DS and Hesselink JR. Cerebral structure on MRI, part1: Localization of age-related changes. *Biological Psychiatry*, 29:55-67, 1991.
- Jernigan TL, Archibald SL, Fennema-Notestine C, Gamst AC, Stout JC, Bonner J and Hesselink JR. Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiology of Aging*, 22:581-594, 2001a.
- Jernigan TL, Ostergaard AL and Fennema-Notestine C. Mesial temporal, diencephalic, and striatal contributions to deficits in single word reading, word priming and recognition memory. *Journal of the International Neuropsychological Society*, 7:63-78, 2001b.
- Johansen-Berg H, Gutman DA, Behrens TEJ, Matthews PM, Rushworth MFS, Katz E, Lozano AM and Mayberg HS. Anatomical connectivity of the subgenual cingulate

- region targeted with deep brain stimulation for treatment-resistant depression. *Cerebral Cortex*, 18(6), 1374-1383, 2008.
- John JP, Wang L, Moffitt AJ, Singh HK, Gado MH and Csernansky JG. Inter-rater reliability of manual segmentation of the superior, inferior and middle frontal gyri. *Psychiatry Research*, 148(2-3): 151-163, 2006.
- John JP, Yashavantha BS, Gado M, Veena R, Jain S, Ravishankar and Csernansky JG. A proposal for MRI-based parcellations of the frontal pole. *Brain Structure and Function*, 212:245-253, 2007.
- Jung RE and Haier RJ. The Parieto-Frontal Integration Theory (P-FIT) of intelligence: converging neuroimaging evidence. *The Behavioral and Brain Sciences*, 30(2): 135-154, 2007.
- Kates WR, Frederikse M, Mostofsky SH, Folley BS, Cooper K, Mazur-Hopkins P, Kofman O, Singer HS, Denckla MB, Pearlson GD and Kaufmann WE. MRI parcellation of the frontal lobe in boys with attention deficit hyperactivity disorder or Tourette syndrome. *Psychiatry Research*, 116(1-2), 63-81, 2002.
- Kaur S, Sassi RB, Axelson D, Nicoletti M, Brambilla P, Monkul ES, Hatch JP, Keshevan MS, Ryan N, Birmaher B and Soares JC. Cingulate cortex anatomical abnormalities in children and adolescents with bipolar disorder. *American Journal of Psychiatry*, 162(9): 1637-1643, 2005.
- Kegeles LS, Malone KM, Slifstein M, Ellis SP, Xanthopoulos E, Keilp JG, Campbell C, Oquendo M, van Heertum RL and Mann JJ. Response of cortical metabolic deficits to serotonergic challenge in familial mood disorders. *Psychiatry: Interpersonal and Biological Processes*, 160(1): 76-82, 2003.
- Kelsoe JR, Cadet JL, Pickar D and Weinberger DR. Quantitative neuroanatomy in schizophrenia. A controlled magnetic resonance imaging study. *Archives of General Psychiatry*, 45(6): 533-41, 1988.
- Kennedy DN, Lange N, Makris N, Bates J, Meyer J and Caviness VS. Gyri of the human neocortex: an MRI-based analysis of volume and variance. *Cerebral Cortex*, 8(4): 372-384, 1998.
- Kikinis R, Shenton ME, Iosifescu DV, McCarley RW, Saiviroonporn P, Hokama HH, Robatino A, Metcalf D, Wible CG, Portas CM, Donnino RM and Jolesz FA. A digital brain atlas for surgical planning, model-driven segmentation, and teaching. *IEEE Transactions on Visualization and Computer Graphics*, 2(3), 232-241, 1996.

- Knaus TA, Bollich AM, Corey DM, Lemen LC and Foundas AL. Variability in perisylvian brain anatomy in healthy adults. *Brain and Language*, 97:219-232, 2006.
- Köhler S, Thomas AJ, Lloyd A, Barber R, Almeida OP and O'Brien JT. White matter hyperintensities, cortisol levels, brain atrophy and continuing cognitive deficits in late-life depression. *The British Journal of Psychiatry*, 196(2): 143-9, 2010.
- Kopelman MD, Lasserson D, Kingsley D, Bello F, Rush C, Stanhope N, Stevens T, Goodman G, Heilpern G, Kendall B and Colchester A. Structural MRI volumetric analysis in patients with organic amnesia, 2: correlations with anterograde memory and executive tests in 40 patients. *Journal of Neurology, Neurosurgery, and Psychiatry*, 71(1): 23-8, 2001.
- Kringelbach ML and Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Progress in Neurobiology*, 72(5): 341-372, 2004.
- Kumar A, Bilker W, Jin Z and Udupa J. Atrophy and high intensity lesions: complementary neurobiological mechanisms in late-life major depression. *Neuropsychopharmacology*, 22(3): 264-74, 2000.
- Kumar A, Schweizer E, Zhisong J, Miller D, Bilker W, Swan LL and Gottlieb G. Neuroanatomical substrates of late life minor depression: A quantitative magnetic resonance imaging study. *Archives of Neurology*, 54:613-617, 1997.
- Kumra S, Giedd JN, Vaituzis AC, Jacobsen LK, McKenna K, Bedwell J, Hamburger S, Nelson JE, Lenane M and Rapoport JL. Childhood-onset psychotic disorders: magnetic resonance imaging of volumetric differences in brain structure. *The American Journal of Psychiatry*, 157(9): 1467-74, 2000.
- Laakso MP, Soininen H, Partanen K, Helkala E-L, Hartikainen P, Vainio P, Hallikainen M, Hanninen T and Riekkinen Sr PJ. Volumes of hippocampus, amygdala and frontal lobes in the MRI-based diagnosis of early Alzheimer's disease: correlation with memory functions. *Journal of Neural Transmission: Parkinson's Disease and Dementia Section*, 9:73-86, 1995.
- Lacerda AL, Hardan AY, Yorbik O and Keshavan MS. Measurement of the orbitofrontal cortex: a validation study of a new method. *NeuroImage*, 19(3): 665-673, 2003.
- Lai TJ, Payne ME, Byrum CE, Steffens DC and Krishnan KRR. Reduction of orbital frontal cortex volume in geriatric depression. *Biological Psychiatry*, 48(10): 971-975, 2000.

- Lindberg O, Ostberg P, Zandbelt BB, Oberg J, Zhang Y, Andersen C, Looi JCL, Bogdanovic and Wahlund L-O. Cortical morphometric subclassification of frontotemporal lobar degeneration. *American Journal of Neuroradiology*, 30(6): 1233-1239, 2009.
- Lyoo IK, Han MH and Cho DY. A brain MRI study in subjects with borderline personality disorder. *Journal of Affective Disorders*, 50(2-3): 235-43, 1998.
- Mackey S and Petrides M. Architectonic mapping of the medial region of the human orbitofrontal cortex by density profiles. *Neuroscience*, 159: 1089–1107, 2009.
- MacLullich AMJ, Ferguson KJ, Deary IJ, Seckl JR, Starr JM and Wardlaw JM. Intracranial capacity and brain volumes are associated with cognition in healthy elderly men. *Neurology*, 59(2): 169-74, 2002.
- MacLullich AMJ, Ferguson KJ, Wardlaw JM, Starr JM, Deary IJ and Seckl JR. Smaller left anterior cingulate cortex volumes are associated with impaired hypothalamic-pituitary-adrenal axis regulation in healthy elderly men. *The Journal of Clinical Endocrinology and Metabolism*, 91(4): 1591-1594, 2006.
- Maher BA, Manschreck TC, Yurgelun-Todd DA and Tsuang MT. Hemispheric asymmetry of frontal and temporal gray matter and age of onset in schizophrenia. *Biological Psychiatry*, 44(6): 413-7, 1998.
- Mansouri FA, Tanaka K and Buckley MJ. Conflict-induced behavioural adjustment: A clue to the executive functions of the prefrontal cortex. *Nature Reviews Neuroscience*, 10:141-152, 2009.
- Mathalon DH, Sullivan EV, Lim KO and Pfefferbaum A. Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. *Archives of General Psychiatry*, 58(2): 148-57, 2001.
- Matsui M, Gur RC, Turetsky BI, Yan MXH and Gur RE. The relation between tendency for psychopathology and reduced frontal brain volume in healthy people. *Neuropsychiatry, Neuropsychology and Behavioral Neurology*, 13(3): 155-162, 2000.
- Matsui M, Suzuki M, Zhou S-Y, Takahashi T, Kawasaki Y, Yuuki H, Kato K and Kurachi M. The relationship between prefrontal brain volume and characteristics of memory strategy in schizophrenia spectrum disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 32(8): 1854-1862, 2008.
- McAlonan GM, Daly E, Kumari V, Critchley HD, Amelsvoort TV, Suckling J, Simmons A, Sigmundsson T, Greenwood K, Russell A, Schmitz N, Happe F,



- Howlin P and Murphy DGM. Brain anatomy and sensorimotor gating in Asperger's syndrome. *Brain*, 127: 1594-1606 2002.
- McCormick LM, Ziebell S, Nopoulos P, Cassell M, Andreasen NC and Brumm M. Anterior cingulate cortex: an MRI-based parcellation method. *NeuroImage*, 32(3): 1167-1175, 2006.
- McLaughlin NCR, Moore DW, Fulwiler C, Bhadelia R and Gansler DA. Differential Contributions of Lateral Prefrontal Cortex Regions to Visual Memory Processes. *Brain Imaging and Behavior*, 3(2): 202-211, 2009.
- Medina KL, McQueeney T, Nagel BJ, Hanson KL, Schweinsburg AD and Tapert SF. Prefrontal cortex volumes in adolescents with alcohol use disorders: unique gender effects. *Alcoholism, Clinical and Experimental Research*, 32(3): 386-394, 2008.
- Medina K, McQueeney T, Nagel B, Hanson KL, Yang T and Tapert SF. Prefrontal cortex morphometry in abstinent adolescent marijuana users: subtle gender effects. *Addiction Biology*, 14(4): 457-468, 2009.
- Moberg PJ, Doty RL, Turetsky BI, Arnold SE, Mahr RN, Gur, R. C., Bilker, W and Gur RE. Olfactory identification deficits in schizophrenia: correlation with duration of illness. *The American Journal of Psychiatry*, 154(7): 1016-1018, 1997.
- Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *British Medical Journal*, 339:b2535, 2009
- Mohlman J, Price RB, Eldreth DA, Chazin D, Glover DM and Kates WR. The relation of worry to prefrontal cortex volume in older adults with and without generalized anxiety disorder. *Psychiatry Research*, 173(2): 121-127, 2009.
- Monkul ES, Hatch JP, Nicoletti MA, Spence S, Brambilla P, Lacerda ALT, Sassi RB, Mallinger AG, Keshevan MS and Soares JC. Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. *Molecular Psychiatry*, 12(4): 360-366, 2007.
- Mueller EA, Moore MM, Kerr DC, Sexton G, Camicioli RM, Howieson DB, Quinn JF and Kaye JA. Brain volume preserved in healthy elderly through the eleventh decade. *Neurology*, 51(6): 1555-1562, 1998.
- Murphy DG, DeCarli CD, Daly E, Gillette JA, McIntosh AR, Haxby JV, Teichberg D, Schapiro MB, Rapoport SI and Horwitz B. Volumetric magnetic resonance imaging in men with dementia of the Alzheimer type: correlations with disease severity. *Biological Psychiatry*, 34(9): 612-21, 1993.

