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The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) in the assessment of early onset dementia

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Abstract

Early onset dementia is the gradual cognitive decline that interferes with independence in everyday activities, when it occurs in people younger than 65 years old (Fadil et al., 2009; American Psychiatric Association, 2013). The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was originally developed to assess cognitive and behavioural changes observed in amyotrophic lateral sclerosis (ALS) (Abrahams et al. 2014); as between 10-15% of ALS patients develop frontotemporal dementia, and an additional 35% develop a milder cognitive impairment of frontotemporal dysfunction (Goldstein and Abrahams, 2013; Strong et al., 2017). The ECAS includes the domains of language, fluency, and executive functions for the assessment of ALS, but it also includes the domains of memory and visuospatial abilities to differentiate changes from other pathologies, such as Alzheimer's Disease (AD) (Abrahams et al. 2014). In addition, the ECAS includes a behavioural interview. In this thesis I explore whether the ECAS is a sensitive test to the types of cognitive and behavioural changes in people with early onset dementia without Amyotrophic Lateral Sclerosis (ALS).

In the first study my objectives were: to investigate the relationship between the ECAS and the Addenbrooke's Cognitive Examination (ACE-III); to investigate the effects of age, education, and IQ on the ECAS, and create appropriate cut-off scores to determine abnormality. I assessed 80 healthy participants divided into four groups according to age and education. The ECAS and the ACE-III had a significant correlation indicating good convergent validity. IQ, followed by age, were the strongest predictors of the total ECAS score. While IQ predicted 46% of the ACE-III variance, it only predicted 24% of the ECAS variance. I created abnormality cut-off scores adjusted for age and education. This research was published in De Icaza Valenzuela et al. (2018).

In the second study my aim was to determine the sensitivity of the ECAS to behavioural variant frontotemporal dementia (bvFTD) without ALS, AD,

primary progressive aphasia (PPA) without ALS, posterior cortical atrophy (PCA) and mild cognitive impairment (MCI). I also validated the ECAS against a comprehensive neuropsychological assessment, and compared it with the ACE-III, for each diagnosis. We additionally performed a qualitative thematic analysis of the ECAS behavioural interviews to determine the differences in themes between the diagnoses of bvFTD and AD. The study included 16 people with bvFTD (without ALS), 32 with AD, 12 with MCI, 13 with PPA, 6 with PCA and 48 healthy controls. The ECAS was more sensitive than the ACE-III to detect bvFTD, AD, MCI and PPA; with equal sensitivity to detect PCA. The anterior functions (comprising executive, fluency and language scores) composite score was sensitive to bvFTD; while the posterior functions (comprising memory and visuospatial scores) composite score was sensitive to AD. The ECAS was able to detect cognitive impairment as determined by a comprehensive neuropsychological assessment in most of the patients. A cut-off of 4 or more behavioural domains affected differentiated well between bvFTD and AD, while different themes emerged between the groups in the qualitative analysis of the behavioural interview.

Finally, for the third study my objectives were: to investigate the relationship between the ECAS and functional severity of dementia; to validate the behavioural interview of the ECAS with other behavioural screens used to assess FTD; and to determine whether the ECAS scores changed over time in bvFTD, AD, MCI, PPA, and PCA. For this purpose, I did a longitudinal study and analysed the correlations between the ECAS with the Clinical Dementia Rating Scale (CDR-FTLD), the Frontal Behavioural Inventory (FBI), and the Frontotemporal Dementia Rating Scale (FRS). I assessed 56 patients on the first assessment, 29 on the second assessment and 13 on the third assessment. The ECAS total score had good convergent validity with the CDR-FTLD severity classification, while the ECAS behavioural screen had convergent validity with the FBI, FRS and CDR-FTLD. I created an impairment cut-off score of 96 to differentiate the groups of questionable versus mild dementia based on the CDR-FTLD. The CDR-FTLD, FIQ, FBI, and FRS

predicted 71.3% of the variance of the ECAS Total Score. The variance of the ECAS behavioural score was predicted 74.7% by the FBI, FIQ and age. FRS was the single variable to predict attrition by 20.4%. In our study there was no significant difference of ECAS scores between assessments.

The ECAS proved to be a valid test to assess the cognitive and behavioural impairments in people with early onset dementia without ALS. It was more sensitive than the ACE-III at detecting dementia in most of the patient groups, with the exception of the PCA group where they had equal sensitivity. The ECAS had also equal sensitivity to detect bvFTD, PPA and PCA as an extensive neuropsychological assessment. It could therefore be used as a first assessment in early onset dementia clinics.

Lay Summary

Dementia is a condition in which there is a gradual cognitive decline that interferes with independence in everyday activities (American Psychiatric Association, 2013). When it occurs in people younger than 65 years old, it is called early onset dementia (Fadil et al., 2009). Dementia is divided by age of onset, as they differ in the proportion of types of pathologies and clinical presentation (Sitek, Barczak and Harciarek, 2015). The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was designed to detect cognitive and behavioural changes in amyotrophic lateral sclerosis (ALS) (Abrahams et al. 2014) as some of these patients develop frontotemporal dementia (FTD). FTD is a dementia in which patients are often impaired in executive functions (planning, initiating actions, multitasking, etc.), language, fluency (ability to generate words) and often have behavioural changes. The ECAS includes subtests of executive functions, language, fluency, memory and visuospatial abilities (ability to process visual and spatial information). It also includes an interview to evaluate the behavioural changes of the patient with a carer or family member. This research was done to explore if the ECAS is sensitive to detect cognitive and behavioural changes in patients with dementia without ALS.

The Addenbrooke's Cognitive Examination (ACE-III) is one of the most widely used cognitive tests for dementia. It includes similar cognitive domains to the ECAS but does not assess executive functions nor behaviour. As the sensitivity of the ACE-III to detect FTD has been inconsistent, I wanted to compare the ECAS with the ACE-III in healthy controls and patients with dementia, including those with FTD. In the first experiment I compared the ECAS with the ACE-III in healthy controls. I also wanted to explore the effects of age, education, and IQ on the ECAS. I found that the ECAS and the ACE-III were correlated, but the ECAS total score depended less on the patients' IQ than the ACE-III. IQ and age predicted part of the total score of the ECAS. I created age (below and above 65 years old) and education (with or without a

university degree) cut-off scores on the total score of the ECAS to be used in the clinical practice.

