Goal-directed Behaviour & Apathy in Parkinson's Disease

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Abstract:

Apathy has been identified as a highly-prevalent symptom of Parkinson's disease (PD) that has a significant effect upon quality of life, even when the motor symptoms of the disease are taken into account. An accumulation of evidence has lead to a proposal that apathy be divided into 3 distinct sub-types: 'emotional-affective', 'cognitive' and 'auto-activation', each of which result in apathy through distinct mechanisms involving different brain regions. The mechanisms through with apathy in PD occurs are unknown, and the importance of understanding this apathetic profile has implications for clinical treatment. Taking the view that apathy is an observable syndrome constituting a quantifiable reduction in goal-directed behaviour (GDB), the aim of this study was to assess which of the underlying mechanisms contributes to apathy in Parkinson's disease. The extant data suggested that patients would exhibit a profile consistent with cognitive, rather than emotional-affective or auto-activation apathy. Performance of 8 PD patients were compared to those of age and education matched controls on a test of goal-directed behaviour, and a series of tasks that tap different areas of cognition whose dysfunction is thought to underlie the distinct apathetic sub-types. Although the results reflected a significant reduction in GDB and a profile of performance consonant with cognitive apathy, the data also suggested that apathy in PD may have a multifactorial aetiology, with additional contributions to GDB reduction from emotional-affective and auto-activation mechanisms. The implications of these findings are discussed along with limitations of the study and avenues for further research.

Table of Contents

Discussion

References

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Introduction

1 Parkinson's Disease

Although descriptions of the collective symptoms of Parkinson's disease (PD) exist from as early as the 12th century BC (by Averroës, also known as Ibn Rushd) (Martin-Araguz, Bustamante-Martinez, Fernandez-Armayor, Ajo & Moreno-Martinez, 2002), the first modern identification of the condition was made by the physician James Parkinson, who named it 'shaking palsy' or 'Paralysis Agitans' after the abnormal gait and tremor he observed in his patients (Parkinson, 1817). In the UK there are thought to be around 200 individuals with PD for every 100,000 of the population, with men slightly more likely than women to develop the disease (Parkinson's Disease Society, 2009). However, there is evidence to suggest that these demographics vary globally as a function of ethnicity and country (Li *et al.*, 1985; Schoenberg *et al*., 1988; Milanov, Kmetski, Lyons & Koller, 2000; Van Den Eeden *et al.*, 2003; McInerney-Leo, Gwinn-Hardy & Nussbaum, 2004). The onset of symptoms typically occurs after the age of 50, although people of any age can be affected, and the average life-expectancy can be reduced by as much as 10 years[1] compared to the general population (Ishihara, Cheesbrough, Brayne & Schrag, 2007).

Parkinson's disease involves the progressive degeneration of brain cells that produce dopamine, a neurotransmitter that aids the modulation of balance and motor control. The precise pathogenesis of PD itself is still the subject of investigation, with potential causes being identified in factors including exposure to toxins such as pesticides and heavy metals, the illicit use of the drug MPTP (Davis et al., 1979; Elbaz & Tranchant, 2007) or in some cases due to genetic factors (e.g. Golbe *et al.,* 1996). However, the majority of cases are idiopathic (non-genetic; ~85%), which suggests a multifactorial etiology for PD that draws on both environmental and genetic factors (De Lau & Breteler, 2006).

[1] For onset 40-64yrs, life expectancy reduces on average from 31 years in the general population to 21 years in the UK.

The principal symptoms in modern diagnostics are considered to involve movement problems such as uncontrollable rhythmic shaking at rest (tremor), muscular stiffness (rigidity), difficulty initiating movement (akinesia) and abnormal gait (Kolb & Wishaw, 1996). The gradual decline in patients' ability to control their movements can also lead to problems with writing (agraphia), bladder control, breathing, swallowing, and control of the facial muscles, which can lead to a loss of facial expression and poor speech articulation (dysarthria)(Stirling & Elliot, 2008). All of these additional symptoms can vary not only from patient to patient, but also on a daily basis within the same individual and have an equally pervasive impact on quality of life (Martinez-Martin, 1998). No cures or preventative treatments have yet been developed, and current medication can only provide relief from the motor symptoms, but this therapy is ultimately unable to affect the progressive neurodegeneration of the disease. The development of treatments to halt the progression of PD through neuroprotective agents has been hindered to some extent by the limited understanding of the catalyst for dopaminergic cell death, or the mechanisms by which such degeneration occurs.

Although Dr. Parkinson characterised the disease primarily as one of disordered movement, with the "*senses and intellects being uninjured"* (Parkinson, 1817/2002, p.223), a large body of evidence now reports the presence of accompanying non-motor symptoms that also have a significant impact upon quality of life. Depression is a common feature of PD in as many as 70% of cases (Burn, 2002) and sleep disturbance may occur in as many as 80% of patients (Tandberg, Larsen & Karlsen, 1999). Erectile dysfunction, a loss of libido and a decreased sense of smell are also well-known aspects of PD (Bronner, Royter, Korcczyn & Giladi, 2004). In addition, some types of cognitive dysfunction are experienced in PD, which are often termed 'executive functions'. These include problems with working memory (Gabrieli, Singh, Stebbins & Goetz, 1996; Beato *et al.*, 2008), procedural learning (Koenig, Thomas-Anterion & Laurent, 1999) and attentional shifting (Moustafa, Sherman & Frank, 2008), as well as deficits in 'theory of mind' processing (Peron *et al.*, 2009) which requires an understanding of the mental states of others. Apathy, traditionally characterised as a loss of interest, motivation, or reduced self-

generated behaviour, is another symptom often associated with PD, and affects quality of life through a reduction in the frequency of self-generated behaviours. Prevalence estimates vary dependant upon the criteria and scales used, (16.5%, Czernecki *et al.*, 2002; 30%, Starkstein *et al.,* 1992; 42%, Pluck and Brown, 2002), but apathy has a considerable negative effect upon quality of life in PD, even when the motor symptoms are taken into account (McKinlay *et al.*, 2008).

Whilst the motor symptoms of this disease are well-researched, comparatively less is known about the cognitive and behavioural disturbances of this disease. The underlying mechanisms involved in many of these behavioural dysfunctions are not well understood, particularly so with apathy, and research into the area has been complicated by the high prevalence of symptom co-morbidity. For example, Shulman, Taback, Bean & Weiner (2001) found that 59% of PD patients had 2 or more cognitive or behavioural symptoms, with a quarter having four or more. This presents a methodological challenge for researchers, as the additional behavioural symptoms associated with the co-morbidity of dementia and depression make it difficult to differentiate symptoms and aetiology. Consequently, when studying cognitive symptoms such as apathy, which can also be a feature of both dementia and depression (Pluck & Brown, 2002), non-demented and non-depressed patients must be sought if anything meaningful can be clearly inferred from the resultant data.

Although it is now becoming clear that apathy can be dissociated from both dementia and depression (Kirsch-Darrow, 2006), strong links appear to exist between various types of cognitive dysfunction and different apathetic characteristics (Czernecki *et al.,*, 2002; Zgaljardic *et al.,* 2006). In attempting to examine this relationship in greater detail, further research will provide insight into the particular apathetic syndrome present in PD and the underlying systems that are disrupted, which in turn, will have implications for future treatment of this facet of the disease. This is particularly relevant given that the non-motor symptoms of PD remain frequently overlooked by clinicians, and remain untreated for the most part (Chaudhuri & Schapira, 2009) in spite of the substantial ramifications for normal daily living. The incomplete understanding and lack of treatment for the

non-motor dysfunctions such as apathy in PD represents a key challenge for future research and therapeutic practice, and consideration of the functional, neurophysiological and neurochemical organisation and connectivity of the brain in PD must be central to any attempt to meet this challenge.

2 The pathophysiology and pathogenesis of Parkinson's Disease

The pathophysiological basis for these symptoms is a progressive degeneration of the cells in the substantia nigra pars compacta (SNpc), the ventral tegmental area (VTA) and the hypothalamus, all of which synthesise the neurotransmitter dopamine (DA). This leads to a global reduction in DA availability, although a large body of evidence indicates a secondary decrease in the activity of other neurotransmitters such as noradrenaline (Scatton, Javoy-Agid, Rououier & Agid, 1983), serotonin (Reisine, Fields & Yamamora, 1977) and GABA (Lloyd, Shemen & Hornykiewicz, 1983). All behaviour relies upon the fluctuating equilibrium of neurotransmitters over the sum of activated brain regions, and various brain regions use different combinations of transmitters in different ways. It is this finely-tuned balancing act which allows for the precise modulation of normal functioning, as various neurotransmitters exert both excitatory and inhibitory effects on neural signalling. The introduction of instability into the system therefore has behavioural consequences, as is the case with the DA imbalance in PD.

Each of the primary degenerating regions affected in PD contain different ratios of DA-producing (melanized) cells, with the SNpc comprised of 84-94% compared to the VTA at 50% (Rao, 2007) and the hypothalamus at 30-40% (Sandyk, Iacono & Bamford, 1987). Each region has extensive projections to other brain regions which form four major dopaminergic pathways: nigrostriatal, mesocortical, mesolimbic and tuberoinfundibular (see Figure 1). The progression of the disease typically begins with the degeneration of the cells in the SNpc and it is not until later in the course of the disease that the melanized cells of the VTA begin to degenerate

(Damier, Hirsch, Agid & Graybiel, 1999). Each pathway innervates different territories and makes distinct contributions to brain function and thus, an examination of the implicated regions and their functional roles can provide some insight into the symptoms present in PD.

3 Motor control and the nigrostriatal pathway

The most dramatic reduction of melanized cells occurs in the SNpc, whose complex and reciprocal interconnectivity with other brain regions is severely disrupted, and this causes the prominent disturbances in movement control found in PD. In the healthy brain, the dopaminergic nigrostriatal pathway extends from the SNpc to the striatum (which comprises the caudate and putamen), and from there, the putamen acts in a modulatory capacity in two ways to help govern output to the pre-motor cortex (Kolb & Wishaw, 1996). The direct pathway connects the striatum to the substantia nigra pars reticulata whose efferent connections to the motor thalamus (which has outputs to the pre-motor cortex) are excitatory. On the other hand, the indirect pathway leads from the striatum to the internal segment of the globus pallidus and tends to inhibit cortical output. The coordination of both cortico-striatal pathways in concert facilitates the control of action sequences, and its normal functioning relies upon the integrity of the nigrostriatal pathway (Hardman *et al.*, 1996). Thus, when the DA availability falls with the SNpc degeneration of PD, the neurochemical equilibrium is disturbed and functioning of this motor circuit is compromised, by a disruption in the equilibrium of excitation and inhibition, causing increased difficulty in effortful motor control.

Although current knowledge of the functioning and connectivity of the basal ganglia is incomplete, existing models of how DA contributes to motor control has aided the development of drug therapies and other treatments that can alleviate some symptoms of PD. The disease is most commonly treated with forms of L-Dopa, a precursor to DA, which can be converted into the active neurotransmitter by the

surviving melanized cells in the brain[2]. In order to ensure that the drug is not broken down in the gut (and to minimise severe side-effects), L-Dopa preparations often include enzyme inhibitors such as carbidopa and beserazide (which inhibit the actions of the enzyme dopa decarboxylase), or the enzyme inhibitor entacapone (which inhibits catechol-O-methyl transferase; COMT) (Stirling & Elliot, 2008). These act to increase the amount of L-Dopa that reaches the brain without being broken down, thus minimising the required dosage to treat symptoms.

In addition to L-Dopa medication, dopamine receptor agonists such as pramipexole or repinerole are also sometimes prescribed. These compounds have a high affinity for dopamine receptors, and help to improve motor symptoms by stimulating the DA receptors in the striatum, which work to improve neural signalling. The dosage and combination of agents used to treat PD is not a precise science, and the combination that works for one patient may be entirely inappropriate for another. Ascertaining the correct course of medication is often a protracted and unpleasant, and is often an unpleasant one. Symptoms arising from complications in the combination of dopaminergic drugs were highlighted as one of the top three major factors contributing to quality of life in PD patients according to recent research (Gomez-Esteban *et al.*, 2007). A relatively new alternative and/or complementary procedure is known as Deep brain stimulation (DBS). This involves implanting fine electrodes into the subthalamic nucleus, which receives a (battery-powered) stimulation in order to reduce its output, improving the processing of afferent motor activity (Freund, 2005).