- Murphy DGM, DeCarli C, McIntosh AR, Daly E, Mentis MJ, Pietrini P, Szczepanik J, Schapiro MB, Grady CL, Horwitz B and Rapoport SI. Sex differences in human brain morphometry and metabolism: An in vivo quantitative magnetic resonance imaging and positron emission tomography study on the effect of aging. *Archives of General Psychiatry*, 53: 585-594, 1996.
- Nagel, B, Medina K, Yoshii J, Schweinsburg AD, Moadab I and Tapert SF. Age-related changes in prefrontal white matter volume across adolescence. *Neuroreport*, 17(13): 1427-1431, 2006.
- Najt P, Nicoletti M, Chen HH, Hatch JP, Caetano SC, Sassi RB, Axelson D, Brnabilla P, Keshevan MS, Ryan ND, Birmaher and Soares JC. Anatomical measurements of the orbitofrontal cortex in child and adolescent patients with bipolar disorder. *Neuroscience*, 413(3): 183-186, 2007.
- Nakamura M, Nestor PG, Levitt JJ, Cohen AS, Kawashima T, Shenton ME and McCarley RW. Orbitofrontal volume deficit in schizophrenia and thought disorder. *Brain*, 131(1), 180-195, 2008.
- Nifosi F, Toffanin T, Follador H, Zonta F, Padovan G, Pigato G, Carollo C, Ermani M, Amista P and Perini GI. Reduced right posterior hippocampal volume in women with recurrent familial pure depressive disorder. *Psychiatry Research*, 184(1): 23-28, 2010.
- Nishitani N, Schurman M, Amunts K and Hari R. Broca's region: from action to language. *Physiology* 20:60-69, 2005.
- Noga JT, Aylward E, Barta PE and Pearlson GD. Cingulate gyrus in schizophrenic patients and normal volunteers. *Psychiatry Research*, 61(4): 201-208, 1995.
- Nolan CL, Moore GJ, Madden R, Farchione T, Bartoi M, Lorch E, Stewart CM and Rosenberg DR. Prefrontal cortical volume in childhood-onset major depression: preliminary findings. *Archives of General Psychiatry*, 59(2): 173-9, 2002.
- Ongür D, Ferry AT and Price JL. Architectonic subdivision of the human orbital and medial prefrontal cortex. *The Journal of Comparative Neurology*, 460(3): 425-449, 2003.
- Ono M, Kubik S and Abernathey CC. *Atlas of the cerebral sulci*. Stuggart: Thieme Verlag, 1990.
- Palomero-Gallagher N, Vogt BA, Schleicher A, Mayberg HS and Zilles K. Receptor architecture of human cingulate cortex: evaluation of the four-region neurobiological model. *Human Brain Mapping*, 30(8): 2336-2355, 2009.

- Pantazis D, Joshi A, Jiang J, Shattuck D, Bernstein LE, Damasio H and Leahy RM. Comparison of landmark-based and automatic methods for cortical surface registration. *Neuroimage*, 49(3): 2479-2493, 2010.
- Pantel J, Schroder J, Essig M, Popp D, Dech H, Knopp MV, Schad LR, Eysenbach K, Backenstrass M and Friedlinger M. Quantitative magnetic resonance imaging in geriatric depression and primary degenerative dementia. *Journal of Affective Disorders*, 42(1): 69-83, 1997.
- Paus T, Otaky N, Caramanos Z, MacDonald D, Zijdenbos A, D'Avirro D, Gutmans D, Holmes C, Tomiauolo F and Evans AC. In vivo morphometry of the intrasulcal gray matter in the human cingulate, paracingulate, and superior-rostral sulci: hemispheric asymmetries, gender differences and probability maps. *The Journal of Comparative Neurology*, 376(4): 664-673, 1996.
- Petrides M. The role of the mid-dorsolateral prefrontal cortex in working memory. *Experimental brain research*, 133(1): 44-54, 2000.
- Petrides M and Pandya DN. Comparative architectonic analysis of the human and the macaque frontal cortex. In: Boller F and Grafman J (Eds.) *Handbook of Neuropsychology*, Vol. 9. Elsevier, Amsterdam, 17-58, 1994.
- Petrides M, Tomiauolo F, Yeterian E and Pandya DN. The prefrontal cortex: Comparative architectonic organisation in the human and the macaque monkey brains. *Cortex*, 48: 46-57, 2012.
- Pfefferbaum A, Sullivan EV, Mathalon DH and Lim KO. Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcoholism, Clinical and Experimental Research*, 21(3): 521-529, 1997
- Prasad KMR, Sahni SD, Rohm BR and Keshavan MS. Dorsolateral prefrontal cortex morphology and short-term outcome in first-episode schizophrenia. *Psychiatry Research*, 140(2): 147-155, 2005.
- Rademacher J, Caviness VS, Steinmetz H and Galaburda AM. Topographical variation of the human primary cortices: implications for neuroimaging, brain mapping, and neurobiology. *Cerebral Cortex* 3(4): 313-329, 1993.
- Rademacher J, Galaburda AM, Kennedy DN, Filipek PA and Caviness VS. Human Cerebral Cortex: Localization, Parcellation, and Morphometry with Magnetic Resonance Imaging. *Journal of Cognitive Neuroscience*, 4(4): 352-374, 1992.

- Raine A, Reynolds G and Sheard C. Neuroanatomical correlates of skin conductance orienting in normal humans: a magnetic resonance imaging study. *Psychophysiology*, 28(5), 548-558, 1991.
- Rajkowska G and Goldman-Rakic PS. Cytoarchitectonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the Talairach Coordinate System. *Cerebral Cortex* 5(4): 323-337, 1995.
- Rajkowska G, Miguel-Hidalgo JJ, Dubey P, Stockmeier CA and Krishnan RR. Prominent reduction in pyramidal neuron density in the orbitofrontal cortex of elderly depressed patients. *Biological Psychiatry*, 58: 297–306, 2005.
- Rajkowska G, O'Dwyer G, Teleki Z, Stockmeier CA and Miguel-Hidalgo JJ. Reduction in calbindin-immunoreactive GABA interneurons in the prefrontal cortex in major depression. *Neuropsychopharmacology* 32: 471–482, 2007.
- Rankin KP, Rosen HJ, Kramer JH, Chaier GF, Weiner MW, Schuff N and Miller BL. Right and left medial orbitofrontal volumes shown an opposite relationship to agreeableness in FTD. *Dementia and Geriatric Cognitive Disorders*, 17(4): 328-332, 2004.
- Ranta ME, Crocetti D, Clauss JA, Kraut MA, Mostofsky SH and Kaufmann WE. Manual MRI parcellation of the frontal lobe. *Psychiatry Research*, 172(2), 147-154, 2009.
- Ratnanather JT, Botteron KN, Nishino T, Massie AB, Lal RM, Patel SG, Peddi S, Todd RD and Miller MI. Validating cortical surface analysis of medial prefrontal cortex. *NeuroImage*, 14(5): 1058-1069, 2001.
- Rauch SL, Shin LM, Segal E, Pitman RK, Carson MA, McMullin K, Whalen PJ and Makris N. Selectively reduced regional cortical volumes in post-traumatic stress disorder. *Neuroreport*, 14(7): 913-916, 2003.
- Raz N, Gunning FM, Head D, Dupuis JH, McQuain J, Briggs SD, Loken WJ, Thornton AE and Acker JD. Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cerebral Cortex*, 7(3): 268-282, 1997.
- Raz N, Rodrigue KM and Acker JD. Hypertension and the brain: vulnerability of the prefrontal regions and executive functions. *Behavioral Neuroscience*, 117(6): 1169-80, 2003.