In the second experiment I compared the ECAS against an extensive neuropsychological assessment, and with the ACE-III, for the diagnoses of behavioural variant frontotemporal dementia (bvFTD), Alzheimer's disease (AD), primary progressive aphasia (PPA), posterior cortical atrophy (PCA) and mild cognitive impairment (MCI). We also analysed the common themes reported on the behavioural interview in bvFTD and AD patients. The ECAS was better at detecting dementia than the ACE-III in the diagnoses of bvFTD, AD, MCI and PPA. The ECAS and the ACE-III were equal at detecting dementia in PCA patients. The ECAS was as good as the neuropsychological assessment at detecting dementia in bvFTD, PPA and PCA; and almost as good at detecting dementia in AD and MCI. The ECAS also detected the same profiles of cognitive impairment found in the neuropsychological assessment. These results make the ECAS very suitable to be used by clinicians to detect dementia over the ACE-III, as a first brief assessment.

Finally, for the third experiment I assessed a dementia population over 3 assessments (6 to 11 months in between assessments) to analyse if there was a change of scores on the ECAS over time. I also investigated if the ECAS and its behavioural interview correlated to functional tests (which measures how impaired the patient is in everyday activities) used to establish the severity of dementia in patients, and other behavioural interviews. The ECAS total score correlated with the functional test, while the behavioural interview of the ECAS correlated with the functional test and the other behavioural interviews. I did not find a difference of ECAS scores over time. I created an abnormality cut-off score for the ECAS total score to differentiate between those with questionable dementia and those with mild dementia.

The ECAS is proved to be a valid test to assess the cognitive and behavioural impairments in people with early onset dementia without ALS. It was better than the ACE-III at detecting dementia in most of the patient groups (bvFTD, AD, MCI and PPA), and detected the same profiles of cognitive impairment found in the neuropsychological assessment. The ECAS could therefore be used as a first assessment in early onset dementia clinics.

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Index of Acronyms

ACE-III	Addenbrooke's Cognitive Examination
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
ANOVA	Analysis of variance
bvFTD	behavioural variant Frontotemporal dementia
CBD	Corticobasal Degeneration
CDR	Clinical Dementia Rating Scale
CDR-FTLD	Clinical Dementia Rating Scale with Language and Behaviour domains
DART	Edinburgh Cognitive Diagnosis Audit Research and Treatment Register
DLB	Dementia with Lewy Bodies
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECAS	The Edinburgh Cognitive and Behavioural ALS Screen
FAS	Controlled Oral Word Association
FBI	Frontal Behavioral Inventory
FRS	Frontotemporal Dementia Rating Scale
FSCRT	Free and Cued Selective Reminding Test
FTD	Frontotemporal dementia
FTD-MND	Frontotemporal dementia with Motor Neuron Disease
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MoCA	The Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
n	Number of participants
PCA	Posterior cortical atrophy
PNFA	Progressive non-fluent aphasia
PPA	Primary progressive aphasia
SD	Standard Deviation
TROG	Test of Reception of Grammar

VOSP	The Visual Object and Space Perception Battery
6CIT	Six-Item Cognitive Impairment Test

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Chapter One
Introduction

1.1 Early onset dementia

Dementia is described as a condition in which there is a gradual cognitive decline that interferes with independence in everyday activities (American Psychiatric Association, 2013). It is labelled as early onset dementia when it occurs in people younger than 65 years old, and as late onset dementia when it occurs at 65 or more (Fadil et al., 2009). Internationally it is estimated that between 2 and 10% of dementia cases have an early onset (Masellis et al., 2013); however, in developed countries this increases to one third of all dementia cases present an early onset (Harvey, Skelton-Robinson and Rossor, 2003). In 2014 the prevalence of early onset dementia in the UK was of over 42,000 people (Prince et al., 2014), and an additional 885,000 people over 65 years old had dementia in the UK in 2019 (Wittenberg et al., 2019).

The most common type of dementia is Alzheimer's Disease (AD), accounting for 62% of the total dementia population (Prince et al., 2014) in contrast, to only 34% of the young onset dementia population (Harvey, Skelton-Robinson and Rossor, 2003). Vascular dementia accounts for 17% of cases of both the total population of dementia, and of the young onset cases, while frontotemporal dementia (FTD) increases from 2% of cases of the total population with dementia to 12% of the young onset cases (Prince et al., 2014; Harvey, Skelton-Robinson and Rossor, 2003). Late onset dementia usually presents with memory decline, while early onset patients often present additional impairments in executive functions, language, and behavioural changes (Sitek, Barczak and Harciarek, 2015). These differences in clinical presentation correspond to the different proportions of dementia types per onset. In addition, there is a higher prevalence of inherited dementia in early onset; as well as a higher incidence of infectious, toxic, metabolic and inflammatory causes for dementia (Rossor et al., 2010; Quach et al., 2014). The low expectation of dementia at a young age, alongside the differences of

clinical presentation between the early versus the late onset patients often result in misdiagnosis and longer times for patients to receive an accurate diagnosis (Draper and Withall, 2016; van Vliet et al., 2013). Incorrect or uncertain diagnoses have been reported in 30-50% of cases of early onset dementia (Bentham and La Fontaine, 2008). Several studies (Luscombe, Brodaty and Freeth, 1998; Werner, Stein-Shvachman and Korczyn, 2009; Svanberg, Spector and Scott, 2011) have pointed out the need of better diagnosis methods in early onset dementia, as treatment can be done more effectively when a diagnosis is made in the early stages, and it can be used as a guide for prognosis (Snowden et al, 2011).

1.2 Types of Dementia

Alzheimer's disease (AD) is characterized by the accumulation of amyloid plaques and neurofibrillary tangles, progressive loss of synapses and neurons, and cholinergic deficits in the hippocampus and cerebral cortex (Hugo, and Ganguli, 2014; Schneider, 2001). Deterioration usually begins in the medial temporal and occipitoparietal regions (Zhou et al., 2010; Sjogren et al., 2000). Some of the genes associated with an increased risk of AD are: APP, MAPT, PSEN1, and APOE ε4 allele (Bonvicini et al, 2019). AD has a gradual onset with a continuous cognitive decline which interferes with daily functioning. The main cognitive domain impaired in AD is memory, but in order to fulfil the diagnostic criteria of the DSM-V, patients must additionally be impaired in another cognitive domain; for example, aphasia (American Psychiatric Association, 2013). The "gold standard" or definite diagnosis of AD can only be done by counting the amyloid plaques and neurofibrillary tangles in a post-mortem examination (Scheltens and Rockwood, 2011). In AD's typical presentation (amnestic), memory and executive functions impairment develop in the earlier stages, while visuospatial and language functions become impaired at later stages (Hugo, and Ganguli, 2014). Some of the memory deficits in AD include impairment in: encoding; recall for recently learned information, previously learned information (such as concepts and facts), and

autobiographical information; semantic memory; working memory; and lack of primacy effect in recall while showing recency effect (Jahn, 2013; Brueggen et al., 2016; McKhann et al., 2011).