Although these therapies have proven successful in attenuating the motor symptoms of PD, it remains relatively unclear how the non-motor symptoms are affected by dopatherapy or stimulation. With the increased acceptance of a relationship between PD and behavioural, emotional and cognitive problems such as apathy, research to examine the nature of these deficits in greater detail will be

[2] Dopamine itself, when ingested, is unable to cross the blood-brain barrier, and is largely broken down by the body's enzymes. It also leads to unpleasant side-effects such as vomiting, hallucinations and postural hypotension (dizziness when standing up).

crucial to the development of effective targeted therapies for this separate set of symptoms.

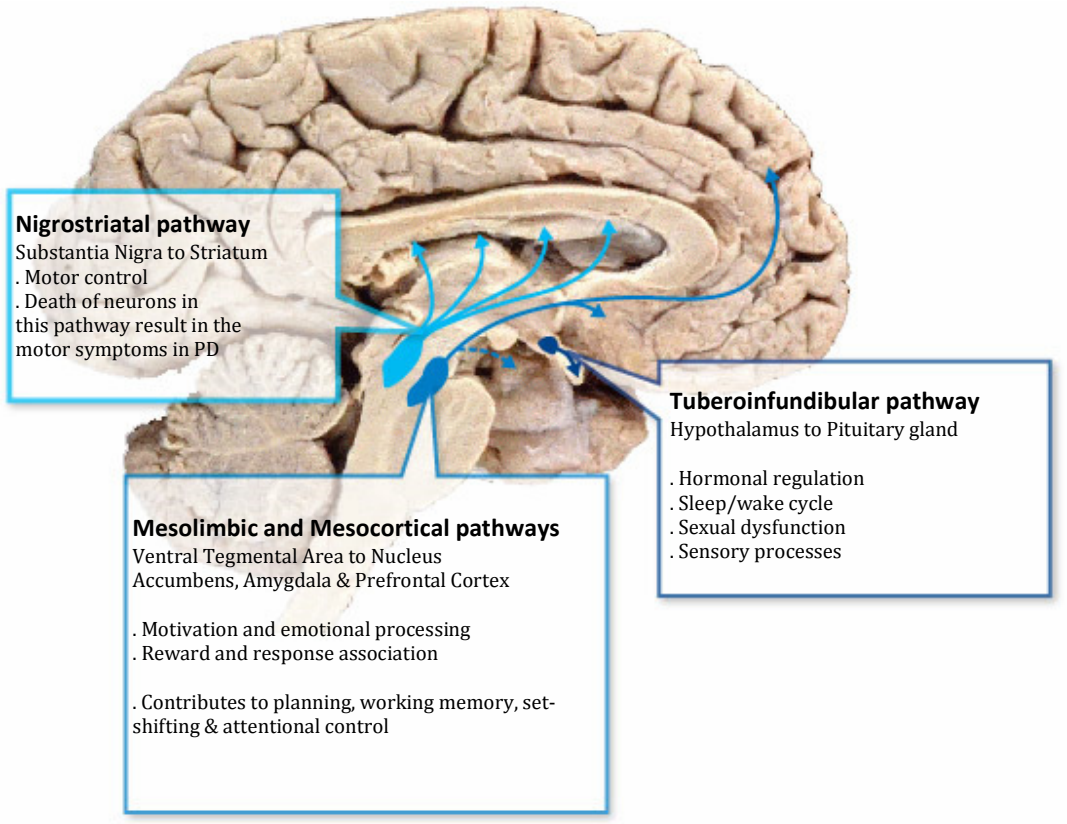


Figure 1. The dopaminergic pathways. Adapted from the Genetic Science Learning Centre (2009).

4 Autonomic dysfunction and the tuberoinfundibular pathway

The tuberoinfundibular pathway, which runs from the hypothalamus to the pituitary gland, is thought to be one of the key centres of regulation for many of the non-motor symptoms found in PD. Dopamine dysfunction in the hypothalamus has been reported in a recent PET study which demonstrated diminished ^{11}C-raclopride binding in the hypothalamus of PD patients in comparison to controls (Politis,

Piccini, Pavese & Brooks, 2008)[3]. This functional axis is known to have a key role in the sleep-wake cycle, and general hormonal and homeostatic balance (for a review, see Sandyk, Iacono & Bamford, 1987), and also receives inputs from the olfactory cortex. Thus, the prevalence of sleep disturbances, poor sense of smell, defects in thermoregulation, hormone imbalance, bladder disturbances and sexual dysfunction in PD may be ascribed to local melanized cell degeneration along this pathway (Chaudhuri, 2009).

However, unlike the relatively effective medication of the motor symptoms through dopatherapy, very few of the non-motor autonomic symptoms respond positively to conventional medication (Chaudhuri & Schapira, 2009), and even when this is the case, conflicts in dosage between symptoms can cause complications. For example, the use of dopaminergic drugs appears to have a variable effect on somnolence (drowsiness) dependent upon the dosage, with low doses causing increased somnolence and higher doses tending to promote wakefulness (Rye & Jankovic, 2002). Indeed, the inefficacy of dopatherapy is not restricted to this domain of non-motor symptoms, but appears to extend to the more cognitive domain of impairments as well.

5 Cognitive dysfunction and the mesolimbic & mesocortical pathways

The types of cognitive dysfunction exhibited in PD can be broadly divided into two categories (Rowe *et al.*, 2008). The first can be termed 'executive' and includes functions of planning, attentional control, working memory and set-shifting, whilst the second can be termed 'emotional' and involves the management of risk and reward-based behavioural control and emotional processing. Both types are thought to be mediated by distinct striato-thalmo-cortical circuits (Alexander & Crutcher, 1990), and both require normally-functioning dopaminergic innervation (Cools, 2006).

The mesolimbic pathway originates from the VTA, and innervates the limbic striatum, including the caudate nucleus, putamen and nucleus accumbens. In turn,

[3] ^{11}C-raclopride is a radioisotope that binds to the dopmainergic receptor types D_2 and D_3, enabling the imaging of receptor availability in a region of interest through Positron Emission Tomography (PET).

these regions modulate the function of various limbic structures such as the amygdala and the ventromedial/orbitofrontal cortex. This area of the frontal lobe contains the secondary and tertiary olfactory cortical areas which process the identity and reward value of odours (Rolls & Bayliss, 1994), which may also account for the decrease in olfactory acuity in PD. In addition, a decrement in the level of DA in this pathway is commonly thought to be a contributing factor to the high levels of depression in PD (Remy, Doder, Lees, Turjanski & Brooks, 2005), which is up to twice as high as for other patients with equivalent disability (Rodin & Voshart, 1986).

Furthermore, this pathway has been linked with the ability to process emotional and motivational information such as reward salience for anticipated stimuli (Brown & Pluck, 2000), although it remains unclear whether or not this area of cognition is impaired in PD. Some reports suggest specific deficits of recognition of emotion in faces such as disgust (Sprengelmeyer, Rausch, Eysel & Przuntek, 1998) and anger (Lawrence, Goerendt & Brooks, 2007), whereas other studies suggest a more general problem with emotional recognition and processing (Kan, Kawamura, Hasegawa, Mochizuki & Nakamura, 2002), or fail to replicate these findings altogether (e.g. Adolphs, Schul & Tranel, 1998; Pell & Leonard, 2005). In terms of processing motivational value, the orbitofrontal cortex has been implicated in this process due to a consistent reduction in sensitivity to reward after lesions to this area (Bechara, Damasio & Damasio, 2000; Rolls, Hornak, Wade & McGrath, 1994). The dysfunction of this region in PD is corroborated by some studies which suggest that patients appear less able than controls to evaluate behavioural risk on measures such as the Iowa Gambling Task (Kobayakawa, Koyama, Mimura & Kawamura, 2008). On the other hand, Rowe and colleagues (2008) reported that PD patients both on and off medication exhibited no deficits on a modified version of the AX-CPT task, (which also requires the unimpaired processing of anticipated reward), and any impairments of decision making based on reward and emotional salience may well be unaffected by dopatherapy (Czernecki *et al*., 2002).

The mesocortical pathway also originates from the VTA, but projects to the prefrontal cortex (Sesack & Carr, 2002), and the operation of the dorsolateral

prefrontal cortex (DLPFC) in particular is thought be sensitive to the functioning of this dopaminergic innervation. For example, Scatton, Rououier, Javoy-Agid and Agid (1982) demonstrated that Brodmann's area 9 (which is a constituent of the DLPFC) exhibits a reduction in DA levels in PD, and is also indirectly affected by secondary mesolimbic DA reductions[4]. The DLPFC has been widely implicated as the centre for 'executive' functioning and altered DA availability in Parkinson's disease has been shown to impair functions such as the inhibition of irrelevant stimuli and updating information into working memory (WM) (Moustafa, Sherman & Frank, 2008), elaboration of self-generated behaviour (Taylor, Saint-Cyr & Lang, 1986), set-shifting, and planning (Dubois & Pillon, 1997).

6 Defining apathy

Apathy is one of the most common non-motor symptoms associated with PD, with some reports of prevalence in up to 42% of patients (Zgaljardic *et al.*, 2004). Traditionally characterised as a loss of motivation or lack of interest, a flattening of affect (Marin, 1991, 1996) or an absence of will (Berrios & Gili, 1995), apathy has been shown to impact severely on quality of life (McKinlay *et al.,* 2008). Often considered a symptom of depression and dementia, it has recently been suggested that apathy is a syndrome in its own right, and has been found in the absence of both, suggesting a clear dissociation (Kirsch-Darrow, 2006; Brown & Pluck, 2000).

Nevertheless, there remains lack of a standardised criteria with which to classify apathy, reflected in the variety of definitions, scales and methods of assessment available (Leentjens *et al.,* 2008). Such a lack of consensus has undoubtedly hindered our understanding of the underlying mechanisms at play in apathy, due in no small part to the difficulty in quantifying *motivation* or *will,* which is seen as the core process behind apathy as characterised by Marin (1991, 1996) and Berrios and Gili (1995). As Levy and Dubois (2006) observe, *motivation* is unsuitable to represent a mechanism underlying apathy because, "*it is a projective psychological interpretation of a given behavioural state*" (p.916). In fact, the very

[4] The anterodorsal portion of the caudate nucleus is part of the mesolimbic pathway but has extensive connections to the DLPCF (Rosvold, 1972).

meaning of apathy (from the Greek, meaning *without passion)* makes allusions to a state that is not directly measurable, and therefore lacks precision.

Consequently, instead of attempting to measure *motivation* as such, only observations of the quantifiable 'behavioural state' should be at the heart of any attempt to classify apathy and its principal mechanisms, as this is independent of interpretation (Pluck & Brown, 2002). From this perspective then, apathy can be characterised as an observable and quantifiable reduction in self-generated behaviours when compared to a previous state, which arises from a pathology of one or more of the systems that produce and control voluntary action, or goal-directed behaviour (GDB) (Levy & Dubois, 2006). This latter term is used to refer to a wide range of intentional actions which can be as simple as reaching to drink from a glass of water, or as complex as going shopping for a list of groceries.

Even the production of the simplest GDB is a very complex undertaking, in spite of its apparent effortlessness, and relies on a numerous stages such as processing the emotional and motivational context of a given action, advanced planning, execution, monitoring and flexibility to accommodate changing situations into the current behaviour, as well as the need to filter out irrelevant information whilst constantly bearing the final goal in mind (Brown & Pluck, 2000; see Figure 2).

Due to our reliance upon such a range of processes for the successful production of GDB, it is likely that the whole system may be disrupted (causing apathy) due to dysfunction in any one of these numerous/implicated/requisite systems. For example, a dysfunction in the system controlling our ability to asses the value of a given action by weighing up both internal and external determinants would result in apathy characterised by an inability to mediate behaviour by its social context and motivational value. Likewise, damage to systems in charge of planning, and at the initiation-execution stage, would severely impair the effective completion of GDB would have a similar effect on the overall outcome (apathy), but each would do so through a separate and distinct dysfunction, resulting in variations of the *type* of GDB affected with the underlying mechanism at fault (Brown & Pluck, 2002).