- Raz N, Torres IJ, Briggs SD, Spencer WD, Thornton AE, Loken WJ, Gunning FM, McQuain JD, Driesen NR and Acker JD. Selective neuroanatomic abnormalities in Down's syndrome and their cognitive correlates: Evidence from MRI morphometry. *Neurology*, 45: 356-366, 1995.
- Raz N, Ghisletta P, Rodrigue KM, Kennedy KM and Lindenberger U. Trajectories of brain aging in middle-aged and older adults: regional and individual differences. *NeuroImage*, 51(2): 501-511, 2010.
- Raz N, Gunning-Dixon F, Head D, Rodrigue KM, Williamson A and Acker JD. Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. *Neurobiology of Aging*, 25(3): 377-396, 2004.
- Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Dahle C, Gerstorf D and Acker JD. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cerebral Cortex*, 15(11): 1676-1689, 2005.
- Raz N, Rodrigue KM, Kennedy KM and Acker JD. Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. *Neuropsychology*, 21(2): 149-157, 2007.
- Riffkin J, Yücel M, Maruff P, Wood SJ, Soulsby B, Olver J, Kyrios M, Velakoulis D and Pantelis C. A manual and automated MRI study of anterior cingulate and orbito-frontal cortices, and caudate nucleus in obsessive-compulsive disorder: comparison with healthy controls and patients with schizophrenia. *Psychiatry Research*, 138(2): 99-113, 2005.
- Rolls ET and Grabenhorst F. The orbitofrontal cortex and beyond: from affect to decision-making. *Progress in Neurobiology*, 86(3), 216-44, 2008.
- Rosen HJ, Perry RJ, Murphy J, Kramer JH, Mychack P, Schuff N, Weiner M, Levenson RW and Miller BL. Emotion comprehension in the temporal variant of frontotemporal dementia. *Brain*, 125:2286-2295, 2002.
- Rosenberg DR, Keshavan MS, O'Hearn KM, Dick EL, Bagwell WW, Seymour AB, Montrose DM, Pierri JN and Birmaher B. Frontostriatal measurement in treatment-naïve children with obsessive-compulsive disorder. *Archives of General Psychiatry*, 54(9): 824-830, 1997.
- Rosso IM, Makris N, Thermenos HW, Hodge SM, Brown A, Kennedy D, Caviness VS, Faraone SV, Tsuang MT and Seiman LJ. Regional prefrontal cortex gray matter volumes in youth at familial risk for schizophrenia from the Harvard Adolescent High Risk Study. *Schizophrenia Research*, 123(1): 15-21, 2010.

- Rupp CI, Fleischhacker WW, Kemmler G, Oberbauer H, Scholtz AW, Wanko C and Hinterhuber H. Various bilateral olfactory deficits in male patients with schizophrenia. *Schizophrenia bulletin*, 31(1), 155-165, 2005.
- Sabb FW, Bilder RM, Chou M and Bookheimer SY. Working memory effects on semantic processing: priming differences in pars orbitalis. *NeuroImage*, 37(1): 311-322, 2007.
- Salat DH, Kaye JA and Janowsky JS. Prefrontal gray and white matter volumes in healthy aging and Alzheimer disease. *Archives of Neurology*, 56(3): 338-44, 1999a.
- Salat DH, Kaye JA and Janowsky JS. Selective preservation and degeneration within the prefrontal cortex in aging and Alzheimer disease. *Archives of Neurology*, 58(9), 1403-1408, 2001.
- Salat, DH, Kaye JA and Janowsky JS. Greater orbital prefrontal volume selectively predicts worse working memory performance in older adults. *Cerebral Cortex*, 12(5), 494-505, 2002.
- Salat D, Stangl P, Kaye J and Janowsky J. Sex differences in prefrontal volume with aging and Alzheimer's disease. *Neurobiology of Aging*, 20(6): 591-596, 1999b.
- Sanches M, Caetano S, Nicoletti M, Monkul ES, Chen HH, Hatch JP, Yeh P-H, Mullis RL, Keshevan MS, Rajkowska G and Soares JC. An MRI-based approach for the measurement of the dorsolateral prefrontal cortex in humans. *Psychiatry Research*, 173(2): 150-154, 2009.
- Sanfilipo M, Lafargue T, Rusinek H, Arena L, Loneragan C, Lautin A, Feiner D, Rotrosen J and Wolkin A. Volumetric measure of the frontal and temporal lobe regions in schizophrenia: relationship to negative symptoms. *Archives of General Psychiatry*, 57(5): 471-480, 2000.
- Sanfilipo M, Lafargue T, Rusinek H, Arena L, Loneragan C, Lautin A, Rotrosen J and Wokin A. Cognitive performance in Schizophrenia: relationship to regional brain volumes and psychiatric symptoms. *Psychiatry Research Neuroimaging* 116: 1-23, 2002.
- Sarkisov S A, Filimonoff IN and Preobrashenskaya NS. *Cytoarchitecture of the Human Cortex Cerebri*. Medgiz, Moscow, 1949.
- Schenker NM, Desgouttes A-M and Semendeferi K. Neural connectivity and cortical substrates of cognition in hominoids. *Journal of Human Evolution*, 49(5): 547-569, 2005.

- Schlaepfer TE, Harris GJ, Tien AY, Peng L, Lee S and Pearlson GD. Structural differences in the cerebral cortex of healthy female and male subjects: a magnetic resonance imaging study. *Psychiatry Research*, 61(3): 129-135, 1995.
- Schlaepfer TE, Harris GJ, Tien AY, Peng LW, Lee S, Federman EB, Chase GA, Barta PE and Pearlson GD. Decreased regional cortical gray matter volume in schizophrenia. *American Journal of Psychiatry*, 151: 842-848, 1994.
- Schretlen D, Pearlson GD, Anthony JC, Aylward EH, Augustine AM, Davis A and Barta P. Elucidating the contributions of processing speed, executive ability, and frontal lobe volume to normal age-related differences in fluid intelligence. *Journal of the International Neuropsychological Society*, 6(1): 52-61, 2000.
- Seidman LJ, Yurgelun-Todd D, Kremen WS, Woods BT, Goldstein JM, Faraone SV and Tsuang MT. Relationship of prefrontal and temporal lobe MRI measures to neuropsychological performance in chronic schizophrenia. *Biological Psychiatry*, 35(4): 235-246, 1994.
- Seidman LJ, Valera EM., Makris N, Monuteaux MC, Boriol DL, Kelkar K, Kennedy DN, Caviness VS, Bush G, Alvardi M, Faraone SV and Biederman J. Dorsolateral prefrontal and anterior cingulate cortex volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging. *Biological Psychiatry*, 60(10): 1071-1080, 2006.
- Semendeferi K, Armstrong E, Schleicher A, Zilles K and Van Hoesen GW. Prefrontal cortex in humans and apes: a comparative study of area 10. *American Journal of Physical Anthropology*, 114(3): 224-241, 2001.
- Semendeferi K and Damasio H. The brain and its main anatomical subdivisions in living hominoids using magnetic resonance imaging. *Journal of Human Evolution*, 38(2): 317-32, 2000.
- Semendeferi K, Damasio H, Frank R and Van Hoesen GW. The evolution of the frontal lobes: a volumetric analysis based on three-dimensional reconstructions of magnetic resonance scans of human and ape brains. *Journal of Human Evolution*, 32(4): 375-388, 1997.
- Semendeferi K, Lu A, Schenker N and Damasio H. Humans and great apes share a large frontal cortex. *Nature Neuroscience*, 5(3): 272-6, 2002.
- Shallice T, Stuss DT, Picton TW, Alexander MP and Gillingham S. Mapping task switching in frontal cortex through neuropsychological group studies. *Frontiers in Neuroscience*, 2(1): 79-85, 2008.

- Sherwood CC, Gordon AD, Allen JS, Phillips KA, Erwin JM, Hof PR and Hopkins WD. Aging of the cerebral cortex differs between humans and chimpanzees. *Proceedings of the National Academy of Sciences*, 108(32): 13029-13034, 2011.
- Smith GE. A new topographical survey of the human cerebral cortex, being an account of the distribution of the anatomically distinct cortical areas and their relationship to the cerebral sulci. *Journal of Anatomy and Physiology*, 41(4): 237-254, 1907.
- Soininen HS, Karhu J, Partanen J, Pääkkönen A, Jousmäki V, Hänninen T, Hallikainen M, Partanen K, Laakso MP, Koivisto K and Reikkinen PJ. Habituation of auditory N100 correlates with amygdaloid volumes and frontal functions in age-associated memory impairment. *Physiology & Behavior*, 57(5): 927-35, 1995.
- Sowell ER, Trauner DA, Gamst A and Jernigan TL. Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. *Developmental Medicine and Child Neurology*, 44(1): 4-16, 2002.
- Staal W, Hulshoff Pol H, Schnack HG, Hoogendoorn MLC, Jellema K and Kahn RS. Structural brain abnormalities in patients with schizophrenia and their healthy siblings. *American Journal of Psychiatry*, 157: 416-421, 2000.
- Stephani C, Fernandez-Baca Vaca G, Maciunas R, Koubeissi M and Luders HO. Functional neuroanatomy of the insular lobe. *Brain structure and function*, 216: 137-149, 2011.
- Sullivan EV, Shear PK, Lim KO, Zipursky RB and Pfefferbaum A. Cognitive and motor impairments are related to gray matter volume deficits in schizophrenia. *Biological Psychiatry*, 39(4): 234-240, 1996.
- Suga M, Yamasue H, Abe O, Yamasaki S, Yamada H, Inoue H, Takei K, Aoki S and Kasai K. Reduced gray matter volume of Brodmann's Area 45 is associated with severe psychotic symptoms in patients with schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, 260:465-473, 2010.
- Suzuki M, Zhou S-Y, Takahashi T, Hagino H, Kawasaki Y, Niu L, Matsui M., Seto H and Kurachi M. Differential contributions of prefrontal and temporolimbic pathology to mechanisms of psychosis. *Brain*, 128(9): 2109-2122, 2005.
- Szeszko PR, Bilder RM, Lencz T, Ashtari M, Goldman RS, Reiter G, Wu H and Lieberman JA. Reduced anterior cingulate gyrus volume correlates with executive dysfunction in men with first-episode schizophrenia. *Schizophrenia Research*, 43(2-3): 97-108, 2000.