However, AD pathology can also be associated with other presentations, such as, logogenic Primary Progressive Aphasia (PPA), Posterior Cortical Atrophy (PCA) and behavioural variant AD (also known as dysexecutive or frontal variant AD) (Xia et al., 2017). Approximately one-third of early onset AD present as an atypical presentation; and although atypical presentations are less common in late onset AD, they still occur in about 6% of cases (Dickerson et al., 2017; Llado and Sanchez-Valle, 2011). Patients with these atypical presentations are often misdiagnosed, take longer to be diagnosed and sometimes receive an inconclusive diagnosis (Llado and Sanchez-Valle, 2011). Lack of knowledge of the clinical presentation of these atypical forms of AD in healthcare providers, alongside the lack of time and resources for cognitive and behavioural testing for dementia, could contribute towards the delay of correctly diagnosing atypical AD patients. Early diagnosis of dementia can be beneficial for the patient; as they can be more involved in the preparations for their future, get access to post-diagnostic support services, and sometimes receive pharmacological treatments of cognitive enhancers, such as cholinesterase inhibitors, which may contribute to symptomatic improvements (Bradford et al. 2009).

The frontal variant of AD presents with memory impairments, in addition to behavioural changes and/or executive function impairments; but it differs from behavioural variant FTD (bvFTD) by having more prominent posterior and temporoparietal atrophy than an anterior atrophy and often carry at least one APOE ε4 allele (Ossenkoppele et al., 2015). Nevertheless, the clinical presentation of behavioural variant AD is so similar to that of bvFTD that between 20% to 40% of patients diagnosed with bvFTD are found to have an AD pathology (Rabinovici et al., 2011; Beach et al., 2012; Ossenkoppele et al., 2013). A study reported that frontal variant AD patients have been shown to

be more impaired in memory and executive functions than bvFTD patients, as well as presenting initially with less behavioural changes (Ossenkoppele et al., 2015). However, the screens they used to measure behavioural changes were not designed for FTD nor AD, as one was a depression scale and the other was a general neuropsychiatric behavioural questionnaire. These tests lacked questions regarding impulsivity, empathy, and sympathy. To explore the behavioural differences between frontal AD and bvFTD the study should have additionally included a behavioural screen specifically made for bvFTD.

Most AD patients will develop behavioural changes at some point during the course of the disease (Mandell and Green, 2011). Apathy is one of the most reported behavioural changes in AD (Radakovic, Starr and Abrahams, 2017; Radakovic et al., 2020). It has been shown to correlate to executive dysfunction (McPherson et al., 2002) and to functional impairment (Gilley et al., 1991). Apathy and depression can occur at any stage of the disease; whilst psychotic features, wandering, irritability, agitation, and combativeness tend to occur in the middle to later stages (Hugo, and Ganguli, 2014). Other behavioural changes that sometimes occur in AD are social withdrawal, disinhibition, aggression, anxiety, and eating and sleeping disorders (Mandell and Green, 2011; Victoroff et al., 2017). Detecting behavioural changes in AD is very important, as they can worsen the person's quality of life, increase impairment in activities of daily living, and increase caregiver stress (Fernández et al., 2010). In addition, behavioural changes have been reported as one of the main reasons for patients to be institutionalized partly due to the burden on caregivers (Hébert et al., 2001; Steele et al., 1990). Addressing possible behavioural changes with patients and their carers in the early stages, could aid patients in how quickly they receive drug treatments and how much support they receive to manage their symptoms; therefore, improving the quality of life of both patients and carers.

There are three types of clinical presentation of frontotemporal dementia: bvFTD and two types of PPA (progressive non-fluent aphasia and semantic

dementia) (Hodges, 2007). Unlike AD, frontotemporal dementia is associated with multiple pathologies (Hodges et al., 2004; Mackenzie et al., 2009; Mackenzie et al., 2010). The major neuropathological subtypes are: those with cellular inclusion bodies of tau (FTD-tau), those with TDP-43 pathology (FTD-TDP), those immunoreactive to the fused in sarcoma protein (FTD-UPS), those immunoreactive to class IV intermediate filaments (FTD-IF) and those lacking distinctive pathology (FTD-ni) (Mackenzie et al., 2010). As its name indicates, the atrophy expected in FTD is from a focal cortical and subcortical nature in the frontal and temporal lobes (Hugo, and Ganguli, 2014). Frontotemporal dementia is characterised by impairments in executive functions and language, and behavioural changes. Some of the genes associated with an increased risk of FTD are: MAPT, GRN, and C9or*f*72 (Bonvicini et al, 2019). GRN mutation has been associated with executive function impairment, whereas MAPT and C9or*f*72 have been associated with language impairment (Poos et al., 2020). The GRN mutation has also been shown to be associated with a faster decline on memory and attention (Poos et al., 2020).

In bvFTD, dysfunction begins in the orbitofrontal cortex (Hornberger et al., 2010); and afterwards expands to the medial frontal cortex, frontal insula, anterior cingulate, and bilateral anterior temporal lobes (Ossenkoppele et al., 2015). Rascovsky et al. (2011) proposed a revised diagnostic criteria for bvFTD, which establishes that three or more of the following symptoms must be present for possible bvFTD:

- behavioural disinhibition - impulsivity, socially inappropriate behaviour, and/or loss of manners
- apathy or inertia
- loss of sympathy or empathy - diminished social interest, personal warmth, and/or responses to other's needs and feelings
- perseverative, stereotyped or compulsive behaviour - speech stereotypy, simple repetitive movements, and/or complex behaviours that are compulsive or ritualistic

- hyperorality and dietary changes - binge eating, change in food preferences, and consumption or oral exploration of inedible objects
- executive deficits with relative sparing memory and visuospatial functions

The criteria for probable bvFTD includes in addition functional decline and imaging consistent with bvFTD via a frontal and/or anterior temporal atrophy, hypoperfusion or hypometabolism (Rascovsky et al., 2011). Although these criteria have shown to be more sensitive to diagnose bvFTD than previous criteria, they still have the disadvantage of being dependent on subjective reports.