This makes a strong case for the introduction of terms for three separate apathetic subtypes: *Auto-Activation*, *Emotional-Affective* and *Cognitive* (Stuss *et al.,* 2000; Levy & Dubois, 2006). The advantage of identifying apathy in higher fidelity allows each to make reference not only to the behavioural state itself, but also the underlying mechanism at fault, and has implications for therapeutic and clinical intervention.

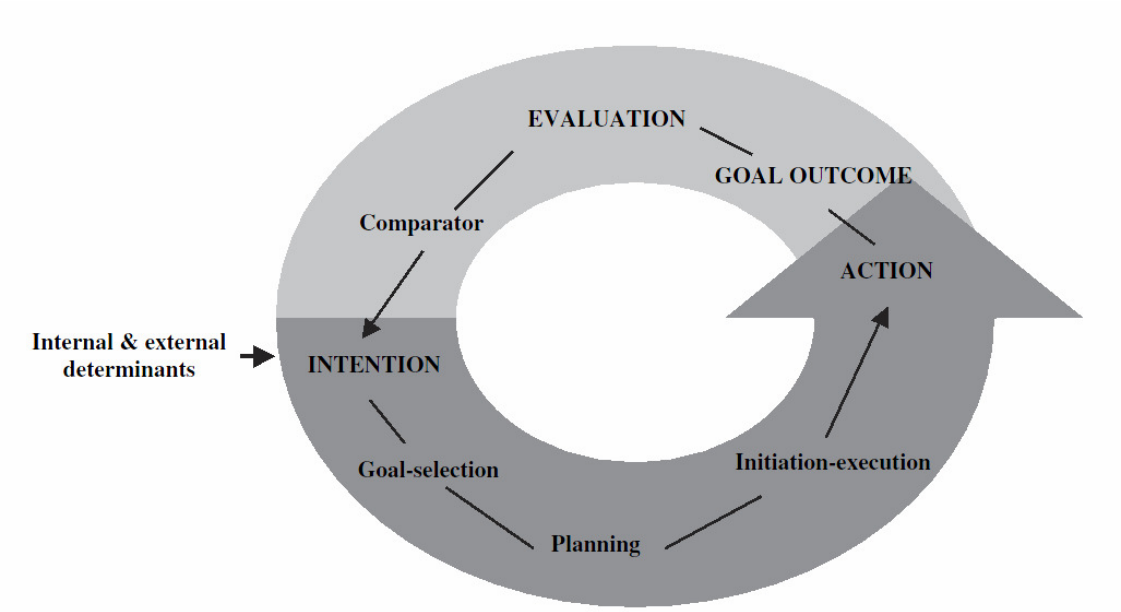


Figure 2. The processes involved in goal-directed behaviour. Levy & Dubois (2006), adapted from Brown & Pluck (2000).

7 The neural correlates of apathy

Knowledge from the pathology of disease and brain injuries that leads to states of apathy can be used to inform cognitive models of GDB and can also lead to a better understanding of the neural instantiations of such systems. This, in turn, can improve knowledge of the type of apathy a certain clinical population may experience (depending upon the brain regions affected), the mechanisms underlying this change in behaviour, and ultimately to a more informed selection of effective therapies and treatments.

It is likely that some of the key systems involved in GDB map onto various permutations of the prefrontal cortex (PFC) – basal ganglia (BG) functional axis. This is supported by the presence of apathy after direct lesions to either the PFC or

various structures of the BG. For example, it is well established that frontal lobe damage results in diminished self-generated behaviours (Stuss & Benson, 1986; Eslinger & Damasio, 1985; for a review, see Stuss, Gow & Heatherington, 1992) and poorer performance on basic neuropsychological tests such as verbal fluency (Masdeu & Shewmon, 1980). General PFC lesions in animals have been shown to result in the blunting of exploratory behaviour and attentional orienting to novel stimuli (Jacobsen, 1936; Mesulam, 1986), whilst some early lesion studies implicated the frontal lobes as having an inhibitory effect, or control over behaviour (Lhermitte, 1983), guiding "*the orienting basis of intellectual activity and the ability to programme that activity"* (Luria & Tsvetkova, 1967, p.6). Likewise, apathy was the most common behavioural disorder in a study of 240 patients following BG stroke (Bhatia & Marsden, 1994), and yields a stark reduction in all types of spontaneous self-generated action (Alexander, Naeser & Palumbo, 1987). Furthermore, apathy is commonly experienced by patients with neurodegenerative diseases that affect the BG, such as progressive supranuclear palsy (PSP) (Aarsland, Litvan & Larsen, 2001; Litvan *et al*., 1998), Huntington's disease (Hamilton *et al.,* 2003) and Parkinson's disease (PD) (Aarsland *et al*., 2001; Pluck & Brown, 2002; Starkstein *et al.,* 1992).

Crucially, the frontal lobes are either directly involved in the vast majority of neurological aetiologies of apathy, or form part of a functional circuit with the BG or other affected non-frontal area. For example, a similar pattern of neural activation and behavioural deficits were found when *either* the PFC or BG of the monkey were lesioned (Battig, Rosvold & Mishkin, 1960; Levy, Friedman, Davachi & Goldman-Rakic*,* 1997), and lesions to the dorsomedial thalamus alone have been shown to elicit hypometabolism in the frontal lobes of a patient exhibiting apathetic behaviour (SPECT – McGilchrist, Goldstein, Jadresic & Fenwick, 1993). Such data have resulted in the proposed organisation of the striato-thalamo-cortical circuits (Alexander *et al*., 1987), in which regions of the PFC and BG play significant roles.

This conceptualisation suggests that each neural structure makes distinct functional contributions to the overall operation of the circuit, which is in line with evidence that the *type* of apathy exhibited is dependant upon the part of the circuit that is damaged. Evidence for this, discussed below, forms the basis for a more

accurate classification of apathy in the form of three distinct apathetic sub-types: Emotional/Affective, Cognitive, and Auto-activation (Stuss, 2000; Levy & Dubois, 2006), in which it is proposed that each sub-type has different apathetic characteristics (and underlying mechanisms) dependant upon the foci of the lesion within the PFC-BG functional axis.

8 Apathetic sub-types

Emotional-Affective Apathy Although the ability to process emotional and affective information is not immediately identifiable with the production of GDB, humans must be able to mediate internally-generated behaviours by social context and motivational value (e.g. Stuss, 2001). A disruption in this ability can lead to apathy through problems with incorporating emotional information into the current behavioural schema and through processing the perceived benefit and emotional salience of future actions (Eslinger & Damasio, 1985). As previously mentioned, these functions are strongly linked to the ventromedial prefrontal cortex (VMPFC), with lesions to this area resulting in inconsistencies in simple preference judgement tasks (Fellows, 2007), and neurons selectively encoding outcome expectancy (Furuyashiki & Gallagher, 2007).

This has clear implications for the involvement of the VMPFC in behavioural control as a neural substrate of the goal outcome monitoring facet in Brown and Pluck's (2000) model. Indeed, the behavioural characteristics of this sub-type of apathy are manifest in decision-making difficulties in real life, impulsivity, a change in the types of stimuli perceived to be interesting, emotional blunting and decreased participation in areas of life considered to be emotional (Levy & Dubois, 2006). The presence and severity of this apathetic sub-type can be assessed by responses to questions regarding concern and emotional response in apathy scales, decreased reward sensitivity on reversal tasks and the ability to decode affective context (Levy & Dubois, 2006).

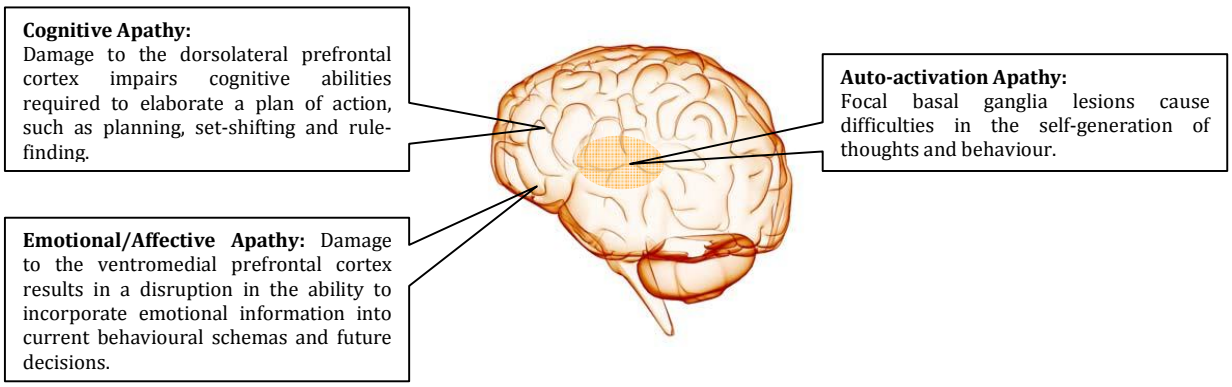


Figure 3. The 3 sub-types of apathy and their neural correlates. Adapted from Levy & Dubois (2006).

Auto-Activation Apathy is characterised by a severe poverty in spontaneous thought or action. Individuals exhibiting this type of apathy often report a mental emptiness, and may spend hours in the same place without taking any undertaking any self-generated behaviour, and yet this severe paucity of self-generated behaviour is in stark contrast to the relatively normal reactivity elicited in response to external stimuli (Levy & Dubois, 2006). This sub-type of apathy is most commonly observed after direct focal lesions to areas of the basal ganglia, and the connectivity and function of this area suggests that the reduction in GDB is induced by a loss of amplification or focalisation of BG output to elicit activation in the frontal lobes (Levy & Czernecki, 2007) and thus a failure to even being initiating the first stage of goal-directed behaviour (Brown & Pluck, 2000). The fact normal reactivity to external stimuli is a feature of this sub-type of apathy proves problematic for its assessment in lab-based neuropsychological testing, where the opportunity to observe periods of inactivity in the participant are rare. However, self-reporting offers one method by which measurement can be made, such as via responses to questions, "*Does someone have to tell you what to do each day?",* or, "*Do you need a push to get started on things?"* (Starkstein et al, 1992).

Cognitive Apathy refers to a quantitative reduction in GDB due to impairments in the cognitive processes required to plan and execute behaviour, such as set-shifting, working memory, rule-finding, the planning and maintenance of competing goals, and the generation of strategies (Levy & Dubois, 2006). Individuals with focal lesions in the DLPFC have specific problems with planning during the Greenwich Task (Burgess, Veitch, Costello and Shallice, 2000), and marked deficits on set-shifting tasks such as the Wisconsin Card Sorting Task (WCST; Stuss *et al.*, 2000) have given rise to the conception of the DLPFC as mediating more 'cognitive' processing. Set-shifting deficits have also been simulated in healthy participants during a Stroop task by using Transcranial Magnetic Stimulation on the right DLPFC (Vanderhasselt et al., 2007). In addition, work by Daffner and colleagues (2000) and Snyder & Chatterjee (2006) suggest this area has a role in sustaining interest in novelty over time and exogenous attentional orienting. It is therefore consonant with the assertion that disruption to the functioning of this area will also result in quantitatively reduced GDB *due to* a disruption in the ability to select one cognitive schema over another, or maintain that schema in mind over time.

Consequently, the types of cognitive impairment that may lead to this sub-type of apathy can be detected by poor performance on tasks such as the WCST or Brixton Spatial Anticipation Task (Burgess & Shallice, 1996) which require pattern-detection and set-shifting, the Tower of London task which requires the maintenance of sub-goals and planning) and a contrast between poor literal fluency and better categorical fluency(Masdeu & Shewmon, 1980; Dubois & Pillon, 1997; Zgaljardic *et al.*, 2006), reflecting a deficit in retrieval strategies (Levy & Dubois, 2006).

9 Aims and hypotheses

It is conceivable that apathy in PD could result from any, or a combination of the mechanisms discussed above, primarily because each of the apathetic sub-types relies upon brain circuits and regions whose normal functioning requires

unhindered dopaminergic innervation, and would all contribute to severe behavioural difficulties without the aid of dopatherapy. Each sub-type has a clear clinical profile and therefore a distinct set of implications for prognosis and treatment choice, making the need to identify the mechanisms at play in PD highly relevant, and yet to date, no attempts have been made to examine the relationship between specific mechanisms underlying apathy and GDB in PD.