- Szeszko PR, Bilder RM, Lencz T, Pollack S, Alvir JM, Ashtari M, Wu H and Lieberman JA. Investigation of frontal lobe subregions in first-episode schizophrenia. *Psychiatry Research*, 90(1): 1-15, 1999a.
- Szeszko PR, Robinson D, Alvir JM, Bilder RM, Lencz T, Ashtari M, Wu H and Bogerts B. Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder. *Archives of General Psychiatry*, 56(10): 913-919, 1999b.
- Takahashi T, Kawasaki Y, Kurokawa K, Hagino H, Nohara S, Yamashita I, Nakamura K, Murata M, Matsui M, Suzuki M, Seto H and Kurachi M. Lack of normal structural asymmetry of the anterior cingulate gyrus in female patients with schizophrenia: a volumetric magnetic resonance imaging study. *Schizophrenia Research*, 55(1-2): 69-81, 2002a.
- Takahashi T, Suzuki M, Kawasaki Y, Hagino H, Yamashita I, Nohara S, Nakamura K, Seto H and Kurachi M. Perigenual Cingulate Gyrus Volume in Patients with Schizophrenia: A Magnetic Resonance Imaging Study. *Biological Psychiatry*, 53: 593-600, 2003.
- Takahashi, T, Suzuki M, Kawasaki Y, Kurokawa K, Hagino H, Yamashita I, Zhou S-Y, Nohara S, Nakamura K, Seto H and Kurachi M. Volumetric magnetic resonance imaging study of the anterior cingulate gyrus in schizotypal disorder. *European Archives of Psychiatry and Clinical Neuroscience*, 252(6): 268-277, 2002b.
- Takeoka M, Kim F, Caviness VS, Kennedy DN, Makris N and Holmes GL. MRI volumetric analysis in rasmussen encephalitis: a longitudinal study. *Epilepsia*, 44(2): 247-251, 2003.
- Tisserand DJ, Pruessner JC, Arigita EJS, Boxtel MPJV, Evans AC, Jolles J and Uylings HBM. Regional Frontal Cortical Volumes Decrease Differentially in Aging: An MRI Study to Compare Volumetric Approaches and Voxel-Based Morphometry. *NeuroImage*, 17:657- 669, 2002.
- Tomaiuolo F, MacDonald JD, Caramanos Z, Posner G, Chiavaras M, Evans AC and Petrides M. Morphology morphometry and probability mapping of the pars opercularis of the inferior frontal gyrus: an *in vivo* MRI analysis. *European Journal of Neuroscience*, 11:3033-3046, 1999.
- Torralva T, Kipps CM, Hodges JR, Clark L, Bekinschtein T, Roca M, Calcagno ML and Manes F. The relationship between affective decision-making and theory of mind in the frontal variant of fronto-temporal dementia. *Neuropsychologia*, 45(2): 342-9, 2007.

- Turetsky B, Cowell PE, Gur RC, Grossman RI, Shtasel DL and Gur RE. Frontal and temporal lobe brain volumes in schizophrenia: relationship to symptoms and clinical subtype. *Archives of General Psychiatry*, 52(12): 1061-1070, 1995
- Tzourio N, Petit L, Mellet E, Orssaud C, Crivello F, Benali K, Salamon G and Mazoyer B. Use of anatomical parcellation to catalog and study structure-function relationships in the human brain. *Human Brain Mapping*, 5(4): 228-232, 1997.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B and Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, 15(1): 273-89, 2002.
- Unterrainer JM and Owen AM. Planning and problem solving: from neuropsychology to functional neuroimaging. *Journal of Physiology*, 99(4-6), 308-17, 2006.
- Uylings HBM, Rajkowska G, Sanz-Arigita E, Amunts K and Zilles K. Consequences of large interindividual variability for human brain atlases: converging macroscopical imaging and microscopical neuroanatomy. *Anatomy and Embryology*, 210(5-6): 423-431, 2005.
- Uylings HBM, Sanz-Arigita EJ, de Vos K, Pool CW, Evers P and Rajkowska G. 3-D cytoarchitectonic parcellation of human orbitofrontal cortex correlation with postmortem MRI. *Psychiatry Research*, 183(1): 1-20, 2010.
- van Elst, LTV, Hesslinger B, Thiel T, Geiger E, Haegele K, Lemieux L, Lieb K, Bohus M, Hennig J and Ebert D. Frontolimbic brain abnormalities in patients with borderline personality disorder: A volumetric magnetic resonance imaging study. *Biological Psychiatry*, 54(2): 163-171, 2003.
- Van Petten C, Plante E, Davidson PSR, Kuo TY, Bajuscak L and Glisky EL. Memory and executive function in older adults: Relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. *Neuropsychologia*, 42:1313-1335, 2004.
- Vogt BA, Nimchinsky EA, Vogt LJ and Hof PR. Human cingulate cortex: Surface features, flat maps, and cytoarchitecture. *Journal of Comparative Neurology*, 359:490-506, 1995.
- Vogt BA. Architecture, cytology and comparative organization of primate cingulate cortex. In Vogt B (Ed.), *Cingulate Neurobiology and Disease*. Oxford University Press, Oxford, 2008.

- Volle E, Gilbert SJ, Benoit RG and Burgess PW. Specialization of the rostral prefrontal cortex for distinct analogy processes. *Cerebral Cortex*, 20(11): 2647-2659, 2010.
- von Economo C and Koskinas GN. *Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen*. Springer, Berlin, 1925.
- Walker AE. A cytoarchitectural study of the prefrontal area of the macaque monkey. *Journal of Comparative Neurology*, 73(1):59-86, 1940.
- Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM and Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, 3: 25, 2003.
- Wible CG, Shenton ME, Fischer IA, Allard JE, Kikinis R, Jolesz FA, Iosifescu DV and McCarley RW. Parcellation of the human prefrontal cortex using MRI. *Psychiatry Research: Neuroimaging Section*, 76:29-40, 1997.
- Wible CG, Anderson J, Shenton ME, Kricun A, Hirayasu Y, Tanaka S, Levitt JJ, O'Donnell BF, Kikinis R, Jolesz FA and McCarley RW. Prefrontal cortex, negative symptoms, and schizophrenia: an MRI study. *Psychiatry Research*, 108(2): 65-78, 2001.
- Wible CG, Shenton ME, Hokama H, Kikinis R, Jolesz FA, Metcalf D and Mccarley RW. Prefrontal cortex and schizophrenia. *Archives of General Psychiatry*, 52: 279-288, 1995.
- Wilde EAA, Hunter JV, Newsome MR, Schiebel RS, Bigler ED, Johnson JL, Fearing MA, Cleavinger HB, Li X, Swank PR, Pedroza C, Roberson GS, Bachevalier J and Levin HS. Frontal and temporal morphometric findings on MRI in children after moderate to severe traumatic brain injury. *Journal of Neurotrauma*, 22(3):333-344, 2005.
- Woods BT, Yurgelun-Todd D, Goldstein JM, Seidman LJ and Tsuang MT. MRI brain abnormalities in chronic schizophrenia: one process or more? *Biological Psychiatry*, 40(7): 585-596, 1996.
- Woodward SH, Kaloupek DG, Streeter CC, Martinez C, Schaer M and Eliez S. Decreased anterior cingulate volume in combat-related PTSD. *Biological Psychiatry*, 59(7): 582-587, 2006.
- Yamasaki S, Yamasue H, Abe O, Suga M, Yamada H, Inoue H, Kuwabara H, Kawakubo Y, Yahata N, Aoki S, Kano Y, Kato N and Kasai K. Reduced gray matter volume of pars opercularis is associated with impaired social

- communication in high-functioning autism spectrum disorders. *Biological Psychiatry* 68(12): 1141-1147, 2010.
- Yamasue H, Iwanami A, Hirayasu Y, Yamada H, Abe O, Kuroki N, Fukuda R, Tsujii K, Aoki S, Ohtomo K, Kato N and Kasai K. Localized volume reduction in prefrontal, temporolimbic, and paralimbic regions in schizophrenia: an MRI parcellation study. *Psychiatry Research*, 131(3): 195-207, 2004.
- Yücel M, McKinnon MC, Chahal R, Taylor VH, Macdonald K, Joffe R and MacQuenn GM. Anterior cingulate volumes in never-treated patients with major depressive disorder. *Neuropsychopharmacology*, 33:3157-3163, 2008.
- Yücel M, Stuart GW, Maruff P, Velakoulis D, Crowe SF, Savage G and Pantelis, C. Hemispheric and gender-related differences in the gross morphology of the anterior cingulate/paracingulate cortex in normal volunteers: an MRI morphometric study. *Cerebral Cortex* 11(1): 17-25, 2001.
- Zald DH. Orbital versus dorsolateral prefrontal cortex: Anatomical insights into content versus process differentiation models of the prefrontal cortex. *Annals of the New York Academy of Sciences*, 1121:395-406, 2007.
- Zilles, K. Cortex. In: Paxinos G, editor. The human nervous system. San Diego (CA): Academic press, p. 757-802, 1990.
- Zilles, K and Amunts K. Centenary of Brodmann's map--conception and fate. *Nature reviews: Neuroscience*, 11(2): 139-145, 2010.
- Zhou S-Y, Suzuki M, Hagino H, Takahashi T, Kawasaki Y, Matsui M, Seto H and Kurachi M. Volumetric analysis of sulci/gyri-defined in vivo frontal lobe regions in schizophrenia: Precentral gyrus, cingulate gyrus, and prefrontal region. *Psychiatry Research*, 139(2): 127-39, 2005.
- Zipursky RB, Lim KO, Sullivan EV, Brown BW and Pfefferbaum A. Widespread cerebral gray matter volume deficits in schizophrenia. *Archives of General Psychiatry*, 49(3): 195-205, 1992.
- Zuffante P, Leonard CM, Kulda JM, Bauer RM, Doty EG and Bilder RM. Working memory deficits in schizophrenia are not necessarily specific of associated with MRI-based estimates of area 46 volumes. *Psychiatry Research: Neuroimaging Section*, 108:187-209.