Patients with bvFTD also present with cognitive impairments in executive functions, social cognition, fluency and verbal memory (Beeldam et al. 2018). Executive functions are the top-down mental processes that are needed for tasks that require attention (Diamond, 2013). Some studies have agreed on a model that sets 3 main executive functions: working memory, inhibition and cognitive flexibility/shifting (Miyake et al., 2000; Lehto et al., 2003). These main executive functions work as a base for other higher executive functions, such as planning, problem solving and reasoning (Diamond, 2013). Working memory is the ability to hold information in our mind and use it effectively; inhibition refers to the ability to control our own attention and behaviour by overriding impulses; and cognitive flexibility refers to the ability shift back and forth between tasks or perspectives, think outside the box and adapt our mindset to the present situation. Patients with bvFTD are often impaired in all three main executive functions, while AD patients are often impaired only in working memory (Stopford et al., 2012; Possin et al., 2013; Johns et al., 2009; Neary, Snowden and Mann 2005; Staffaroni et al., 2020). Executive dysfunction in bvFTD has been linked to a more severe functional impairment when compared to other forms of FTD (Moheb et al., 2017). As there are no definitive biomarkers for bvFTD, diagnosis depends on clinical profiles of impairment which often causes bvFTD patients to struggle to receive a diagnosis by being dismissed as “normal”, or by being misdiagnosed with AD

or psychiatric disorders (Rascovsky et al., 2011). Therefore, there is a need to improve awareness of the clinical presentation of bvFTD, and to improve the cognitive and behavioural assessments currently used for the diagnosis of bvFTD.

Primary Progressive Aphasia (PPA) is a focal dementia characterized by an impairment in language functions (Mesulam, 2001), usually associated with left hemispheric frontotemporal cortical atrophy (Teipel, et al., 2014). The pathologies associated with PPA are divided in four classes: a) AD, b) histopathological abnormalities associated with tau-positive immunoreactivity, c) TDP-43 pathology, and d) FTD histopathological negative for tau immunoreactivity but positive to ubiquitin immunoreactivity (Chare et al., 2014). Gorno-Tempini et al. (2011) have proposed a classification of PPA for reliability of research with three types: a) progressive non-fluent aphasia (PNFA) characterised by agrammatism, effortful and halting speech, and impaired comprehension of syntactically complex sentences; b) semantic dementia with features of impaired naming, impaired single word comprehension and object knowledge, and may also show dyslexia or dysgraphia; and c) logopenic PPA which includes impaired single-word retrieval in speech and naming, impaired repetition of sentences, and phonological errors. There is no clear distinction of which of these pathologies causes each type of PPA, as the three pathologies have been found in each type (Grossman, 2010). Nevertheless, a majority of PNFA patients have tau pathologies, a majority of semantic dementia have TDP-43, and a majority of logopenic PPA patients have AD (Marshall et al., 2018; Chare et al., 2014). As with bvFTD, there is not a single reliable diagnostic test for PPA, instead clinical presentation and imaging are used for diagnosis. However, there are some atypical cases that do not conform clearly to any of these subtypes of PPA. In addition, there has been some criticism regarding the lack of supporting evidence to validate logopenic PPA criteria (Rascovsky and Grossman, 2013); but a more recent neuroimaging study has found distinct

anatomical and functional patterns between the three types of PPA (Routier et al., 2018).

Posterior Cortical Atrophy (PCA) is a rare progressive syndrome characterised by atrophy of posterior brain regions with an emphasis in a decline in visual processing (Crutch et al., 2017). Some of the aetiologies underlying PCA are AD (most common), CBD, dementia with Lewy Bodies (DLB), and prion disease (Crutch et al., 2013). The main clinical manifestations of PCA are visuospatial and visuoperceptual impairments (Coppi et al., 2014). PCA patients typically have early onset, therefore they are usually younger than amnestic AD patients and they present less impairment in memory and fluency (Crutch et al., 2013; Mendez et al., 2002). Verbal memory, language, executive functions and behaviour are often relatively spared in the early stages of the disease (Crutch et al., 2017). Crutch et al. (2017) proposed diagnostic criteria for PCA based on three or more of the following: agnosia (faces, places, fingers, objects, and/or simultanagnosia), apraxia (dressing, limb, oculomotor and/or optic), acalculia, agraphia, alexia, constructional dyspraxia, vision loss, left/right disorientation, and/or space perception deficit. PCA patients are often misdiagnosed, some of the contributing factors for a delayed diagnosis might be the rarity of the disease, its variable presentation, and patients are often referred to ophthalmologists who might not identify the disease (Crutch et al., 2013). Furthermore, the visual impairments PCA patients present can pose additional challenges to how they are assessed cognitively.

Vascular dementia is the second most common cause of dementia and is the result of large and/or small vessel disease (Hugo and Ganguli, 2014). For diagnosis there should be a history of transient ischemic attacks or a stroke related to the cognitive decline (Hugo and Ganguli, 2014). Some of the factors that define the subtypes of vascular dementia are the location of changed tissue, the degree of involvement of extra and intracranial vessels, the nature of the vascular pathology, and the extent of the damage (Kalaria, 2016). Vascular dementia often presents in combination with AD (Jellinger, 2008).

Mild Cognitive Impairment (MCI) can be defined as an impairment in one or more cognitive domains, with evidence of change from a previous level, while preserving independence in functional abilities (Albert et al, 2011). The concept of MCI was originally intended to describe patients who were considered to have mild AD but who did not meet the required diagnostic criteria of impairment in two or more cognitive domains (Mufson et al., 2012). As it is not a specific concept and its clinical presentation can vary (although the most common is amnestic), the pathological substrates in MCI can also vary to include (but not limited to) amyloid-beta plaques, neurofibrillary tangles, neuronal loss (particularly in the hippocampus and entorhinal cortex), synaptic degeneration, structural changes on the medial temporal lobe, reduced cortical cholinergic activity, neurotrophic abnormalities, endosomal and oxidative stress, and vascular disease (Mufson et al., 2012). It is sometimes considered a state between normal cognitive ageing and early dementia, particularly AD (Petersen, 2004). However, some MCI patients remain stable, others recover, and others progress to different dementia types (Winblad et al., 2004). Impairment in visuospatial memory in those with early onset, and verbal memory in those with late onset have been found to be predictors of progression to AD (Ye et al., 2012). Prevalence has been found to be about 16% of older adults without dementia (Petersen et al., 2010), and rates of conversion to dementia have been found between 3% to 15% per year (Farias et al., 2009). Subjective cognitive impairment refers to self-experienced decline in cognition that is not explained by a medical condition nor substance, but with a normal performance on standardised cognitive assessments (Jessen et al., 2014). Subjective cognitive impairment has been associated with future cognitive decline (Jessen et al., 2014), but also with some personality traits and depression (Reid and MacLullich, 2006). Accurate appraisal of cognition and therefore self-awareness of individual capacities varies between patients (Roberts, Clare and Woods, 2009).