The overlap between the brain regions implicated in each of these apathetic sub-types and the dopaminergic pathways that are known to be affected in PD suggest that any one or a combination of these sub-types may contribute to a reduction in GDB in PD: The nigrostriatal pathway innervates regions which, when damaged result in *Auto-Activaiton* apathy; the mesolimbic pathway appears to innervate the VMPFC, whose dysfunction results in *Emotional-Affective* apathy; and the mesocortical pathway projects to the DLPFC, the dysfunction of which contributes to *Cognitive* apathy. However, recent research focussing on non-demented PD patients who are normally medicated suggests that they are more severely impaired on tasks relating to the 'cognitive' rather than the 'emotional-affective' or 'auto-activation' domains of apathy (Czernecki *et al.*, 2002, Zgaljardic *et al.,* 2006). In addition, the anti-Parkinson medication is targeted at the mitigation of motor symptoms that arise from the dysfunction with the BG, suggesting that non-motor symptoms with BG aetiology may well also be positively affected. Furthermore, recent studies suggest that emotional processing in well-medicated PD patients is not impaired (Pell & Leonard, 2005). Therefore, it is likely that the largest contributor to the apathetic state (defined as a reduction in GDB) seen in PD is the cognitive subtype.

In summary, the aim of the current study is to characterise the apathetic profile in PD, making specific reference to the proposed underlying mechanisms. It is predicted that patients receiving their normal regimen of anti-Parkinson therapy will exhibit a quantitative reduction of GDB when compared to controls, and will show impaired performance on tests of executive ability rather than 'emotional-affective' or 'auto-activation'.

Methods

1 Participants

Eleven patients with Parkinson's disease (PD) who attended the NHS Outpatient Movement Disorders Clinic at the Western General Hospital in Edinburgh were recruited for the study. Overall inclusion criteria consisted of English as a first language, a score above cut off on both the ACE-R (82 or below) and HADS (8 or above), no history of other neurological problems or complications, and sight and hearing adequate to allow participants to complete all aspects of the test battery. Further inclusion criteria were idiopathic PD, well-managed motor symptoms that would not interfere with participation in written tests, and status as a returning (rather than newly-referred) attendee of the clinic. Of the 11 individuals recruited, 1 was excluded on the basis of a score above cut-off on the HADS, indicating a 'probable' presence of depression, and 2 more on the basis on invasive neurosurgery (to install deep brain stimulators; DBS) which may have had confounding effects on task performance. Eight non-demented and non-depressed PD patients were therefore included, and their disease severity (as assessed by the POPM) was between the first two stages of the disease symptomology.

The main demographic characteristics of both patient and control groups, along with clinical information for patients, are summarised in Table 1 for ease of reference.

Table 1. *Demographic characteristics of participants and patient clinical information*

	Patients		Controls	
	Mean	SD	Mean	SD
N	8	-	8	-
M:F	6:2	-	4:4	-
Age	70.25	5.39	70.25	5.7
Education	15.75	2.31	16.88	2.42
NART IQ	117.88	7.26	122.62	6
Age at onset	63.38	6.23	N/A	N/A
Disease duration	6.88	4.85	N/A	N/A
POPM	1.88	1.25	N/A	N/A

NOTE. M:F = Male to Female ratio. Age, education, age at onset and disease duration are calculated in years. Age at onset is the age at which diagnosis of PD was made, disease duration is the time since diagnosis. NART = National Adult Reading Test, POPM = Parkinsonism Progression, Onset and Mortality scale. N/A = not applicable.

All patients were tested whilst receiving their prescribed regime of dopamine replacement therapy (DRT), which varied by both type and dosage, as illustrated by Table 2**:** carbidopa + L-Dopa (Sinemet, n=3), carbidopa, L-Dopa and entacapone (Stalevo, n=2), or benserazide + L-Dopa (Madopar, n=1). Some patients were also taking dopamine receptor agonists Pramipexole (n=3) or Repinerole (n=1). Seven patients were also taking non-PD medication for various conditions, but none of the medications are known to have any significant effects on cognitive performance.

Table 2. *Details of anti-Parkinson medication in PD participants*

Patient	Pramipexole	Stalevo	Repinerole	Madopar	Sinemet
1	†	-	-	-	-
2	-	†	-	-	-
3	-	-	-	-	†
4	†	-	-	†	-
5	-	-	-	-	†
6	-	†	†	-	-
7	-	-	-	-	†
8	†	-	-	-	-

NOTE Sinemet includes Co-careldopa, Sinemet+ and Sinemet 275.

Eight control subjects were selected from the Psychology department Volunteer Participant Panel at the University of Edinburgh, and were matched to the patients by age and years of full-time education as closely as possible. The mean age of this group was the same as controls (ranging from 62-77yrs). A two sample t-test shows that the patient and control groups are ostensibly well-matched on age, $t(14) = 0$, $p = 1$, *ns,* and education, $t(14) = -0.951$, $p=.3578$, *ns.*

This study was approved by the University of Edinburgh PPLS Ethics Committee and the NHS Lothian Research and Ethics Committee.

2 Procedure and materials

Both patients and controls gave their written informed consent to take part in the study, after having been fully briefed and receiving satisfactory responses to any questions. General background information was then taken, including details of education, employment background, a check for any history of neurological problems, and details about diagnosis and medication regime was also taken where appropriate. For the PD group, testing took place at the patient's home in all cases, and was spread out over two consecutive mornings where possible, in order to avoid fatigue effects and other confounds that could contribute to fluctuations in performance (e.g. time medication taken). However, due to time constraints and the availability of the patients, 2 patients were tested on consecutive afternoons, and another 2 patients completed the battery in a single visit (with the inclusion of frequent breaks). Testing of controls took place in the Psychology department at the University of Edinburgh, and participants were given a modest honorarium to compensate them for their travel expenses.

The battery included tasks administered orally, paper and pencil tasks and a computer was required for both the Six Elements Task (SET) and the Yoni Task. In both instances, the computer-based tasks were run on a Toshiba Satellite Pro

(Windows OS) with a screen resolution of 1280 x 800 pixels for the on-screen stopwatch in the SET, and 800 x 600 pixels for the Yoni task.

Neuropsychological Assessment

Addenbrooke's Cognitive Examination – Revised (ACE-R; Mioshi, Dawson, Mitchell, Arnold & Hodges, 2006). The ACE-R is a brief but comprehensive screening tool that has been shown to have high sensitivity and specificity for the detection of cognitive dysfunction and the differential diagnosis of a wide range of dementias including Atypical Parkinsonian Syndromes and Dementia with Lewy Bodies (Lonie, Tierney & Ebmeier, 2009). It is suitable both in a test environment as well is in day-to-day clinical settings (Larner, 2007), and also has the advantage of yielding an MMSE score, which is a well used and understood measure of global cognitive function amongst health professionals. Administration typically takes around 16 minutes, and scoring relates to 5 domains that assess separate cognitive domains: *Attention & Orientation, Memory, Fluency, Language, and Visuospatial.* The lower cut-off score of 82 has a sensitivity of 84% and a specificity of 100%, and a score of 88 carries a sensitivity of 94% and specificity of 89%, although it is important to also examine individual domain scores in order to assess the pattern of impairment.

In addition, the ACE-R contains sections for both literal and categorical verbal fluency, whereby the participant is required to produce as many words beginning with the letter P (literal) or as many animals as possible (categorical) within one minute. These two tasks are differentially sensitive to the self-activation of cognitive strategies (a tendency towards poor literal and relatively spared categorical), and thus are sensitive to dysfunction thought to underlie the *Cognitive* apathetic subtype in the DLPFC, according to Levy & Dubois (2006). As a consequence, this data will be taken as an additional measure of the functioning underlying cognitive apathy.

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) is used as a general assessment of anxiety and depression, and although it is not designed to be an accurate diagnostic tool, the HADS has been shown to have acceptable reliability and validity for identifying potential psychiatric disorders (Herrmann, 1997). It takes the form of a self-report scale of a total of 14 items, split into 7 that relate to depression and 7 for anxiety. Each item can be scored on a Likert scale of 0-3, and the sub-scores for depression and anxiety are simply the sum of these ratings for each of the two sections ranging from 0-21. A higher score represents a greater level of depression or anxiety, where scores between 8 and 10 represent doubtful cases, and scores of 11 or higher are considered to be valid cases. One of the questions on the depression scale requires a response to the statement, *"I feel as if I am slowed down".* Although this item was designed to detect slowing associated with depression, this would also universally apply to PD patients, and as a result, the depression scale cut-off was raised by three points for the patient group in order to account for this.

The Parkinsonism Onset, Progression and Mortality scale (POPM; Hoehn & Yahr, 1967) was used as a gauge of disease severity. The scale requires no administration, but rather is based upon observation of the patient's current condition. These observations are then related to 5 stages as specified below in order to determine the patient's stage of disease:

Stage One

1. Signs and symptoms on one side only
2. Symptoms mild
3. Symptoms inconvenient but not disabling
4. Usually presents with tremor of one limb
5. Friends have noticed changes in posture, locomotion and facial expression

2. Stage Two
    1. Symptoms are bilateral
    2. Minimal disability
    3. Posture and gait affected

3. Stage Three
    1. Significant slowing of body movements
    2. Early impairment of equilibrium on walking or standing
    3. Generalized dysfunction that is moderately severe
4. Stage Four
    1. Severe symptoms
    2. Can still walk to a limited extent
    3. Rigidity and bradykinesia
    4. No longer able to live alone
    5. Tremor may be less than earlier stages
5. Stage Five
    1. Cachectic stage
    2. Invalidism complete
    3. Cannot stand or walk
    4. Requires constant nursing care

The National Adult Reading Test – Revised (NART; Nelson & Willison, 1991) is used as a short measure of pre-morbid IQ that involves reading a list of 50 irregularly- (non-phonetically) spelled words out loud. A score of 1 is given if the word is pronounced correctly, and the total score is used to give a pre-morbid IQ (PFSIQ) score via a standardised conversion table. The basis of this test is that as pronunciation relies more on previous knowledge than it does on an individual's current mental state, it has been shown to have a high correlation with pre-morbid IQ, and the ability to pronounce this type of word is robust to mild dementias (Strauss, Sherman & Spreen, 2006).

The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) is a brief assessment of intelligence that uses both verbal and non-verbal measures and is appropriate for administration up to an age of 89 years. The 2-subtest form (given in this instance) consists of *Vocabulary* and *Matrix Reasoning* scales and takes around 15 minutes to complete. For the *Vocabulary* section, participants are required to give the meanings of a series of words that become increasingly abstract with progression, and scores are given on the detail and accuracy of the description (based on example responses provided). The *Matrix Reasoning* subtest presents the subject with a series of grids displaying a pattern with one element missing, and the

object is to choose the most appropriate shape or design from one of 5 possible responses to complete this pattern. The scores for both elements were converted to age-scaled t-scores (using the standardised conversion tables provided) and then aggregated to form the full FSIQ-2 score. Stability coefficients for the WASI FSIQ-2 score are .88 for adults.

Executive Functioning

The Brixton Spatial Anticipation Task (BSAT; Burgess & Shallice, 1996) has been developed to be sensitive to executive dysfunction, by relying upon rule-detection and set-shifting. The tasks is presented in the form of a 56-page booklet, each of which show the same 2x5 array of discs whose positions are numbered from 1 to 10. On each page, one of the discs will be coloured blue (the rest are white), and this disc moves in sequence from position to position as the pages are turned. The object of the task is for the participant to predict the position of the disc on the next page, based on the current pattern, and thus accurate prediction requires rule-detection and set flexibility. During the task, the pattern changes without warning, and the participant is therefore required to adapt their prediction strategy to account for the newly-emergent pattern. The total number of incorrect predictions from the 56 trials is then converted into a scaled score from the table provided on the score sheet, where higher scaled scores reflect better performance.