## **Appendix C: Participant Information Sheet**



Psychology  
SCHOOL of PHILOSOPHY, PSYCHOLOGY and LANGUAGE SCIENCES

The University of Edinburgh  
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Edinburgh EH8 9JZ

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### **Information Sheet for Participants**

#### **Study title: “Changes in Thinking, Cortisol and Ageing”**

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

#### **What is the purpose of the study?**

The extent to which people decline with age is the subject of huge variability, and attempts to better understand why some people age more successfully than others is the subject of intense interest. One factor that may have a bearing on

cognitive decline with age is the body's ability to regulate the production of a naturally occurring steroid called cortisol. Whilst short bursts of this chemical are used by the body to help us cope with stressful situations, a lack of control over its production can occur as the body ages, resulting in chronically high cortisol levels, which may affect certain brain regions. Using a battery of psychological tests and questionnaires, brain imaging techniques, and salivary cortisol measures, we hope to investigate whether higher cortisol levels in old age are associated with differences in specific brain structures, and also changes in specific types of cognition when compared to other old and young participants.

### **Do I have to take part?**

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

### **What will happen to me if I take part?**

The study requires you to perform a series of tests, some of which take place on a computer and some of which are paper and pencil. It is estimated that the interview is 80 minutes long. If you need a break at any time you are free to do so. The tasks could be carried out at the Department of Psychology, University of Edinburgh, 7 George Square at a time of your convenience.

During the interview, there are tests in which we would like to record you. This is because the tests require you to tell us the answers out loud. By recording your answers, we do not need to write everything down immediately as you say it, which saves time. We will ensure, however, that these recordings will be stored securely and they will be destroyed once your answers have been written down and scored.

### **What do I have to do?**

Firstly, the researcher would go through the information sheet with you and give you the opportunity to ask any questions. If you agree to take part, you would be asked to perform some tasks in the form of questionnaires, “paper and pencil tests and computer tests. These tests are similar to word games and puzzles. The instructions for each test would be explained to you beforehand. All tests use materials presented in spoken, read or picture form and your responses are spoken, written or button presses.

### **What are the possible disadvantages and risks of taking part?**

All interviews will take place in the morning for the purposes of consistency, and due to the length of the interview you may find testing to be tiring, but you are free to take a break at any time. If you feel distressed at any time during the interview, it is important that you let the interviewer know straight away. If you feel distressed at any time after the interview, you may contact Simon Cox on 0131 650 3455.

### **What are the possible benefits of taking part?**

There will be no direct benefit to you by taking part, and your individual results will not be revealed to you. However, we will make any future publications of the findings available to you. It is hoped that this research will improve our understanding of the changes in thinking and behaviour that people experience with aging and may influence care practices in the future.

### **What if something goes wrong?**

Whilst we do not anticipate any adverse effects from taking part in this study, if you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you can contact us at any time.

### **Will my taking part in this study be kept confidential?**

If you do decide to take part, we will notify your GP of your enrolment in the study. All information which is collected about you during the course of the research will be kept strictly confidential. Any pre-existing information from LBC waves will have your name and address removed so that you cannot be recognized from it. You will be allocated an anonymous ID code during testing which will be used in place of your name on any future publications.

### **What will happen to the results of the research study?**

The results of the research will be published in appropriate peer-reviewed scientific journals for distribution to other healthcare professionals. Talks and presentations may be made at meetings and conferences. In all cases, your name and personal details will not be identified.

### **Who is organising the research?**

The study is being organised by Mr Simon Cox (a Phd Student), together with Dr Sarah MacPherson, Prof Alasdair MacLulich and Prof Ian Deary from the University of Edinburgh. The study is being carried out for educational purposes.



### **Who has reviewed the study?**

This study has been granted ethics approval by the Lothian Research Ethics Committee, and the Philosophy, Psychology and Language Sciences Research Ethics Committee at University of Edinburgh.

### **Contact for further information**

If you wish to ask anything further, please contact Simon Cox via the address below:

Department of Psychology, PPLS  
7 George Square  
Edinburgh, EH8 9JZ

Or via the following telephone number or email address:

Mr. Simon Cox on 0131 650 3455 ([s.r.cox@sms.ed.ac.uk](mailto:s.r.cox@sms.ed.ac.uk))

Dr MacPherson on 0131 650 9862 ([sarah.macpherson@ed.ac.uk](mailto:sarah.macpherson@ed.ac.uk))

Prof. Alasdair MacLullich ([a.maclullich@ed.ac.uk](mailto:a.maclullich@ed.ac.uk))

Prof. Ian Deary ([iand@ed.ac.uk](mailto:iand@ed.ac.uk))

Thank you for reading this information sheet. You will be given a copy to keep. If you have understood the contents of this sheet and wish to take part, please complete the consent sheet on the next page. If you have any questions please feel free to ask them now.

# **Cortisol, Cognition and the Ageing Prefrontal Cortex**

## **Standard Operating Procedures LBC Participants**

Created 22<sup>nd</sup> January 2010 – SRC  
Amended 6<sup>th</sup> September 2010 – SRC  
Amended 4<sup>th</sup> October 2010 – SRC  
Amended 15<sup>th</sup> October - SRC

**S.O.P.: Introduction and Background****Equipment Setup**

Laptop: Once plugged in and powered up, enable the wireless internet by holding the blue Fn button and pressing F11. Next, double-click on the wireless helper (bottom right of the task bar) and select Refresh Network List. It should then automatically detect and connect with the Central network.

Next, open Firefox and log in when prompted to do so by the university Central login page. This will enable the Matlab license to self-authenticate when running the Reversal Learning task.

Touch-Screen: Both the SVGA and USB cables should be connected to the laptop (left hand side), the power cable plugged in and the monitor switched on. Configuring the laptop for a cloned display is done as follows:

- Start > Control Panel > Display > Settings  
Drag either screen one of screen two until it partially overlaps and then release the mouse button. Answer YES to the on-screen prompt and click APPLY
- Double-click on the red ATI button on the bottom right of the taskbar.  
Select display settings and click on the 'clone' option.

**Introduction and welcome**

The researcher will ensure that they arrive at the front entrance of 7 George Square in good time to meet the participant at the arranged time. Welcome the participant and thank them for returning to participate in this study. Show them to the testing booth (B72) and briefly explain what the visit will entail, including how long the visit will take. Ensure that the participant understands that they are free to ask any questions or stop/withdraw at any time. Make sure the participant has read and understands the Information Sheet.

Allow time for the participant to ask any questions and ensure they are satisfied with any responses given. Once they are happy to proceed, ask them to read and sign the Consent Form. Participants must sign and date the form themselves. The researcher should also sign and date this form. All forms and answer sheets should be completed in pen. If during the testing session or marking, any errors need to be amended, the initial entry should be scored through with a single line and all changes should be initialed and dated by the researcher and comments left where appropriate.

**Checklist**

Ensure that participants have brought:

- 1 x morning saliva sample
- 1 x evening saliva sample
- Sample collection sheet (completed)
- 2 x State Trait Anxiety Inventory (STAI) forms Y1
- 1 x State Trait Anxiety Inventory (STAI) form Y2
- Note down the rough time they woke up this morning
- Check that they have not had anything to eat or drink in the last 30mins (for saliva sample).

If they have forgotten to bring anything with them, highlight the postal address on the information sheet and ask if they would be able to send these in the post with a note of their name and LBC number (offer to compensate them for postal charges incurred).

**Saliva Test Kit (T1):**

[Thank for completing the above items]. As before, I'm going to ask you to give us another saliva sample. The swab can be placed either inside the cheek like a dental swab, or chewed gently until completely saturated.

Note down the relevant information on the sampling sheet.

**STATE element of the STAI:**

Next, I would like you to fill out just this half of this questionnaire [indicate State form], so I can get an idea of how you are feeling today. Please read the instructions at the top and then circle the number for each statement that best describes how you currently feel.

## **Cortisol, Cognition and the Ageing PFC**

### **S.O.P.: Cognitive Tests**

Introduce the cognitive tests.

We're now going to do some thinking and memory-type tests. I'll be asking you to do a number of things today like asking you to remember some things and solving some problems. You will find some of the tasks easy, and some may be more difficult. Also, most people don't answer every question correctly or finish every item, but please give your best effort on all of the tasks.

The cognitive tests will take a total of 80minutes. Participants should be made aware that they are free to take a break at any time and be offered tea\*/coffee\*/water although this must allow for 30 minutes to elapse before the end of the battery for the final saliva sample.

\* decaffeinated

### **BATTERY RUNNING ORDER**

**Self-Ordered Pointing Task**

**Reversal Learning\***

**D-KEFS Tower**

**Faux Pas test**

**Simon Task**

**Moral Dilemmas**

**\* if a second participant is booked in to attend testing, the first to arrive will change rooms after completion of the Reversal Learning task.**

**Self-Ordered Pointing Task** (instructions adapted from Strauss et al 2006

Compendium of Neuropsych. Tests, p.471:

<http://books.google.co.uk/books?id=dvE1mzbqI14C&printsec=frontcover&dq=strauss+compendium+tests&client=firefox-a&cd=1#v=onepage&q=&f=false>)

In this task, the first screen you will be presented with contains 12 abstract pictures in a certain order. In all, you will see 12 screens, and each one contains the same pictures, but each has a different arrangement.

I want you to touch one picture at a time, and once you have chosen, the configuration will change. I want you to touch a different picture each time. Once you choose a picture, you should not choose it again.

Do you understand?

First of all, we will do a short practice session with just 4 pictures.

**END OF SUBTEST**

### **Reversal Learning – Part A (Deterministic)**

Now I am going to ask you to attempt a task on the computer.

[SHOW INSTRUCTION SHEET] A pair of objects similar to those on the instruction sheet will appear on the screen, and you will have to choose between them by pressing either LEFT [3] or RIGHT [4].

You have a short period in which to make your choice each time. If you make a correct choice, you will gain 25 pence, but if you make an incorrect choice or are too slow to decide, you will lose 25 pence. Your job is to try to gain as much virtual money as possible.

You will be told whether you have won or lost money after each selection, and then your running total will be displayed.

Are you ready?

Say **Go** clearly, then begin the session [press 5].

Write down any comments made during the test.

If asked for additional advice during the experiment, say **I'm afraid I can't give you any help for this task. Please continue to accumulate as much money as you can.**

Press SPACE to end the session.

### **Reversal Learning - Post Test Interview A [audio tape]**

Can you give me a brief summary of what you think the test involved?