Differences in cognitive profiles between early onset and late onset dementia have been found for some types of dementia. Patients with early onset AD are

often more impaired in attention, executive functions, visuospatial abilities and visual memory than those with late onset (Smits et al., 2012; Park et al., 2015). Patients with late onset FTD are often more impaired in visuospatial abilities and memory than those with early onset (Shinagawa et al., 2008). While no differences in cognition have been found between early onset and late onset MCI (Ye et al., 2012). Early onset dementia patients generally deteriorate faster and have a higher mortality risk than those with late onset (Koedam et al., 2008; Stanley and Walker, 2014).

1.3 Cognitive Screening and Brief Assessments for Dementia

The most common dementia screens used in the UK in primary care are the Mini-Mental State Examination (MMSE), the Six-Item Cognitive Impairment Test (6CIT), The Montreal Cognitive Assessment (MoCA) and the Addenbrooke's Cognitive Examination (ACE/ACE-R/ ACE-III) (Larner, 2017). The MMSE (Folstein, Folstein and McHugh, 1975) is a very brief cognitive screening tool (10 min administration time), which has been shown to be sensitive to the different types of dementia (Tombaugh and McIntyre, 1992; Alexopoulos et al., 2010; Kaszás et al., 2012). In 2004 it was estimated to be used by over 90% of neurologists in the UK (Davey and Jamieson, 2004) and severity ranges of scores for dementia have been defined (Perneczky et al., 2006). However, sensitivity values to dementia have ranged between 36% to 93%, and it has consistently been shown to be less sensitive than the Addenbrooke's Cognitive Examination and/or the MoCA in different dementia diagnoses, including AD, FTD, and Parkinson's (Larner, 2012; Matias-Guiu et al., 2017; Alexopoulos et al., 2010; Kaszás et al., 2012; Schultz-Larsen, Lomholt, and Kreiner, 2007). In addition, the MMSE has shown a low sensitivity to MCI, as well as a lower accuracy to detect dementia in those with a lower education (Nasreddine et al., 2005; Jacova et al., 2007; Narasimhalu et al., 2008; Mitchell, 2009). MMSE scores have correlated moderately to prior cognitive ability (Dykiert et al., 2016), and large interrater variability has been found (Davey and Jamieson, 2004). Further limitations of the MMSE arise as a consequence of its brevity, as the MMSE lacks an assessment of executive

functions and the memory assessment is minimal (only 3 out of 30 points are memory related, which are objects recall) (Carnero-Pardo, 2014). Therefore, the MMSE provides a general score for cognition, but it is not able to provide a profile of cognitive impairment to differentiate between diagnoses.

The Six-Item Cognitive Impairment Test (6CIT) (Katzman et al., 1983) is a very brief cognitive screen. It is slightly shorter than the MMSE, does not require the patient to be literate or to handle a pen, and it has clear rules to avoid interpretation errors (Tujil et al., 2011). However, it only includes one question of memory, two calculations, and three orientation questions; therefore, its utility in primary care settings has been questioned (Larner, 2017). Nevertheless, a study has found the 6CIT to be more sensitive but less specific for a dementia diagnosis than the MMSE (Abdel-Aziz and Larner, 2015). The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) was originally developed as a short cognitive screen for MCI. It includes the domains of visuospatial/executive, naming, memory, attention, language, abstraction and orientation; and has a maximum score of 30 points (Larner, 2017). Although the MoCA has shown to be more sensitive to detect MCI (Nasreddine et al., 2005) and bvFTD (Freitas et al., 2012) than the MMSE, some studies have found the MMSE to be more sensitive to AD than the MoCA (Matias-Guiu et al., 2017). The MMSE, the 6CIT and the MoCA have been used to assess general cognition and have the advantage of being very brief in their clinical application. However, their modern counterparts have an advantage in their focus of providing individual domains to differentiate profiles of impairment between diagnoses. This difference has caused modern brief assessments to be more sensitive to detecting cognitive impairment on individual dementia diagnoses.

The Addenbrooke's Cognitive Examination (ACE-III) (Hsieh et al., 2013) is a longer and more comprehensive screening test for dementia. It includes the domains of attention, memory, fluency, language and visuospatial abilities; and it has shown to be more sensitive to AD (Matias-Guiu et al., 2017) and

everyday functional impairments (Giebel and Challis, 2017) than the MMSE and the MoCA. The ACE-III does not assess executive functions apart from verbal fluency and there is no assessment of behavioural abnormalities; therefore, the validation study in AD and FTD proposed bvFTD diagnosis to be confirmed with an additional behavioural inventory and functional assessment (Hsieh et al., 2013). Furthermore, the sensitivity values given in this study (sensitivity 93-100%, specificity 96-100%) were given for a general diagnosis of dementia that comprised AD, PPA, and bvFTD. A study which compared the ACE-III between different dementia diagnoses in an early onset population, found that the lowest sensitivity was towards the bvFTD group (in comparison to AD, PPA, and PCA) (Elamin et al., 2015).

The ACE-III has been validated in dementia for those over 75 with a group of AD and vascular dementia patients (sensitivity 82%, specificity 77%) (Jubb and Evans, 2015); and to cognitive impairment after stroke (sensitivity 66-100%, specificity 1-35%) (Lees et al., 2017). However, its sensitivity to detect FTD, and particularly bvFTD has been inconsistent (Yoshida et al., 2011; Elamin et al., 2016). A study found that the ACE-III was sensitive to dementia (sensitivity 86-100%, specificity 79-95%) with a group that included a bigger sample of bvFTD (n=82), but also included AD (n=69), PPA, corticobasal syndrome, PCA, mixed FTD-MND and other dementias (So et al., 2018). Nevertheless, this study stated that there were significant age and education differences between their healthy control sample and the dementia group, which could have skewed the results. The same study provided cut-offs per diagnosis (AD, bvFTD, PNFA, and logopenic PPA) and for mild, moderate and severe dementia according to the CDR (So et al., 2018). However, this study also stated that the cut-offs should be used with caution as statistical assumptions were violated. The authors did not clarify what assumptions were violated; however, both PPA groups had 23 patients each, therefore the study probably did not include enough patients per severity stage per diagnosis.