The inability to identify rules and shift cognitive set has been heavily identified with lesions to the DLPFC (Stuss & Benson, 1984; Shallice, 1982) and also constitute specific characteristics of the cognitive apathetic-subtype (Levy & Dubois, 2006; Pluck & Brown, 2002). In addition, recent lesion data has linked abnormal performance on the BSAT with focal lesions to this area of the brain (Reverbi, Lavaroni, Gigli, Skrap & Shallice, 2005; Martinaud *et al.,* 2009), therefore performance on this test is one suitable gauge of cognitive impairment consistent with DLPFC dysfunction and cognitive apathy.

The Hayling Sentence Completion Task (HSCT; Burgess & Shallice, 1996) is another task designed to be sensitive to dysexecutive syndrome, and does so by

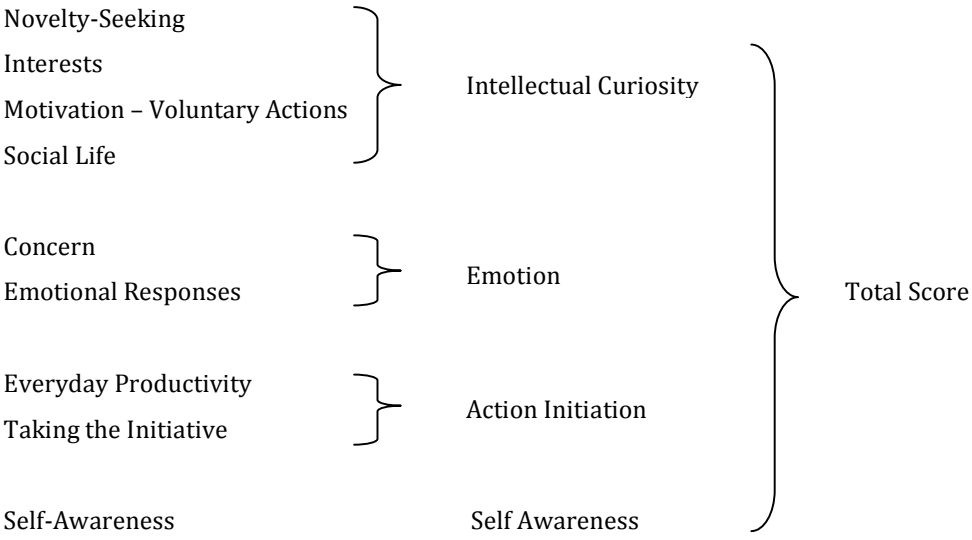
gauging the ability to initiate and also inhibit linguistically salient responses. The test comes in two parts, both of which require the participant to complete the missing word at the end of a sentence. In the first part, the response given must be appropriate to the sentence (e.g. Too many men are out of…[ppt. responds] *work*) and a response time is scored. The second half requires that the word produced be as unrelated to the sentence as possible (e.g. The captain wanted to stay with the sinking…[ppt. responds] *bulb*). In order to do this, the participant must inhibit the strongly salient response and search for an alternative, which yields a response time and score for relatedness. The three scores are then combined and converted into an overall score, where higher scores denote better performance.

WAIS – Digit Span subtest (WAIS-R; Wechsler, 1981) is used as a short measure of working memory performance. The tester reads out a series of random digits and the participant is required to repeat these out loud. The first part of the test begins with a string of 3 digits, and increases in length to a maximum of 9 digits with 2 trials for each length. In this part, the string must be repeated by the subject in the same order in which it was presented, and the trial is stopped when both trials for a particular length are incorrect. The second part of the test begins with a 2-digit-string, and the object is to repeat the numbers back in reverse order (the discontinue rule remains the same). Scores are based on the number of correct responses in both conditions, and are then converted by age to a final scaled score using a standard conversion table.

Experimental Measures

The Lille Apathy Rating Scale Revised (LARS; Sockeel et al., 2006) is a relatively new rating scale which is used to quantify various facets of apathy. The scale is administered in a structured interview, and covers 33 items relating to 9 domains, each having a possible total score of between -4 and +4. The scores for each item are aggregated into one of four factorial sub-scores which have been shown to measure distinct aspects of apathy: *Intellectual Curiosity, Emotion, Action Initiation* and *Self-Awareness* which are then summed to give a total score (see Figure 1).

Figure 1. *The domains and apathetic factors measured in the LARS*



If an individual scores between -36 and -22, they are classified as non-apathetic; scores between -21 and -17 reflect slight apathy, between -16 and -10 is moderate, and scores from -9 to +36 denote severe apathy. The LARS has been shown to have good reliability, specificity and sensitivity (Sockeel *et al., 2006)* which make it an excellent candidate for examining the characteristics and severity of apathy in Parkinson's disease.

In terms of its utility in testing the hypotheses in this study, Levy & Dubois (2006) observe that the emotional-affective apathetic sub-type can be assessed in apathy scales by questions such as, "*Does anything interest you?", "Are you concerned about your condition?"* and, *"Are you interested in new things?".* Although these example questions do not come from the LARS itself, but rather from Marin's (1990) Apathy Scale, Sockeel and colleagues (2006) developed the LARS based on a

combination of their clinical experience and the Apathy Scale. As a consequence, questions similar to the examples above have been expanded into the Intellectual Curiosity sub-score. Furthermore, the Emotion component of the LARS is designed to reflect emotional blunting and therefore would also be a measure sensitive to Emotional-Affective apathy.

In addition, responses to the Action Initiation score will be taken as the only available measure of Auto-Activation apathy. The absence of additional measures is due to the absence of opportunity to assessing this particular subtype in a test battery. It is characterised by a severe lack of self-generated behaviours in contrast to relatively normal responses to exogenous stimuli. Unfortunately, a test battery is entirely composed of measurements based on participant's responses to a given stimulus, and therefore self-report is the only way in which potential inactivity can be quantified in this setting.

The Yoni Task (Shamay-Tsoory & Aharon-Peretz, 2007) is a computer-based task which has demonstrated sensitivity to the functioning of the VMPFC. The task was programmed in E-Prime and is designed to assess the understanding of another's mental state based on visual (eye gaze or facial expression) and verbal cues. The tasks contains 98 trials which each contain a face in the centre of the screen and four coloured objects or faces in each of the four corners[5]. The goal is to select the most appropriate response from one of the four options (by pressing the key that corresponds to that corner) based upon the context as dictated by a sentence at the top left of the screen, in combination with the available visual cues. There were two primary conditions, each with two levels: *Affective* and *Cognitive*, with an additional control condition *Physical* which also had two levels, and was used to ensure that participants understood the task and were not merely responding to eye-gaze direction (see Figure 2). For all conditions, producing the correct response required either first order (for level1) or second order (for level 2) inference, so whilst only a level one inference would be required to ascertain which

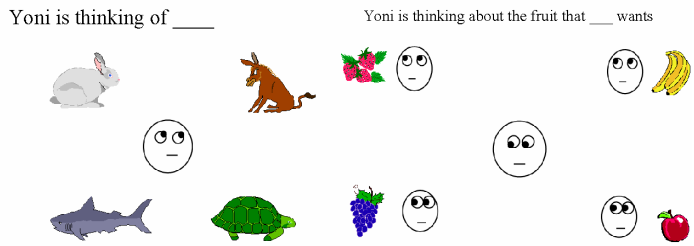
[5] In each trial, all four options are drawn from the same category (e.g. all fruit or all cartoon faces).

object Yoni loves/is thinking about/is close to, a second order inference would be required to understand Yoni's beliefs or emotions in relation to the beliefs or emotions of others. Additionally, the task included some trials where Yoni's eye gaze did not indicate the correct response, although the presence of other cues meant that the correct response could still be deduced. The effect of eye gaze on judgement accuracy and response time was examined as an ecologically valid distractor (rather than arrows, for example, which do not appear beside heads in day-to-day life); a potential social cue whose processing may be affected in some way.

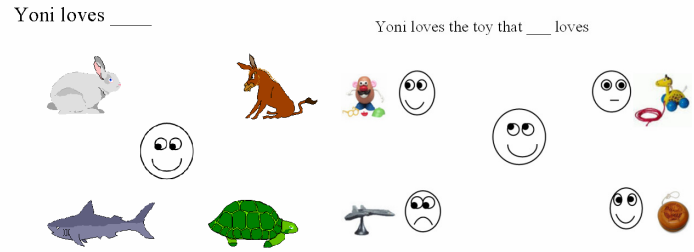
The task is scored in terms of accuracy (a percentage of correct responses) and the output also yields a reaction time, as processing difficulties with this type of task are manifest in a longer period required to make a decision, rather than purely in terms of accuracy.

Figure 2. *Examples of YONI task trials requiring 1st and 2nd order Cognitive, Affective and Physical judgements*

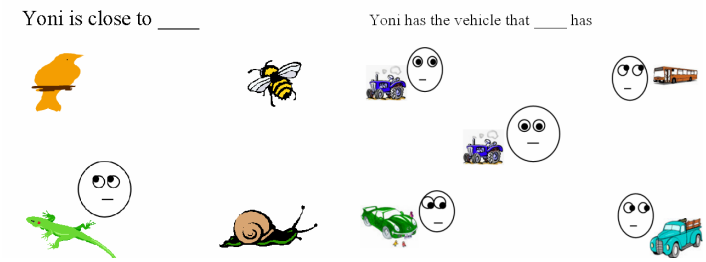
1st and 2nd Order Cognitive Trials



1st and 2nd Order Affective Trials



1st and 2nd Order Physical Trials



Patients with specific focal lesions to the VMPFC were shown to achieve significantly lower accuracy for the second-order *Affective* condition than healthy age-matched controls (Shamay-Tsoory & Aharon-Peretz, 2007), and therefore this test is appropriate for examining the functioning of a brain region known to contribute to the *Emotional-Affective* apathetic subtype.

The Six Elements subtest from the Behavioural Assessment of the Dysexecutive Syndrome (BADS; Wilson et al., 1996). The BADS was designed in order to ascertain the implications of cognitive dysfunction on day-to-day living, and the Six Elements Task (SET) was selected for its ecological validity and ability to quantitatively assess goal-directed behaviour. In the task, the subject is presented with three types of task, all of which have two parts: *Dictation* A & B, *Pictures* A & B, *Arithmetic Problems* A & B. The two dictation tasks require the participants to describe the best holiday they have ever had, and any memorable event in their life. The pictures are presented in two booklets marked A and B, and the object is simply to write down the names of as many pictures in order as possible. Similarly, Arithmetic A and B are booklets containing basic arithmetic problems, whose solutions are also to be written down on the blank sheet of paper provided. The subject is informed that they will not be able to complete everything within the allotted 10 minutes, but that they must attempt at least something from each of the 6 tasks within that time. In addition, they must remember not to attempt two tasks of the same type back-to-back. They are provided with a timer to help them plan their time. Scoring involves recording the order in which the tasks where attempted along with the time spent on each. In order to produce the Raw Score, the number of times that a rule was

broken is subtracted from the number of tasks attempted (out of a possible six). Finally, if the total time spent on any one task exceeds 271 seconds, an additional point is deducted, giving the Total Profile Score, with a maximum of 4 points. The performance of the Six Elements Task was recorded on video camera and later reviewed in order to ensure accurate scoring.

3 Statistical Analysis

The statistical analyses for this study were performed using R version 2.9.1 for MS Windows. Initial examination of the data was carried out using descriptive statistics (including skewness and kurtosis values), graphical plots (such as histograms and quantile-quantile plots) and the Shapiro-Wilks test for normality of distribution. Comparisons of performance between patients and controls on tests where the data were normally distributed (as determined by an F-test) were performed using a two-sample t-test. Non-parametric two-sample comparisons were conducted using the 2-sample Wilcoxon Rank Sum test[6].

Both accuracy and reaction times on the Yoni task were analysed using 2x3 repeated measures ANOVAs with judgement type (*Cogntive, Affective or Physical)* as the within-subjects factor, and group as the between subjects factor. Any outliers for reaction times on the Yoni task which were the product of interference during the task (e.g. a partner or carer entering the room)[7], were noted down during testing, and the reaction time was omitted from the analysis. Further outliers (+/- 3SD) were examined on an individual basis in the context of both overall SD and the SD of its own trial category in order to ascertain their number, extremity and possible cause (e.g. simply the presentation of a new part e.g. Part B or C). Reaction

[6] This test is appropriate for independent samples and is equivalent to the Mann-Whitney U-test. The Wilcoxon Rank Sum test should not be confused with the Wilcoxon Signed-Rank Test for use with matched pairs.