How could you gain and lose points?

Can you describe what you were thinking at the beginning of the test?

What happened later in the test, and how did you respond?

**END OF SUBTEST**

### **D-KEFS Tower test** [this task is timed]

This task requires the participant to replicate a particular arrangement of discs on three pegs from an initial starting point, given a picture of what the end point should look like. However, in this task, there are 2 rules which must be obeyed:

- 1) Only one disc can be moved at a time
- 2) A larger disc may not rest on a smaller disc at any time.

If the examinee does not solve item 1 in one move, or item 2 in 2 moves, demonstrate the correct solution in each case. Do **not** demonstrate the correct solution for items 3-9.

The wooden base should be placed in the horizontal position (longways, running left to right) near to the edge of the table closest to the participant so that it can easily be reached. The stimulus booklet should be placed in an easel position closer to the researcher, but ensuring that it is still easy for the examinee to read the instructions. Place the 5 discs next to the wooden base.

#### **Discontinue Rule**

Discontinue the task after 3 consecutive failures.

OR

At the end of the indicated time limit:

Items 1-3:	30s
Item 4:	60s
Items 5-6:	120s
Item 7:	180s
Items 8-9:	240s

A single move is based on the following criteria:

*Move initiation occurs when the examinee lifts the disc completely off the peg. Move completion occurs when the examinee takes his or her hand completely off the disc.*

Say: I want you to use these pieces to build a tower to look like a design I will show you in a moment. Before you start, I will put the pieces in place. I want you to build the tower using the fewest number of moves possible.

Pointing to the rules on the stimulus page, say: There are two rules to follow: First, move only one piece at a time, using just one hand. And second, never place a big piece on top of a little piece. Do you have any questions?

Arrange the discs as depicted in the stimulus booklet for the Item Starting Position. Ensure that the ending position for the appropriate Item number is visible to the participant and say:

Now make yours look like the one in this picture. Begin.



Start timing and record the following on the record sheet:

Estimated first-move time.

Total number of moves to completion

Number of rule violations

Total completion time.

Tower correct (Y/N)

Remove the discs from the wooden base and place them with the others. Then say:

I have some more towers for you to build. For each one, work carefully so that you use the fewest number of moves possible. Remember, move only one piece at a time, and never place a big piece on top of a little piece. Tell me when you have finished.

Repeat to completion or discontinue rule.

**END OF SUBTEST**

**Faux Pas task:**

Say Now I am going to give you a number of short stories to read. You don't have to read these out loud. After each story there are a number of questions that I am going to ask you. To save you having to write this down, I will ask you out loud and record your responses.

You are allowed to refer back to the story booklet at any time, as this is not a memory test.

Are you ready?

Give the story booklet to the participant, and say Just let me know when you have read the first story.

Start the audio recorder.

Ask the questions related to the first story, then repeat to completion.

Turn off audio recorder.

**END OF SUBTEST**

### **Simon Task**

Check that participant has never suffered from any sort of colour-blindness.

Read through the on-screen instructions with the participant:

Your task is to respond to the images presented to you by pressing the appropriate key.

At the centre of the screen, you will see a fixation point (a cross) which you should focus on. The cross will then disappear and you will be presented with a square.

If the square is RED, press the button labelled 'Red'; If the square is GREEN, press the 'Green' button.

Try to answer as quickly and accurately as possible. If you make an error, or you are simply too slow to respond, you will see a row of exclamation marks (!!!!!!!!!)

Do you understand what you have to do?

Press the space bar to begin.

**END OF SUBTEST**

**Moral Dilemmas**

This next experiment requires you to read a series of dilemmas. Some of them represent day-to-day scenarios, but others depict very difficult situations. After having read each scenario, you will be asked a question about whether you could take a particular course of action to resolve the dilemma. Respond by pressing Y if you would carry out the action or N if you would not.

Please try to put yourself in the situation described, and answer honestly, as there are no right or wrong answers and often, either course of action is equally defensible.

Read through the on-screen instructions.

Please try to remember to advance to the next screen *as soon as* you have finished reading each screen and you are happy you have understood it.

Please press the spacebar when you are ready to begin and follow the instructions on screen.

**END OF SUBTEST**

**MacArthur Scale of Subjective Social Status**

Say I'd like you to take a look at these two scales. You will see that on each page there is a ladder which represents peoples' standing in the community on this sheet [INDICATE] and how well off people are on this sheet [INDICATE].

Please take a minute to read the instructions at the top of each sheet and then fill them out as instructed. Feel free to ask me if something seems unclear.

Provide the participant with a pen.

**END OF SUBTEST**

**STATE element of the STAI:**

Before we finish, I would like you to fill out this questionnaire again [indicate], so I can get an idea of how you are feeling now. Please read the instructions at the top and then tick the box for each statement that best describes how you currently feel.

**Saliva Test Kit (T2):**

Finally, I'd like to collect one more saliva sample from you.  
Provide Salivette and administer as before.

**END OF TEST**

Thank participant for taking part, allow opportunity to ask any further questions and ensure they have a copy of the information sheet with contact details. Also make sure travel expenses have been reimbursed before showing them to the front entrance of 7 George Square. They may wish to arrange for a taxi, or may have arranged for a friend/relative/partner to pick them up, in which case make them feel welcome to wait in the concourse until their transport arrives.

## **Cortisol, Cognition and the Ageing PFC**

### **S.O.P.: Cognitive Test Scoring**

#### **D-KEFS Tower task**

##### **Achievement Score**

Sum all points gained from each of the completed trials (score ranges vary from 0-2 points to 0-4 points dependant upon the trial difficulty).

##### **Mean First-Move Score**

Total 1<sup>st</sup> Move Scores ÷ Total # Administered Items

##### **Time Per Move Ratio**

Total Item-Completion Times ÷ Total # Moves

##### **Move Accuracy Ratio**

Total # Moves ÷ Total # Minimum Moves

##### **Rule Violations Per Item Ratio**

Total # Rule Violations ÷ Total # Item Administered

#### **Faux Pas Task**

For each story containing a FP, the subject gets 1 point for each question answered correctly.

##### **First question: "Did anyone say something they shouldn't have said?"**

Faux pas stories: Correct: Yes Incorrect: No

Control stories: Incorrect: Yes Correct: No

##### **Second question: "Who said something they shouldn't have said?"**

Any answer that unambiguously identifies the correct person is correct.

story about calling little girl a boy: Mary (also acceptable: the neighbor)

story about crystal bowl: Anne (also acceptable: the hostess, or the woman who got married, etc.)

story about lawyers: Claire (also acceptable: the woman, or the woman in a bad mood, etc.)

story about curtains: Lisa (also acceptable: the friend)

story about cancer joke: Robert (also acceptable: the guy who came in late)

story about losing story contest: Jake (also acceptable: the guy who won)

story about spilled coffee: Tim (also acceptable: the guy who spilled his coffee)

story about new kid in school: Joe (also acceptable: Joe and Peter)

story about surprise party: Sarah (also acceptable: the woman who spilled the coffee)  
story about pie: Joe (also acceptable: Kim's cousin)  
Subjects who answer "no" to the first question don't get asked this question and score a 0 for this one.

**Third question: "Why shouldn't they have said it?"**

Any reasonable answer that makes reference to the faux pas is acceptable. The subject does not have to explicitly mention mental states, as in, "He didn't know about the guy who was sick with cancer, but everyone else did." It is sufficient to say, "Because John is terminally ill," or because the guy standing right there is married to a lawyer," or "you shouldn't walk into a new apartment and criticize it; you don't know who bought what." This question only gets scored as incorrect if the person's answer doesn't reflect an understanding of the faux pas, that is, of what would have been offensive. Examples (from amygdala patients):

"The neighbor shouldn't have called her little.

Kids like to feel grown up." (Misses the point that Sally is a girl, not a boy.)

"Claire shouldn't tell him she needs her coffee." (Misses the insult to Roger.)

"You shouldn't come into a meeting late." (Doesn't mention the inappropriate joke.)

Subjects who answer "no" to the first question don't get asked this question, and score a 0 for this one.

**Fourth question: "Why did they say it?" or "Why do you think they said it?"**

Again, any reasonable answer that makes reference to the faux pas is acceptable. As long as the subject's answer indicates that they understand that one of the story characters didn't know something or didn't realize something, it is correct, even if they do not explicitly mention mental states. This question gets scored as incorrect if the subject seems to think that the person said it deliberately. Some more examples, also from patients:

"Tim shouldn't order around other customers. He just basically went up to an equal and said, 'On your knees, boy.'" (Doesn't reflect an understanding that Tim mistook Jack for someone who worked at the restaurant.)

"He was trying to put Christine down, make himself one up by gloating." (Doesn't reflect that he didn't know Christine was in the contest.)

"She was trying to make Helen feel jealous." (Looks like a confabulation, and doesn't mention surprise party.) Some patients also just say, "I don't know," which also gets a zero.

Subjects who answer "no" to the first question don't get asked this question, and score a 0 for this one.

**Fifth question: Did X know that Y?**

Again, this is to test whether they realize the faux pas was unintentional. Scoring is straightforward.



**Sixth question: How did X feel?**

A test of subjects' empathy for the story characters. Should reflect feelings of hurt, anger, embarrassment, disappointment, as appropriate.

**Seventh and eighth questions:**

Control questions. These should tell you if the person has gotten confused and forgotten the details of the story. Answers are pretty obvious. These are scored separately from the other questions.

Examples for faux pas stories,

In the story, where was Sally? "At her aunt Carol's house." (I think one subject said, "In the doorway next to her aunt," and I scored it as correct.)

In the story, what had Jeannette given Anne for her wedding? "A crystal bowl," "a bowl."

In the story, what did Robert's wife do for a living? "She was a lawyer."

In the story, what had Jill just bought? "New curtains," "curtains."

In the story, what had Jean West just told people in the meeting? "VP had cancer."

In the story, who won the competition? "Jake."

In the story, where was Jack standing? "By the cashier."