In other languages the ACE-III has shown sensitivity to distinguish between dementia, and MCI and controls; though, these studies did not include sensitivity per diagnosis and the percentage of each patient group varied between studies. In the Chinese version, the ACE-III was sensitive to MCI (sensitivity 75%, specificity 89%) and dementia vs MCI and controls (sensitivity 94%, specificity 83%) (Li et al., 2019). In this study the dementia group included patients with AD, vascular dementia, mixed dementia, Lewy bodies, Parkinson's disease, and bvFTD. The Japanese version was also validated in MCI (sensitivity 77%, specificity 92%) and assessed dementia vs MCI and controls (sensitivity 82%, specificity 90%) (Takenoshita et al., 2019). Their dementia group included patients with AD, bvFTD, vascular dementia, Lewy bodies, and others; however, only 23% of those patients did not have AD. The Malay version was sensitive to dementia against healthy controls (sensitivity 90%, specificity 82%) (Kan et al., 2019). However, it was not very sensitive to discern between MCI and dementia (sensitivity 63%, specificity 63%). The Malay version only included patients with AD (60%), vascular dementia and mixed dementia for their dementia group. The Spanish version was also sensitive to differentiate between dementia and healthy controls (sensitivity 83%, specificity 80%) (Matias-Guiu et al., 2015). Although it is to be noted that this study was the one with the most diverse group of dementia, having only 54% AD, while the rest had vascular dementia, mixed dementia, Parkinson's disease, alcoholic dementia, Lewy bodies, and frontotemporal dementia (including bvFTD and PPA). Individual sensitivity values and abnormality cut-off scores should be given for different dementia diagnoses so that patients are not overlooked or misdiagnosed in their initial assessments, more so if executive functions and behavioural questionnaires are not included in the assessment. Other brief assessments could be more suitable for the assessment of FTD, in particular bvFTD, than the ACE-III; as it lacks a domain of executive functions separate to the fluency domain, and it does not include a behavioural questionnaire.

1.4 The ECAS

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was originally developed to assess cognitive and behavioural changes observed in amyotrophic lateral sclerosis (ALS) (Abrahams et al. 2014); as between 10-15% of ALS patients develop FTD, and an additional 35% develop a milder cognitive impairment of frontotemporal dysfunction (Goldstein and Abrahams, 2013; Strong et al., 2017). Previously existing screening tests did not include the full range of cognitive and behavioural changes related to ALS and did not account for possible physical disabilities. The ECAS administration time is ~20 mins and has a maximum total score of 136. In addition, the ECAS includes a 10-question behavioural interview, to complete with the carer or family members, that comprises the five domains of the diagnostic criteria for bvFTD (Rascovsky et al., 2011). The domains included are apathy or inertia; disinhibition; hyperorality and altered food preferences; loss of sympathy or empathy; and perseverative, stereotyped, compulsive or ritualistic behaviour. It also includes 3 questions regarding psychotic symptoms including delusions, hallucinations and paranoia.

The ECAS includes assessments of the domains of language, fluency, and executive functions which are typically affected in ALS, but it also includes assessments of the domains of memory and visuospatial abilities to differentiate changes in ALS from other pathologies, such as AD (Abrahams et al. 2014). The ECAS provides two composite scores to differentiate these clinical profiles: ALS-Specific Composite Score and ALS Non-Specific Composite Score. The language domain includes the tasks of naming, comprehension, and spelling. Impairments in these three functions have been found in bvFTD and PPA with similar tests (Saxon et al., 2017; Riello et al., 2018; Shim et al., 2012; Sonty et al., 2003). Fluency has also been found impaired in bvFTD and PPA (Ranasinghe et al., 2016; Sonty et al., 2003). The domain of executive functions in the ECAS assesses all three main executive functions unlike other brief cognitive assessments. Reverse digit span assesses working memory, alternation assesses cognitive flexibility/shifting,

and sentence completion assesses inhibition. This domain additionally includes an assessment of social cognition, which has been found to be impaired in FTD and ALS (Snowden, et al., 2003; Girardi, MacPherson, and Abrahams, 2011). The sentence completion task of the ECAS was based on the Hayling Sentence Completion test, which has been shown to be sensitive to bvFTD (Hornberger et al., 2008). Memory is assessed by story recall, which has been found to be impaired in MCI and AD; and has been identified as a predictor of beta-amyloid positive status (Mahendra, Bayles and Harris, 2005; Mueller et al., 2020; De Simone et al., 2017). The tasks from the visuospatial abilities domain were based on The Visual Object and Space Perception Battery (VOSP), in which AD patients have shown to be impaired (Salimi et al., 2019).

The ECAS has been validated for cognitive impairment in ALS patients against a comprehensive neuropsychological examination demonstrating high sensitivity and specificity in detecting cognitive impairment (sensitivity 85-100%, specificity 80-85%) (Niven et al., 2015; Pinto-Grau et al., 2017). Niven et al. (2015) validation study included multiple tests for each of the domains of the ECAS. Some of the tests incorporated were Phonemic verbal fluency index, Hayling Sentence Completion test, Reading the mind in the Eyes, Brixton Spatial Anticipation test, Boston Naming Test, Test for Reception of Grammar, the VOSP, and the BIRT Memory and Information Processing Battery. The ECAS was sensitive to cognitive impairment in ALS and was validated against the comprehensive neuropsychological assessment. However, some patients who were impaired on the ECAS, were only impaired on an individual test on the neuropsychological assessment; and therefore, did not meet the criteria established in the study to be labelled as impaired on the neuropsychological assessment. These criteria specified impairment as being impaired in two out of three or one out of two tests in any domain. In three out of four of these cases, patients scored very close to the abnormality cut-off scores of the ECAS; which could bring to question if the ECAS can elicit some false positives in ALS patients, or is the ECAS being better at discerning a

cognitive impairment in ALS than some of the tests used in standard neuropsychological assessments. A follow up of these cases could have been of interest, to see if the patients progressed to be classified as cognitively impaired, or remained cognitively stable, or improved their ECAS scores by a couple of points to not be in the impaired range anymore.