[7] All attempts were made to ensure that disturbances were kept to a minimum

times that were a single and extreme case within a particular trial type were omitted from analysis, whereas times that were marginally outwith the cut off and/or were one of several similar values in the same trial type were included.

The wide cut off score was adopted because high variance is a feature of this mixed design task; the consecutive presentation of different types of trial is more ecologically valid (more reflective of a real life situation), and thus it is important that the RTs reflect much of the variance that is a product of processing difficulties induced by this mixed presentation.

Results

1 Matching patient and control groups

As clearly demonstrated in Table 1, the patient and control groups did not differ significantly in terms of age, education, pre-morbid (as determined by the NART) or current intellectual abilities (as determined by the WASI). It is important to note that both groups had higher overall intellectual functioning than average on the NART (Controls = 93rd %ile; Patients = 87th %ile) and on the WASI (Controls = 97th %ile; Patients = 95th %ile).

Table 1
Characteristics of Parkinson patients and control subjects

	Patients		Controls			
	Mean	SD	Mean	SD	*t*	p
N	8	-	8	-	-	-
Age	70.25	5.39	70.25	5.70	0	1
Education	15.75	2.31	16.88	2.42	-0.951	0.358
NART IQ	117.88	7.26	122.62	6.00	1.427	0.176
WASI IQ	124.00	12.22	130.62	6.25	1.365	0.194

NOTE. NART=National Adult Reading Test, WASI = Wechsler Abreviated Scale of Intelligence. SD = Standard Deviation

2 Background neuropsychological battery –mental state scales

Addenbrooke's Cognitive Examination – Revised (ACE-R)

The group comparison of scores on this screening tool is necessary to ascertain the relative mental state of the two groups. In addition, individual scores were checked against the recommended cut off scores (Possible dementia <88, probable dementia <82). No participants scored below 82, and only one patient was found to have scored below the upper cut off, recording a score of 84. However, a specific deficit in performance on the memory components of the test account for

>46% of errors. Given the age of 77 years, and the fact that this patient's ACE-R profile was not globally impaired, it was decided not to exclude this participant.

The basic MMSE scores between patients (M=29, SD=1.07) and controls were compared using a 2-sample t-test, and were not found to be significantly different, t(14) = 1.82, *ns*. Overall ACE-R scores were then compared, and patients (*M*=92.00, *SD*=4.04) were found to have scored significantly lower than controls (*M*=96.75, *SD*=2.60), *t*(14) = 2.80, *p* = .0145, one-tailed, *d* = 1.495. The large effect size indicates a non-overlap of around 70% between the two groups.

Further comparison of the group means by sub-components of the ACE-R demonstrated that patients had performed significantly worse than controls on Memory and Language only, as illustrated in Table 2.

Table 2
Comparisons of performance on sub-tests of the ACE-R

	Patients		Controls			
	Mean	SD	Mean	SD	*t*	p
Attention /18	18.00	0	17.88	0.35	1	0.833
Memory /26	22.13	2.17	24.75	1.17	-3.02	0.005**
Fluency /14	11.38	1.85	12.63	2.50	-1.14	0.137
Language /26	24.75	0.71	25.75	0.46	-3.35	0.002**
Visuospatial /16	15.75	0.46	15.75	0.71	0	0.5

NOTE. "/" indicates the highest possible score on each sub-test, SD=Standard Deviation

Hospital Anxiety and Depression Scale (HADS)

Examination of the individual scores of participants compared to the cut-off scores (>7) revealed that no participants could be classified as depressed based on this scale. The scores of two patients (7, 7) and one control (8) scored at or above the cut-off score for anxiety, but given the proximity to cut-off and the fact that the effects of anxiety on cognitive performance may not be detrimental (Bierman, Comijs, Jonker & Beekman, 2005), these cases were not excluded.

Analysis of the self-reported HADS questionnaire was undertaken using the non-parametric Wilcoxon Rank Sum (R-S) test, which indicated that patients

(*M*=3.13, *SD*=1.55) were significantly more depressed than controls (*M*=1.13, *SD*=0.99), *W* = 55.50, *p* = .00632, one tailed. There was no difference in the anxiety scores between groups (Patients *M*=3.5 *SD*=2.33; Controls *M*=3.38 *SD*=2.13), *W* = 30.5, *ns*.

3 Executive functioning

Brixton Spatial Anticipation

The successful completion of the Brixton task requires a number of 'executive' processes such as rule detection and set-shifting. These processes are widely associated with the DLPFC, whose dysfunction is thought to result in cognitive subtype of apathy. The total profile score ranges from 1 (Impaired) to 10 (Very Superior), with 5 being classed as moderate average. A Wilcoxon R-S test revealed that overall performance for the patient group constituted 'Moderate Average' and they were significantly impaired in their ability to detect the rules on this task, compared to controls, whose average performance was 'Average', *W* = 7, *p* = .003757, one-tailed (see Figure 1).

Hayling Sentence Completion

As detailed above, the final profile scores represent the ability of participants to inhibit linguistically salient responses, and impairment in this task would be suggestive of a deficit in an area of cognition associated with cognitive apathy. The scoring system for the profile score is the same as for the Brixton test. A 2 sample comparison using the Wilcoxon R-S test indicated a significantly poorer performance for the patient group (*M*=3.75, *SD*=1.83, Low Average) in comparison to the performance of controls (*M*=6.43, *SD*=0.79, Average), *W* = 4.5, *p* = .003308, one-tailed (See Figure 1).

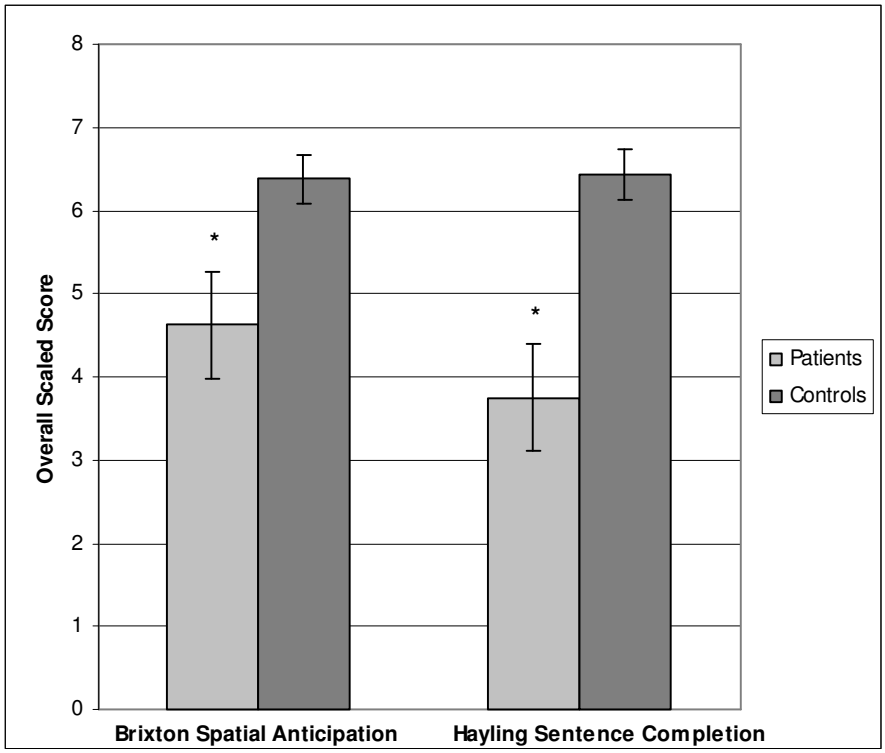


*Figure 1. The mean overall scaled scores and standard error of the mean scores on the Brixton Spatial Anticipation and Hayling Spatial Completion tasks, by group. * = p<.01*

4 Verbal Fluency

Two types of score were obtained for measures of verbal fluency: those for categorical fluency (naming as many animals as possible in 1 minute), and those for literal fluency (as many words beginning with P as possible in 1 minute). Whilst the former appears to rely less upon the types of cognition subserved by the DLPFC, impairment in the latter type of task has been shown to reflect dysfunction in this brain region (Levy & Dubois, 2006). As a result, a score profile on these two tests that would reflect characteristics of cognitive apathy constitutes a significant reduction in the number of words produced by patients for the literal fluency test, contrasting with a comparable of words on the categorical fluency test, when compared to controls.

A two-sample t-test for categorical fluency demonstrated that patients and controls were not significantly different, $t(14) = -0.0604$, *ns*. Conversely, the same comparison for literal fluency reflected a significant impairment in patients (M=14,

SD=4.54) compared to controls (*M*=19.88, *SD*=4.45), *t*(14)= -2.614, *p* = .01021, *d* = 1.40, one-tailed. Figure 2 illustrates the differential performance on these two types of verbal fluency. Note the large effect size, indicating 61.8% non-overlap between the two samples.

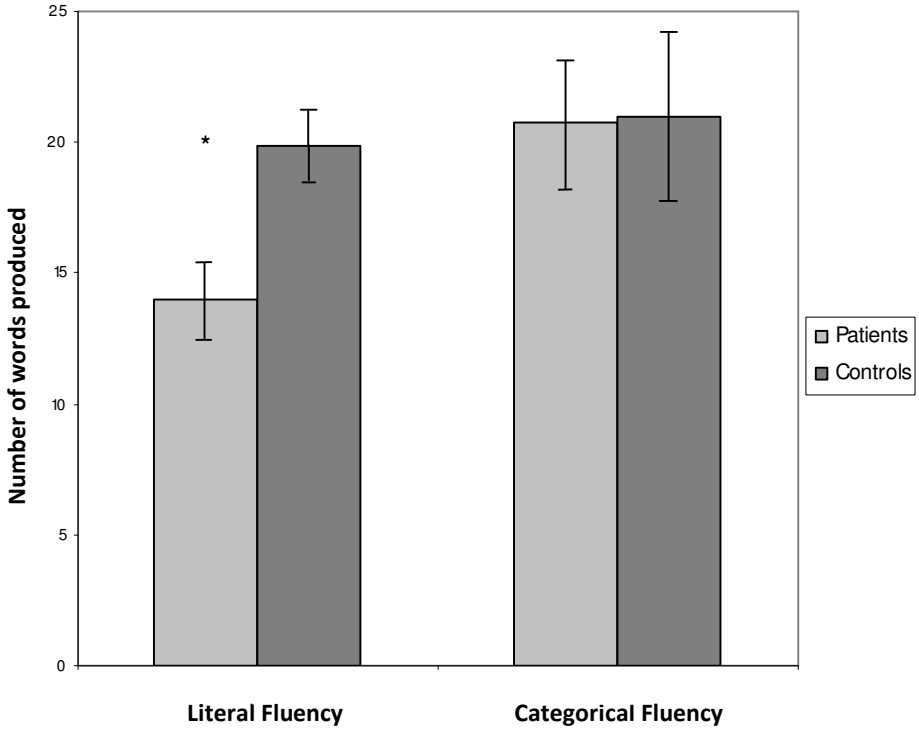


*Figure 2. The mean and standard error of mean number of words produced on Literal and Categorical Verbal Fluency Tasks. * = p<.05*

5 The Lille Apathy Rating Scale – LARS

The LARS was used in order to characterise various aspects of daily living that are affected by apathetic syndromes, based on rated responses during a structured interview with the participant. The total LARS score lies between -36 and +36, with lower scores indicating lower levels of apathetic behaviour. Overall, patients (*M*=-21, *SD*=6.68) were found to be significantly more apathetic than controls (*M*=-29.63, *SD*=5.76), *W* = 54, *p* = .01172, one-tailed.

Further comparisons were then conducted on the LARS subscales (scores between -4 and +4) to identify the apathetic profile in more detail. The scores are

described by Figure 4. Patients scores reflected higher degrees of apathy than controls on the *Intellectual Curiosity (W* = 53.5, *p* = .01281), *Action Initiation* (*W* = 58.5, *p* = .002294) and *Self-Awareness* (*W* = 53.5, *p* = 0.00989) sub-scales. However, analysis did not reflect any significant difference between patients (*M*=-21, *SD*=) and controls (*M*=-21, *SD*=) for the *Emotion* sub-scale, W = 38.5, *ns*.