In the story, where was Mike while Joe and Peter were talking? "In the stalls (cubicles)."

In the story, who was Helen's husband throwing a surprise party for? "Helen."

In the story, what kind of pie had Kim made? "Apple."

Dorsolateral frontal patients, for example, often got some of these wrong. One patient said the surprise party was for Sarah's birthday, and that Helen was upset because her husband was throwing a party for another woman, and she wondered if they were having an affair.

All subjects get asked these questions, even if they answer "no" to the first question.

Overall, there are a total of 60 points that subjects can get on the faux-pas-related questions on the 10 faux pas stories. Someone who answers "no" to the first question for a story will get 0 points for that whole story. On the 10 control stories, score 2 points if they get it correct that no one said anything they shouldn't have said, 0 if they say someone said something they shouldn't have said, for a total of 20 points on the control stories. Score 1 point each for control questions on these stories.

Report separate scores for faux-pas-related questions on the faux pas stories, control questions on the faux pas stories, the faux-pas-related question on the control stories, and the control questions on the control stories. Then you can get a feel for if they are making more faux-pas-related errors (theory of mind errors) than errors on the factual control questions.

If anyone answers any of the control questions incorrectly, their other errors for that story should be interpreted with caution. You can throw out their other answers for that story and score their answers on the remaining stories, calculating a percent correct out of 54 points total, or 48 or whatever.

Discrepancies between answers to the first question and to the fifth question should be noted.

**State and Trait Anxiety Inventory (STAI)**

Responses from the State and Trait portions of the inventory should be scored in accordance with the following tables:

## Scoring Key for Y-1

	Not at all	Somewhat	Moderately	V Much so
1	4	3	2	1
2	4	3	2	1
3	1	2	3	4
4	1	2	3	4
5	4	3	2	1
6	1	2	3	4
7	1	2	3	4
8	4	3	2	1
9	1	2	3	4
10	4	3	2	1
11	4	3	2	1
12	1	2	3	4
13	1	2	3	4
14	1	2	3	4
15	4	3	2	1
16	4	3	2	1
17	1	2	3	4
18	1	2	3	4
19	4	3	2	1
20	4	3	2	1

## Scoring Key for Y-2

	Not at all	Somewhat	Moderately	V Much so
21	4	3	2	1
22	1	2	3	4
23	4	3	2	1
24	1	2	3	4
25	1	2	3	4
26	4	3	2	1
27	4	3	2	1
28	1	2	3	4
29	1	2	3	4
30	4	3	2	1
31	1	2	3	4
32	1	2	3	4
33	4	3	2	1
34	4	3	2	1
35	1	2	3	4
36	4	3	2	1
37	1	2	3	4
38	1	2	3	4
39	4	3	2	1
40	1	2	3	4

<b>Lothian Birth Cohort 1936 Study</b> <b>S.O.P.: Pre-Test Materials</b>
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Included with their appointment letter, participants will receive a copy of the STAI and an saliva sampling kit. Instructions will guide participants through completion of this, and tell them to bring it to their test visit. At this time, the researcher will check the STAI for errors or omissions which the participant will be asked to amend before they leave\*. The researcher should also ensure the participant number and initials are marked on all items, and that the appropriate fields for the saliva samples are filled in.

# **Appendix E: Manual Tracing - Previous Frontal Pole Boundary**

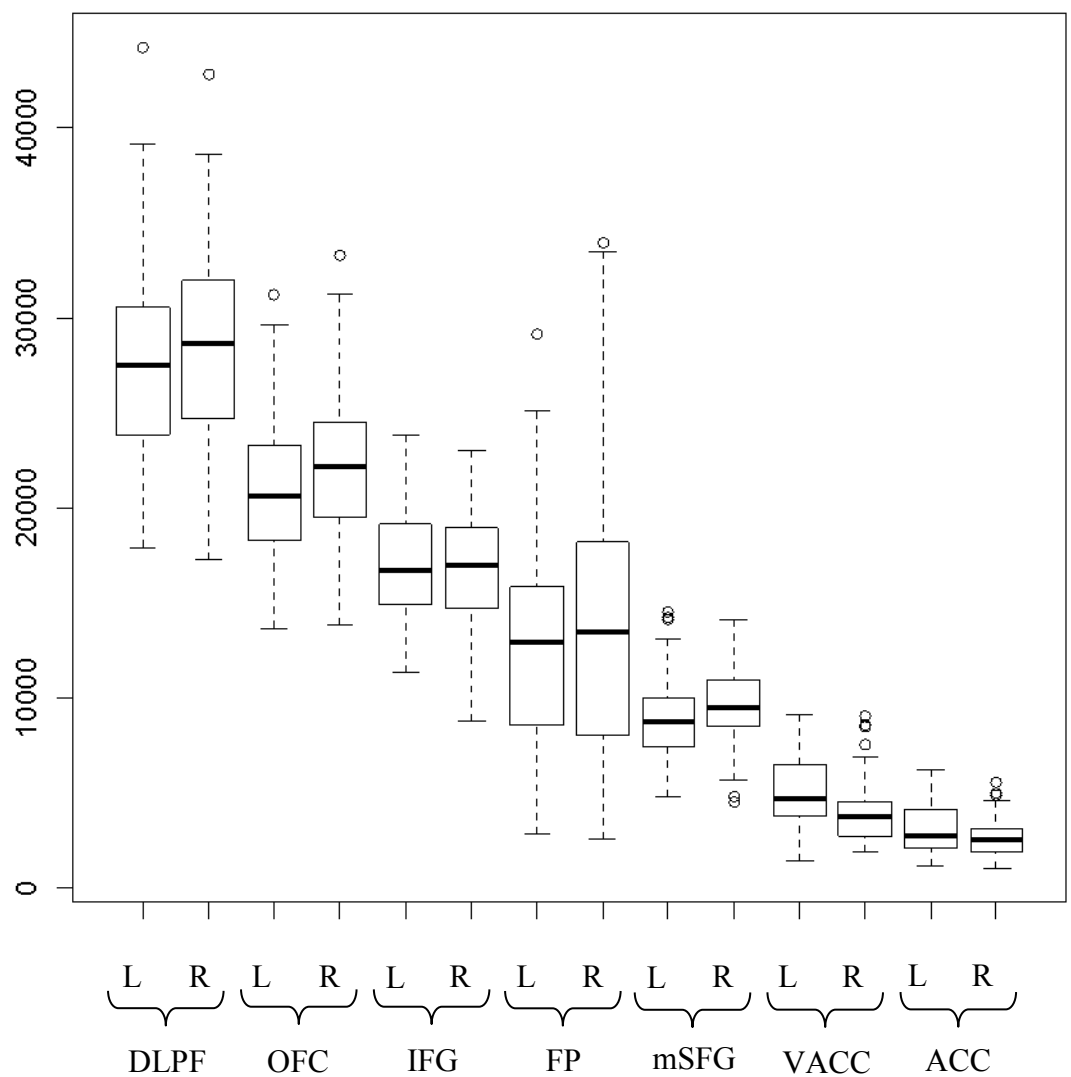


Figure E. Boxplot of the raw volumes (mm<sup>3</sup>) of frontal sub-regions ( $n=88$ ) derived using the frontal pole boundary at the anterior termination of the olfactory sulcus (after John et al., 2007). DLPFC: dorsolateral prefrontal cortex, OFC: orbitofrontal cortex, IFG: inferior frontal gyrus, FP: frontal pole, MSFG: medial superior frontal gyrus, VACC: ventral anterior cingulate cortex; ACC: (dorsal) anterior cingulate cortex,

Table E. Raw volumes of brain sub-regions ( $n = 88$ ) derived using the frontal pole boundary at the anterior termination of the olfactory sulcus (after John et al., 2007).

<b>Region</b>	<b>Side</b>	<b>Mean Volume (mm<sup>3</sup>)</b>	<b>SD</b>	<b>Min</b>	<b>Max</b>	<b>SD % of Volume</b>
<b>Dorsolateral</b>	L	27645	5185	17971	44317	18.76
	R	28645	5299	17345	42817	18.50
<b>Orbtofrontal</b>	L	21080	3679	13675	31217	17.45
	R	22091	3800	13919	33334	17.20
<b>Inferior frontal</b>	L	16961	2940	11355	23951	17.34
	R	16958	3270	8773	23055	19.28
<b>Frontal Pole</b>	<i>L</i>	<i>12826</i>	<i>5630</i>	<i>2851</i>	<i>29157</i>	<i>43.90</i>
	<i>R</i>	<i>14054</i>	<i>7196</i>	<i>2543</i>	<i>33986</i>	<i>51.20</i>
<b>mSFG</b>	L	8968	2159	4868	14602	24.08
	R	9715	2025	4564	14191	20.84
<b>Ventral ACC</b>	L	5028	1892	1452	9197	37.63
	R	3985	1527	1922	9138	38.31
<b>Dorsal ACC</b>	L	3116	1261	1139	6302	40.45
	R	2682	966	1059	5598	36.03

mSFG: Medial superior frontal gyrus, ACC: anterior cingulate cortex, L: Left, R: Right.

## Appendix F: Correlations Between Tract FA and Cortisol

Table F. Correlations between cortisol levels and measures of tract fractional anisotropy.

	Genu	Splenium	Arcuate		ATR		Cingulum		Uncinate		ILF	
			L	R	L	R	L	R	L	R	L <sup>◇</sup>	R <sup>◇</sup>
Morning	.06	.14	.03	.02	-.15	.01	.03	-.03	.18	.02	.06	.03
Evening <sup>a</sup>	-.10	-.01	-.09	-.09	-.15	-.01	.07	.04	-.09	-.08	<b>-.22<sup>†</sup></b>	-.10
Diurnal	-.05	<b>-.21<sup>†</sup></b>	-.02	-.02	.10	-.03	.01	-.01	-.14	.02	-.06	-.07
Start <sup>a</sup>	-.05	-.06	.03	.00	.13	-.03	-.06	-.04	-.16	-.03	-.11	-.04
End <sup>a</sup>	-.03	-.13	-.04	.09	-.01	-.15	-.05	-.01	-.10	-.02	-.02	-.07
Reactive	.04	-.04	-.02	.09	-.14	-.02	.03	.11	.18	.09	.15	.03

Significances not corrected for multiple comparisons, <sup>†</sup> trend (0.05 < p < 0.08). <sup>a</sup> log transformed, <sup>◇</sup> non-parametric variable, Spearman method used. ATR: anterior thalamic radiation; ILF: inferior longitudinal fasciculus. Diurnal denotes the slope, where a negative value reflects decreasing cortisol levels from the first to second time points.