Niven et al. (2015) also suggested a borderline range that could optimize the clinical use of the ECAS; and pointed out the need for specific age and education impairment cut-offs, as there were significant correlations between these variables and the ECAS scores. Pinto-Grau et al., (2017) created abnormality cut-offs for an Irish population on the ECAS by age and education; although, they were much higher than the ones originally proposed by Abrahams et al. (2014). Additionally, some of the cut-offs for abnormality proposed for the domains were not congruent with the trend expected by the effect of age and education on the groups. For example, within the memory domain one would expect there to be an age effect with older adults having a worse performance. In contrast, for those with an education higher than 12 years, the cut-off for abnormality is higher for people over 65 than what it is for people younger than 65, which contrasts with those with a lower education as the cut-off is higher for the younger group. Poletti et al. (2016) also created age and education cut-off scores for the Italian population which were much closer to the original ones (Abrahams et al., 2014), albeit the ones for a lower education level were lower than expected. It is to be noted that these studies had different ages for the classification of younger versus older patients; the age division was of 65 years old for Pinto-Grau et al., (2017), while the age division on Poletti et al. (2016) was of 60 years old. The differences of results however may also be explained due to differences in the populations and versions used for each study.

The ECAS has been shown to have convergent validity with the MoCA, the Frontal Assessment Battery and the Consortium to Establish a Registry for Alzheimer's Disease plus Scale (Poletti et al., 2016; Lulé et al., 2015).

Alternative versions of the ECAS have been developed to avoid practice effects (Crockford et al. 2018a), and reliable change indices are available to assess change (Crockford et al. 2018b) on repeated assessments. The ECAS has also been compared with the King's Clinical Staging System in ALS, where it was found that ALS-Specific cognitive impairment and behavioural changes were more frequent with severe disease stage in ALS indicating some progression through the disease course (Crockford et al. 2018c). The ECAS has shown to raise awareness of the possible cognitive and behavioural changes ALS patients might experience, while also prompting discussions regarding the end-of-life care and providing economic benefits by reducing assessment times with clinicians. (Hodgins, Mulhern and Abrahams, 2019). Furthermore, the ECAS has been translated to Chinese (Ye et al., 2016), German and Swiss-German (Lulé et al., 2015), Greek (Kourtesis et al., 2019), Italian (Poletti et al., 2016), Norwegian (Taule et al., 2019), Spanish (Mora et al., 2017), Dutch (Bakker et al., 2019), American English, Croatian, Czech, French, Hebrew, Japanese, Polish, Portuguese, Russian, Slovak, Slovenian, Swedish and Welsh (see http://ecas.psy.ed.ac.uk).

The ECAS has been used to correlate cognitive impairment in ALS patients without dementia to regional distributions of pathology (Gregory et al., 2020). In this study patients were previously assessed with the ECAS during their life, and brain tissue was analysed post-mortem. They found that the ALS-Specific Composite Score of the ECAS predicted with 100% specificity the TDP-43 pathology in extra-motor areas. The study also found a correlation between the individual domains of the ECAS to TDP-43 pathology in specific brain regions which have been previously found to be sensitive to those domains.

One study looking at the reliability of the ECAS has criticised some aspects of the test (Díaz et al., 2019). One of the criticisms stated that the ECAS requires patients to have suitable ability for oral and motor responses, as any deficit could be overestimated. This criticism was based on their finding that there was a higher percentage of participants impaired on the ECAS than on the

neuropsychological assessment. However, only a third of their participants completed both the ECAS and the neuropsychological assessment, while the other participants completed one or the other. Therefore, a true comparison cannot be formed based on the total percentage of patients. Not to mention, the ECAS is precisely one of the few tests which actually accommodates for disabilities, by allowing the patient to respond either spoken or written and with a verbal fluency index calculation to control for the time it takes for the patient to respond.

The ECAS has been validated in AD on a Greek sample (Kourtesis et al., 2020), in which it was found to have a sensitivity similar to the ACE-III (ECAS total score sensitivity 95%, specificity 97%; ACE-III sensitivity 97%, specificity 97%). The ECAS has also been validated for the use of Parkinson's disease and progressive supranuclear palsy against an extensive neuropsychological assessment (Foley et al. 2018). The study found that the ECAS fluency score was able to differentiate between diagnoses (sensitivity 82%, specificity 80%), The ECAS total score was also sensitive to progressive supranuclear palsy against healthy controls (sensitivity 91%, specificity 86%), and MCI in Parkinson's disease versus Parkinson's disease without cognitive impairment (sensitivity 88%, specificity 100%). A comparison has also been made on the Greek sample between ALS and AD in which the ECAS ALS Non-Specific Composite Score (memory and visuospatial domains) was sensitive to differentiate these diagnoses (Kourtesis et al., 2019). When compared to healthy controls, patients with ALS-FTD and patients with bvFTD have been found to be impaired on the ECAS and the ALS-Specific Composite Score, but also surprisingly on the ALS Non-Specific composite score (Saxon et al., 2020). This study showed evidence of convergent validity with four neuropsychological tests but did not include a comprehensive neuropsychological assessment nor other cognitive screens. The tests included were the Graded Naming test, Palpa spelling, part B of the Hayling Sentence Completion test, and Judgment of Preference from the eye gaze test. These tests assess language and executive functions similar to the

subtasks of naming, spelling, sentence completion and social cognition from the ECAS. Convergent validity was shown by correlating the ECAS subtask with the corresponding neuropsychological test and by comparing their sensitivity to detect impairment based on abnormality cut-off scores made with the control group. The ECAS could be useful to differentiate between the diagnoses of frontal variant AD and bvFTD, as it includes anterior and posterior subscores (ALS-Specific Composite Score and ALS Non-Specific composite score) and a behavioural questionnaire based on the diagnosis criteria of bvFTD.