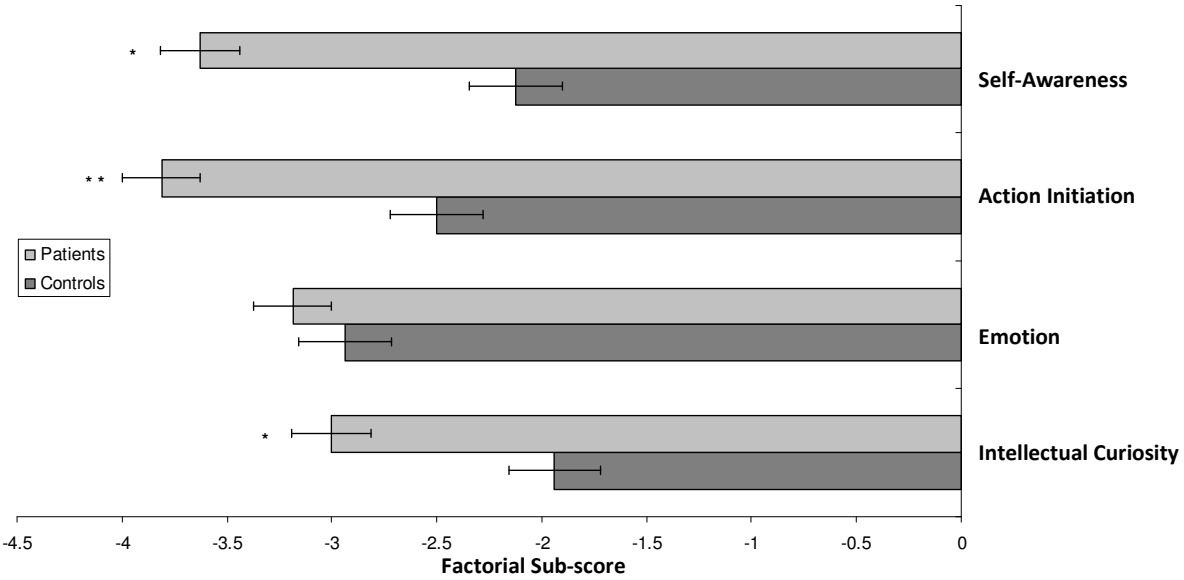


Figure 3. The mean factorial subs-scores and standard errors on the Lille Apathy Scale, by group. A lower (more negative) score indicates a greater degree of apathy. ** = p<.05, ** = p<.01*

6 Goal-directed behaviour and Six Elements Task performance

In order to test the prediction that PD patients would demonstrate significantly reduced GDB as measured by the overall Profile score of the SET, the scores of the two groups were compared using a Wilcoxon Rank Sum Test. The results supported the prediction, showing a reduced score in patients (*M*=2.88, *SD*=0.64) in comparison to flawless performance by all controls (*M*=4, *SD*=0), *W*=4, *p*<.001, one-tailed. On average, patients (*M*=5, *SD*=1.20) attempted fewer tasks (*W* =16, *p*= .01613, one-tailed) than controls (*M*=6, *SD*=0). However, there was no significant difference in the mean number of rule-breaks (Patients *M*=0.63, *SD*=0.92; Controls *M*=0, *SD*=0), *W* = 44, *p* = 0.9731, or the amount of tasks that lasted <271

seconds (Patients *M*=0.13, *SD*=0.79; Controls *M*=0, *SD*=0), *W* = 36, *p* = 0.8697. Table 3 details the individual scores for the patient group.

Table 3
Individual patient scores on the Six Elements Task

Patient	No. Tasks	Rule-breaks	>271 seconds	Profile Score
1	5	0	0	3
2	6	1	0	3
3	6	2	0	3
4	4	0	0	3
5	6	0	1	3
6	4	2	0	2
7	3	0	0	2
8	6	0	0	4

The total profile score = (Number of tasks – Rule breaks) – 1 if any task was attempted for more that 271 seconds.

7 Emotional processing on the Yoni task

Group performance on the Yoni task was examined in order to help test the hypothesis that PD patients would not demonstrate any dysfunction in emotional processing. This deficit is noted as one of the types of processing that can, when impaired, lead to a reduction in GDB characterised as emotional apathy (Levy & Dubois, 2006). This type of cognition has been shown to be subserved by the VMPFC and recent research indicates that this test is sensitive to dysfunction in this region, particularly on performance on the 2nd order affective judgements (Shamay-Tsoory & Aharon-Peretz, 2007). Table 4 details the mean accuracy and reaction time for both groups across conditions.

Accuracy on First-order judgements

A repeated measures 2x3 ANOVA showed that there was no difference between the scores of the two groups [F(1,44) = 0.520, *ns*] and there was no effect of type (*Affective, Cognitive or Physical)*[F(1,44) = 1.995, *ns*]. In addition, the interaction between group and type showed that the pattern of accuracy did not differ significantly between groups (F(1,44) = 0.281, ns].

Reaction time of first-order judgements

The initial analysis revealed that there was a significant difference between the reaction times of the two groups, with patients significantly slower than controls [$F(1,44) = 4.103$, $p<.05$). However, there was no effect for type of judgment [$F(1,44) = 0.75$, *ns*] nor any difference in the patterns of reaction times between the two groups [$F(1,44) =0.442$, *ns*].

Accuracy of second-order judgements

As with the first-order judgements, there was no significant difference between the accuracy of the two groups when making second-order judgements [$F(1,44) = 0.232$, *ns*]. The accuracy did not vary between the types of judgement either [$F(1,44) = 0.651$, *ns*] and there was no significant variation in the pattern of errors between groups [$F(1,44) = 1.246$, *ns*].

Reaction time of second order judgements

There was no significant difference between the reaction times of the two groups [$F(1,44) = 0.909$, *ns*], but the type of judgement was found to have had a significant effect on both groups' reaction times [$F(1,44) = 6.762$, $p=0.013$]. A pairwise comparison using the Bonferroni adjustment was carried out, and this revealed that both groups were significantly quicker to respond to the *Physical* judgements only ($p<0.05$). The variation in reaction times relative to the judgement type was not found to be significantly different between patients and controls [$F(1,44) = 1.111$, *ns*].

Accuracy with eye-gaze distractor

SMALL SENTENCE OR TWO DETAILING WHAT THE EYE GAZE WAS ALL ABOUT. A two-sample t-test found no significant difference between the accuracy of controls and patients both when they gaze was indicating the correct response, $t(14) = -0.952$, $p = .357$, or when it was behaving as a distractor, $t(14) = 0.052$, $p = .960$). In addition, there were no significant differences between the reaction times of the two groups in either condition ($p>.05$).

Table 4

The mean accuracy and reaction times for patients and controls on the Yoni task.

	Patients		Controls	
	Accuracy (%)	RT	Accuacy (%)	RT
Cognitive 1st Order	98.75 (0.04)	3673.16 (1324.10)	100.00 (0.00)	3480.13 (980.97)
Affective 1st Order	97.50 (0.05)	4650.28 (1470.24)	96.25 (0.07)	3502.14 (833.25)
Physical 1st Order	95.31 (0.06)	3588.38 (1451.97)	98.44 (0.04)	2833.48 (642.65)
Cognitive 2nd Order	86.54 (0.12)	10370.91 (4275.20)	83.65 (0.12)	8658.25 (2220.50)
Affevtive 2nd Order	87.89 (0.08)	8203.99 (2944.62)	89.84 (0.05)	7227.43 (1711.46)
Physical 2nd Order	85.42 (0.13)	6751.12 (2990.80)*	90.63 (0.12)	7127.10 (2267.76)*
Eye Gaze Correct	92.41 (0.06)	8834.56 (3879.28)	95.09 (0.05)	7480.52 (1761.44)
Eye Gaze Distractor	86.11 (0.15)	10479.51 (4461.10)	85.76 (0.12)	9144.63 (1921.84)

*Standard deviations are in brackets. Controls were on average quicker at making judgements in all of the first order tasks. In addition, both groups were significantly quicker on the second order physical judgements than on the second order cognitive or affective judgements. * = p<.05*

Discussion

1 Summary of aims

The aim of the current study was to examine apathy (defined as a reduction in GDB) in Parkinson's disease (PD). In particular, the goal was to quantify any reduction in GDB, identify areas of impairment amongst the mechanisms that contribute to goal-directed behaviour (GDB), and relate this profile of dysfunction to the three apathetic sub-types, as outlined by Pluck & Brown (2002) and Levy & Dubois (2006) in order to characterise the apathetic profile in PD. It appears that no attempt to study the relationship between these apathetic sub-types in the light of quantifiable GDB has previously been carried out, but the examination of such a relationship clearly has implications for future treatment and prognosis.

The level of apathy was determined by comparing the performance of patients with mild PD to those of well-matched control subjects on the Six Elements Task (SET) and the overall score on the Lille Apathy Rating Scale (LARS). The SET is thought to be an ecologically valid measure of GDB, representing a more challenging and complex task including the processing of delayed intentions and competing demands more akin to tasks encountered in daily life, and the LARS is a reliable and sensitive tool appropriate for gauging the affects of apathy on various aspects of daily living. In addition, the performance of patients and controls was compared on several measures which pertain to cognitive functions underlying the apathetic sub-types. The Yoni task and the Intellectual Curiosity and Emotion sub-categories of the LARS were used to examine the function of the VMPFC, whose dysfunction is implicated in *Emotional-Affective Apathy*. Verbal fluency (literal vs. categorical), along with the Hayling and Brixton tasks, were used to examine the functioning of the DLPFC, associated with *Cognitive Apathy*. The sole measure for *Auto-Activation Apathy* in this study was the Action Initiation section of the LARS. Together, this study and the test battery was designed to explore two main hypotheses investigated in this study:

1) that normally-medicated PD patients would exhibit a higher degree of apathy than controls;
2) that these patients would also exhibit a profile of deficits relating to *Cognitive Apathy,* rather than *Emotional-Affective* or *Auto-Activation Apathy.*

These predictions were based on the fact that there is significant dopaminergic innervation to functional circuits associated with all three apathetic subtypes; although the contribution to a reduction in GDB could be multi-factorial, current literature suggests that well-medicated patients tend to show predominantly executive deficits. Evidence from this study concerning both of these hypotheses will be discussed, in turn, below.

2 Overall degree of apathy in PD

Results showed that patients' overall profile score on the SET was significantly lower than that of the controls, and that patients' overall LARS score was significantly higher, indicating a greater degree of apathy. By inference, the findings of this study support the hypothesis that PD patients are more apathetic than controls, exhibiting a greater quantitative reduction in GDB. This is consistent with previous findings, which characterise apathy as a core feature of PD (e.g. Zgaljardic *et al.,* 2004), even when patients are taking their normal regime of dopatherapy that effectively alleviates the motor symptoms of the disease.

3 Apathetic Sub-Types in Parkinson's disease

Emotional-Affective Apathy The results of this study also show that performance on the Yoni task was not significantly different between patients and controls. The inability to decode affective context as measured by the Yoni task has been linked to damage to the VMPFC, which results in a clear deficit when making second order affective judgements (Shamay-Tsoory & Aharon-Peretz, 2007). In

addition, this area of cognition has been identified as contributing to the successful generation of goal-directed behaviour by processing the emotional salience of current and future action (Pluck & Brown, 2002), and by the fact that Emotional-Affective apathy is a characteristic of focal lesions to the VMPFC. In addition, there was no significant difference between the patient and control group on scores of the Emotion scale of the LARS, suggesting that medicated PD patients do not experience reduced emotional reactivity/blunting in their day-to-day lives. This appears to be consistent with much of the current literature, which reports that medicated patients with mild PD do not appear to have difficulties in emotional processing (e.g. Pell & Leonard, 2005).

However, the responses from the Intellectual Curiosity element of the LARS do not support this study's second hypothesis. In response to questions such as "*In general, do you decide to do things, or does someone push you a little?"*, PD patients scored more negatively than controls, indicating they are more severely affected. As a consequence, there is contradictory evidence within this study concerning the contribution of Emotional-Affective apathy to the reduction in GDB in PD.