## Appendix G: Cortisol & Cognitive Change

Table G. Pearson correlations between cortisol levels and cognitive ability corrected for age 11IQ and peak IQ.

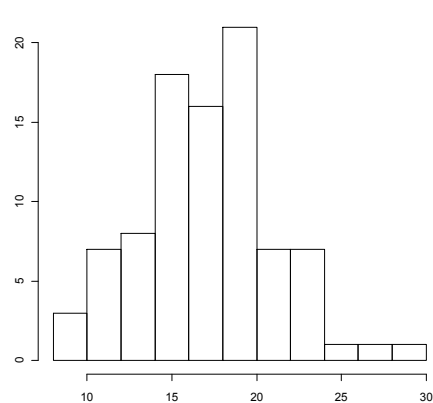
	<i>g</i>	Speed	Immediate	Delayed
<b>WAKING</b>	-.04(.09)	-.06(.01)	.11(.16)	.04(.12)
<b>EVENING</b>	.05(-.04)	.06(-.02)	-.03(.00)	-.03(-.03)
<b>Diurnal Slope</b>	-.02(-.13)	.02(-.04)	-.18(-.19)	-.11(-.16)
<b>START</b>	<b>-.28*</b> (-.08)	<b>-.36**</b> (-.21*)	<b>-.34**</b> (-.20 <sup>†</sup> )	<b>-.33</b> (-.17)
<b>END</b>	<b>-.36**</b> (-.16)	<b>-.35**</b> (-.21*)	<b>-.28*</b> (-.14)	<b>-.30**</b> (-.15)
<b>Reactive Slope</b>	.02(-.04)	.08(.04)	.15(.13)	.11(.07)

\*p<.05, \*\*p<.01, <sup>†</sup> trend (.08<p>.05). Cognitive measures controlled for peak IQ (National Adult Reading Test) are shown in parentheses. Significant associations are shown in bold face.

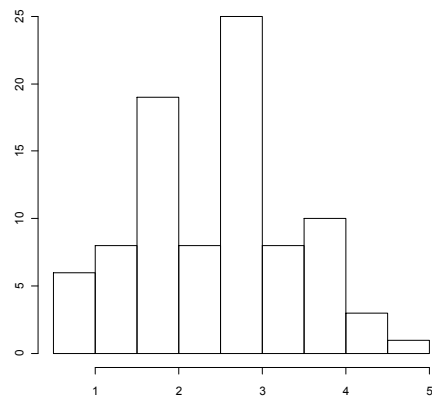


**Appendix H: Histograms of Variables**

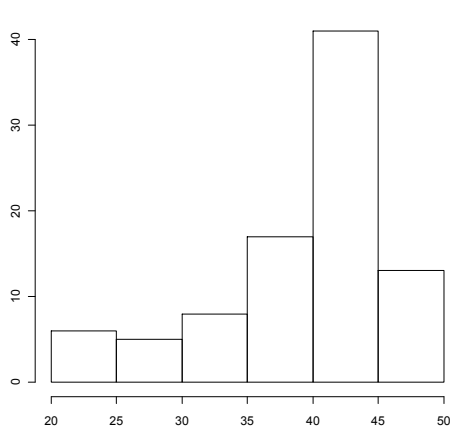
**D-KEFS Tower:**



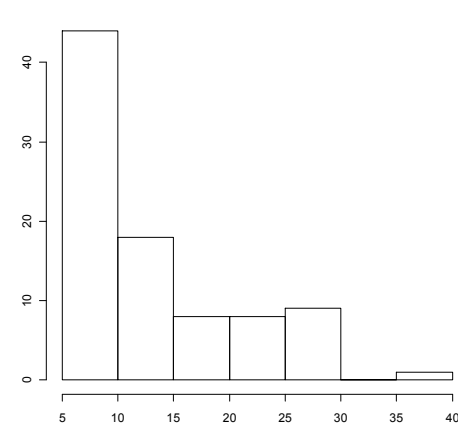
**SOPT Mean repetitions:**



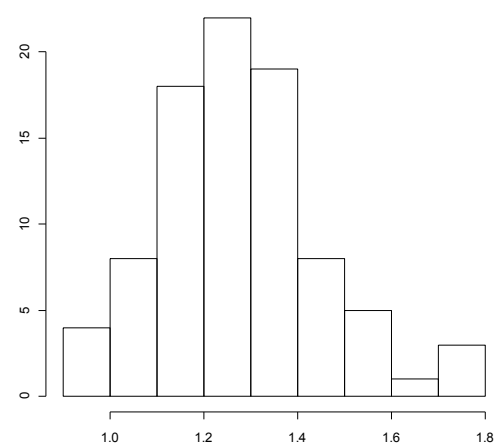
**Faux Pas Test:**



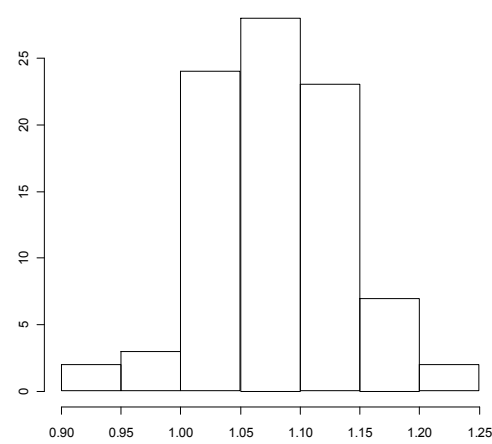
**Reversal Learning Total Errors :**



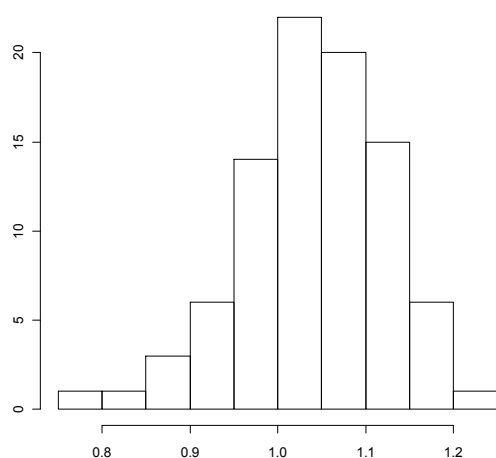
**Simon Task – Post-Error Slowing**



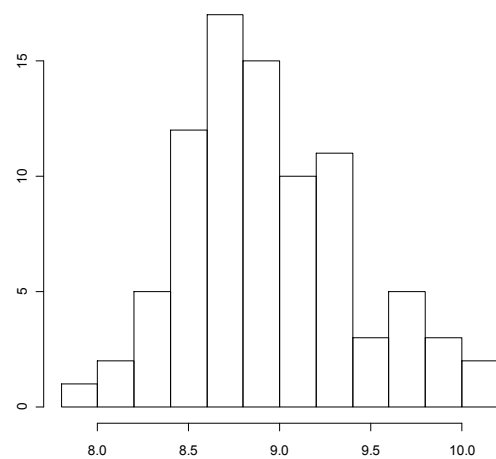
**Simon Task – Simon Effect**



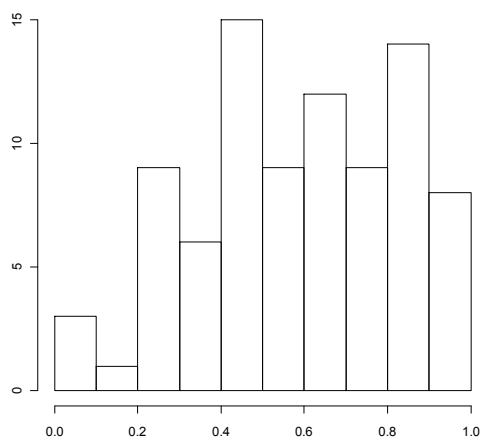
**Simon Task – Simon Effect by direction**



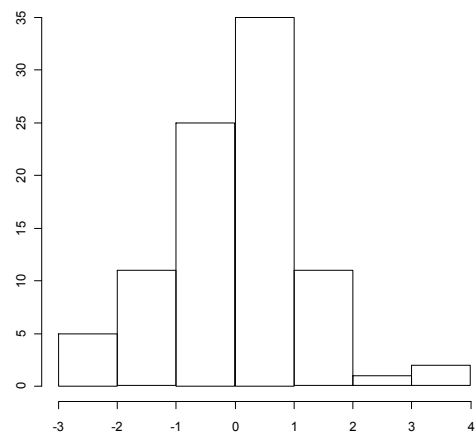
**Dilemmas Task – log mean RT**



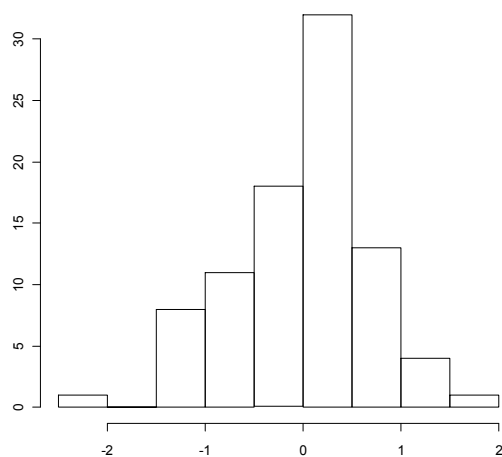
**Dilemmas Task - % Endorsement**



***g***



**gspeed~g residuals**



**gmemory~g residuals**