Cognitive Apathy The analysis of scores on verbal fluency shows a clear dissociation in patients' performance between literal and categorical, when compared to controls. Whilst there was no significant difference between the two groups when asked to generate as many animals as possible in 1 minute, this is contrasted with a non-significant difference between group means for the literal fluency task. This profile is consistent with previous studies showing a similar pattern of spared and impaired fluency (e.g. Masdeu & Shewmon, 1980; Dubois & Pillon, 1997; Zgaljardic *et al.*, 2006; Beato *et al.,* 2008). This is thought to reflect an underlying deficit in retrieval strategies and is consistent with dysfunction in the DLPFC, lesions to which lead to a characteristic *Cognitive Apathy* (Levy & Dubois, 2006).

Furthermore, lesions to this brain region are also associated with impairments in executive functions such as rule-detection, set shifting and linguistic inhibition, which are all areas of cognition identified as indicators of cognitive apathy through DLPFC dysfunction (Brown & Pluck, 2000; Levy & Dubois, 2006).

Although the Hayling and Brixton tasks are relatively new, and therefore evidence directly linking poor performance with lesions to the DLPFC is relatively scarce, some recent evidence is suggestive of such an association (Nathaniel-James & Frith, 2002; Reverbi *et al.,* 2005; Martinaud *et al.,* 2009).

Taking the patients' results of impaired Brixton and Hayling performance together with the dissociation between spared categorical and impaired literal fluency, it can be inferred that this profile of test performance is consistent with that specified by Levy & Dubois (2006) for *Cognitive Apathy*, in support of this study's hypothesis.

Auto-Activation Apathy The finding that PD patients reported a significantly greater degree of apathy in the Action Initiation sub-scale of the LARS does not support the hypothesis that *Auto-Activation* apathy would be a feature of well-medicated PD patients. This was based on the fact that this sub-type of apathy is thought to be caused by focal BG dysfunction. Although the neurodegeneration in PD severely affects the nigrostriatal pathway (and subsequent function of the BG), dopaminergic therapies are aimed at the resultant motor symptoms, and therefore it was suggested that the contribution of this type of apathy to the reduction in GDB in PD may also be mediated by dopatherapy. However, these results would suggest that anti-Parkinson drugs are not able to prevent dysfunction from pervading the daily lives of patients, although the assumption that the LARS is an appropriate measure are discussed later in this section.

4 Limitations & Further Research

The high IQ level in both groups is reason for a potential reduction in generalisability. Even with a more adequate sample size, it could certainly be argued that attempts to apply these results to PD patients in general would be ill-advised. There does not appear to be any literature to support the idea that PD patients tend to have higher IQs and therefore it is unlikely that this sample is representative of the general PD universe in this respect. Rather, it is plausible that this sampling bias

reflects an artefact of the recruitment process, and it is well-known that research volunteers tend to be better educated (e.g. Rosenthal & Rosnow, 1991). However, it is also possible that, in the domain of neurodegenerative disease and cognitive decline or dysfunction, patient groups with higher-than-average IQs may yield a more conservative picture of the disease effects on the generation of GDB. For example, a longitudinal study on the effects of IQ on cognitive and functional outcomes in Alzheimer's disease (Starr & Lonie, 2008) demonstrated the protective effects of IQ (as measured using the NART) on cognition, which in turn had a positive effect on activities of daily life. Although it appears that no such data exist for PD, it seems reasonable to suggest that IQ may have a similar mitigating effect on the cognitive symptoms of the disease, and therefore upon apathy severity, making these findings a conservative estimate of the true apathetic profile in PD. However, further research using a longitudinal design is required before this conclusion can be either corroborated or refuted.

Sampling bias during recruitment may also be a reason for the exclusion of PD patients who may display profiles associated with *Emotional-Affective* apathy. The recruitment process requires patients to express their interest in participating, and from the types of impairment pertaining to each apathetic subtype, it is certainly possible that those with *Cognitive* apathy are more likely to show an interest: their cognitive dysfunction is limited to mainly 'executive' processes which would not interfere with their interest in participation. On the other hand, difficulties with the interpretation of positive or negative outcomes of a given choice, and decreased involvement in affective elements of life (such as volunteering your time for a study), which are associated with *Emotional-Affective* apathy, could quite readily explain a lack of interest in participation and thus produce a bias against this hypothetical population of PD patients. A larger sample size and more varied recruitment strategies would aid the robustness of the sample to such bias, although the fact that recruitment is a voluntary process will always result in distortion of the sample against those less predisposed to volunteer.

A further limitation arises from the ceiling effect in control subjects on the SET task, which was our quantitative measure of GDB. It suggests that the utility of

the SET as a measuring strategy is compromised, causing a reduction in the measured true mean and variance. This underscores the difficulty of selecting a task that is able to strike a balance between task difficulty and task sensitivity, and provide a true reflection of both groups' abilities whilst avoiding both floor and ceiling effects. Although, in this case, a significant difference was found between groups in spite of the control group clustering effect, the SET did not, in this instance, appear to have the sensitivity to reflect the true reduction in GDB in PD, which may be much greater than is suggested here.

In addition, it would have been preferable to include a more balanced range of tasks for *Emotiona-Affective* apathy, had the length of the test battery permitted. Specifically, a reversal learning task, such as the AX-CPT task would have been beneficial to give a more rounded view of the functions pertaining to this apathetic sub-type. This task is not only specified as having a relation to dysfunction in ventromedial frontal areas, but also a task specifically referred to by Levy & Dubois (2006) as indicative of Emotional-Affective apathy. When using the authors' definitions of the apathetic sub-types, it would perhaps have been more robust to adhere to the tasks specifically highlighted. This is perhaps compounded by the large amount of literature supporting the reliance on a normally functioning VMPFC for successful completion of the AX-CPT task (Levy & Dubois), whereas the Yoni task, although elegant, has been used in a single lesion study, although this was supportive of the task's sensitivity to the same brain region (Shamay-Tsoory & Aharon-Peretz, 2007).

The use of the LARS to effectively measuring apathy in this population may also be flawed. In defining apathy as a quantitative reduction in GDB, the measurement of GDB at two points (t1 and t2) is implicit: the quantitative reduction being equal to the difference between these two sampling points. In a cross-sectional study such as this, control participants are used to provide a 'baseline' or normal performance/behaviour or whatever is being measured. However, such an approach may not be suitable for the detection of GDB-reduction via the LARS. This is because it measures the effects of apathy on aspects of daily living, and as a consequence, a cross sectional design assumes that the aspects of daily life being

examined are at a given baseline for all individuals. However, there is no way to know whether individuals with PD who score high on apathy scale *now* (t2) were actually any different pre-morbidly (t1). Instead we must rely on the assumption that the age- and education-matched control participants reflect this t1 state.

However, the heterogeneous nature of levels of engagement in daily life suggests that such an assumption is weak at best, particularly given the small sample size. As self-report appears to be the only practicable cross-sectional measure of lab-based assessment for the Auto-Activation apathy in particular, future studies should look to assess the current state of behaviour with direct reference to with previous states, preferably with the corroboration of a partner or carer (such as the patient/carer version of the LARS currently under development; Sockeel *et al; 2006*). Although the comparative costs and logistics of longitudinal assessment may seem prohibitive, this approach would represent the most sound approach to measuring reduction in GDB, although a cross-sectional design with a large-enough sample size would also serve to control for individual differences to some extent.

One major limitation of this study is the fact that all patients were receiving their normal regime of anti-Parkinson medication, and therefore we cannot necessarily suggest that this profile of behaviour is purely a function of PD. Rather, any inferences must be limited to those patients who are receiving their regular anti-Parkinson medication, titrated to deal with the motor symptoms of the disease. As discussed in the introduction, many different types of medication exist for PD, which work in different ways and are effective for different individuals, but all of which are prescribed with the primary aim of mitigating motor symptoms through increasing DA availability in the BG. However, it is not fully understood how the non-motor symptoms of the disease, including apathy, are affected by the different ways in which PD medication acts on the function of other brain regions that rely on innervation from other dopaminergic pathways, but the range of medication used by patients in this study combined with the small sample size prohibits investigation of this dynamic.

In addition, this cross-sectional study does not allow us to chart the apathetic profile as the disease progresses. Such data would certainly inform the provision

and choice of therapies at different stages of the disease. Although the POPM is a well-known and widely-used scale, it is perhaps not an appropriate tool for disease severity in this context. Because dopatherapy is designed to regulate motor symptoms, and all members of the patient group were on medication, it is unsurprising that the POPM scores were relatively low, and all that the POPM can report is the effective medication of motor symptoms. Additionally, limited sample size in this study meant that analysis into type and degree of apathy as a function of disease severity would have lacked power, but this may be one very interesting line of future research.

One promising technique for gauging disease severity is by using the combination and dosage of prescribed anti-PD medication (see Rowe *et al.,* 2008), which could facilitate a more accurate means by which to investigate the relationship between apathetic sub-type and disease severity in the future. New research is beginning to emerge that is suggestive of different types of cognition being differentially sensitive to DA modulation. For example, Cools and colleagues (2001) demonstrated that dopatherapy impairs orbito-frontal function but remediates DLPFC dysfunction (although they did not specify the types and variety of dopatherapy being taken by patients). Furthermore, Rowe and colleagues (2008) demonstrate that this variability also exists as a function of dosage strength. It follows that as the dosage level increases, so different types of cognition experience different effects (see Figure 1). This being the case, it would be reasonable to predict that whilst patients with less severe PD (and therefore lower doses) may exhibit cognitive apathy, very severe cases would show more emotional (and possibly auto-activation) apathy. This dynamic may well help to explain the contradictory results in the literature regarding the dysfunction of emotional and reward processing, but more importantly, would have implications for the development and selection of treatments complimentary to dopatherapy. For example,

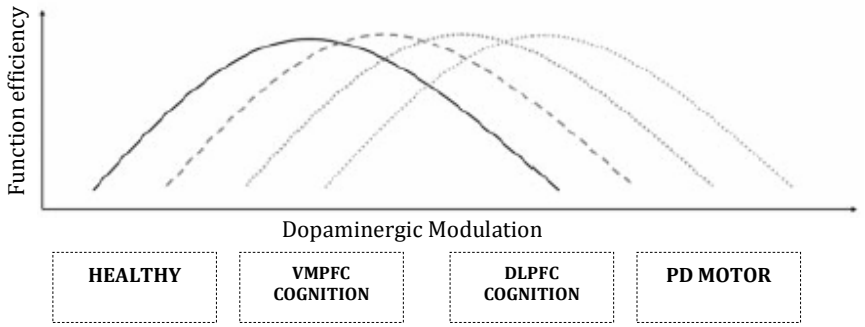


Figure X A schematic demonstrating the relationship between dopaminergic modulation and neural functional efficiency. The rightward shift in dopaminergic modulation caused by the need to treat motor symptoms in PD has a differential effect on cognitive domains.

5 Conclusions

The results from this study add to the evidence characterising apathy as a key symptom of PD, distinct from depression and dementia, using a recent definition of apathy as a quantitative reduction in goal-directed behaviour. However, the extant data does not entirely support the hypothesis that only performance on tests pertaining to the *Cognitive* subtype would be impaired in normally-medicated PD patients, compared to age- and education-matched controls. There is certainly evidence to support the idea that dysfunctions of this type significantly contribute to the quantitative reduction in GDB in PD, but the findings of this study intimate a more complex picture. Some evidence for the contribution of both *Emotional-Affective* and *Auto-Activation* sub-types to reductions in GDB is suggested, which may not be affected by normal PD medication. Although the sample size is too small to make firm claims, and there are a number of other limitations to be considered, this study provides a basis for further research into the characterisation of the apathetic profile in PD, with the ultimate aim of feeding into clinical practice and informing the development of future therapies to target the apathetic symptoms in PD. For example, a preliminary study into the effects of executive task-training on GDB outcomes has yielded positive results (Sammer, Reuter, Hullmann, Kaps & Vaitl, 2006). This suggests that the practice of developing strategies to identify and cope with areas of life affected by executive dysfunction may be one avenue for the

development of a therapy aimed at *Cognitive* apathy, although further systematic work identifying the precise apathetic mechanisms at play in PD is of critical importance to realising this goal.

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Appendix