1.5 This Thesis

In this thesis I explore whether the Edinburgh Cognitive Examination ALS Screen (ECAS) (Abrahams et al., 2014) is a sensitive test to the types of cognitive and behavioural changes in people with early onset dementia without Amyotrophic Lateral Sclerosis (ALS). Given that previous studies had shown that the ECAS scores were related to age and IQ/education, in the first study I looked at the effect of these two variables on performance and created age (below and above 65) and education (with or without a university degree) abnormality cut-offs within a healthy population. I also compared performance between the ECAS and the ACE-III. In the second study I validated the ECAS against a comprehensive neuropsychological assessment and compared it with the ACE-III in groups of patients with bvFTD, AD, PPA, PCA and MCI. As part of the second study, I also determined whether the behavioural interview of the ECAS had additional value in distinguishing between bvFTD and AD through a qualitative thematic analysis of the interviews. Finally, for the third study I investigated the ECAS in assessing changes over time in a dementia population; and looked at the relationship with the Clinical Dementia Rating Scale (CDR-FTLD) (Knopman et al., 2011), the Frontal Behavioral Inventory (FBI) (Kertesz et al., 1997), and the Frontotemporal Dementia Rating Scale (FRS) (Mioshi et al., 2010). I additionally looked at how the ECAS related to functional severity of dementia.

The overarching aim of this thesis was to investigate the validity of the ECAS in assessing people with early onset dementia without ALS.

More specifically I aimed to:

- Determine the sensitivity of the ECAS to bvFTD without ALS, AD, MCI, PPA, and PCA.
- Assess its validity in assessing the different profiles of cognitive and behavioural impairments in people with dementia, by comparing it to a) one of the most commonly used dementia screening test in the UK, the ACE-III, and b) to comprehensive neuropsychological assessment.
- Determine the effect of age, education, and IQ on the ECAS in a healthy population.
- Determine whether the themes reported in the behavioural interview differed between diagnostic groups of bvFTD and AD.
- Investigate the relationship between the ECAS and functional severity of dementia.
- To validate the behavioural interview of the ECAS with other behavioural screens used to assess FTD.
- Determine whether the ECAS scores changed over time in bvFTD, AD, MCI, PPA, and PCA.

Chapter Two

The Edinburgh Cognitive and Behavioural ALS Screen; relationship to age, education, IQ and the Addenbrooke's Cognitive Examination-III.

2.1 Introduction to article

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) has been previously validated in Amyotrophic Lateral Sclerosis (ALS) against an extensive neuropsychological assessment. However, a direct comparison with another short cognitive screen had not been explored prior to this research. Comparing the ECAS against another short cognitive screen was important to explore its potential advantages or disadvantages against other widely used cognitive screening assessments for future clinical use. Because the ECAS was developed for ALS, it already had the advantage of including the option for verbal or written answers to adjust for motor impairments. However, it was unknown how it would compare to other short screens in terms of ceiling or floor effects, and how much demographic factors would have an effect on the ECAS in comparison to other screens. I chose to compare the ECAS against the ACE-III, as they both are multidomain with similar assessment times; and the ACE-III is one of the most commonly used cognitive tests in the UK to diagnose dementia.

In addition, the effect of demographic factors on the ECAS had not been explored previously on a British population. It had been previously shown that age and education had an effect on the scores of the ECAS when assessed on other populations. Therefore, the following study was done to explore the hypothesis that age and education would have an effect on the scores on the ECAS with a British population, and if this hypothesis was to be true, to create age and education cut-off scores accordingly for future clinical use.

The following article overleaf was published in the Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration Journal in October 2018 and is reported verbatim here. The published article is included on Appendix II. The additional information marked at the end of the chapter was not included in the original publication. The reference for this article is: Mónica M. De Icaza Valenzuela, Thomas H. Bak, Suvankar Pal & Sharon Abrahams (2018): The Edinburgh Cognitive and Behavioral ALS screen: relationship to age, education, IQ and the Addenbrooke's Cognitive Examination-III, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 19, (7-8), 585-590. (DOI:10.1080/21678421.2018.1491601).

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Research Article

The Edinburgh Cognitive and Behavioral ALS Screen; relationship to age, education, IQ and the Addenbrooke's Cognitive Examination-III.

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2.1.1 Abstract

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was developed to assess cognitive and behavioural changes common in Amyotrophic Lateral Sclerosis and other diseases affecting motor functions. It focuses on domains typically affected by the frontotemporal syndrome (executive and language functions, fluency and behaviour), but assesses also memory and visuospatial functions. *Objectives*: (A) To investigate the relationship between the ECAS and the Addenbrooke's Cognitive Examination (ACE-III). (B) To investigate the effects of age, education, and IQ on the ECAS and create appropriate cut-off scores to determine abnormality. *Methods*: (A) 57 healthy participants (aged 35-80) were assessed with the ECAS, the Wechsler Abbreviated Scale of

Intelligence (WASI-II), and the ACE-III. (B) 80 healthy participants (aged 51-80) were divided into four groups according to age and education; and were tested with the ECAS and the WASI-II. *Results:* The ECAS and the ACE-III have a good convergent validity with a significant correlation. Regression analysis revealed that IQ, followed by age, were the strongest predictors of the total ECAS score. IQ predicted 24% of the ECAS and 46% of the ACE-III variance. Education was not a significant predictor over and above IQ for both the ECAS and the ACE-III. Abnormality cutoff scores adjusted for age and education are presented. *Conclusions:* The ECAS shows good convergent validity with the ACE-III, but is less influenced by intelligence and presents less ceiling effects. The inclusion of an executive function assessment and behavioural interview in the ECAS makes it particularly useful for the assessment of frontal lobe disorders.

Key words: *ECAS, education, age, IQ, frontotemporal dementia, screen, cognition, behaviour*

2.1.2 Introduction

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was developed to assess the cognitive and behavioural changes associated with amyotrophic lateral sclerosis (ALS) (Abrahams et al. 2014) since a significant percentage of these patients develop a fronto-temporal degenerative syndrome (Goldstein and Abrahams, 2013; Strong et al., 2017). The neuropsychological profile of ALS is somewhat heterogeneous and previous existent cognitive screening tests did not assess the full range of cognitive and behaviour change present in ALS, and most were not suitable for patients with physical disability. The ECAS has proven to be sensitive to detect the changes in executive functions, fluency, and language in patients with ALS; in addition, it was designed to differentiate these changes from those found in other pathologies, including Alzheimer's disease (Abrahams et al. 2014). It has also been validated against

extensive neuropsychology showing high sensitivity and specificity (Niven et al., 2015; Pinto-Grau et al., 2017) and against other screening tests including the Frontal Assessment Battery, Montreal Cognitive Assessment (MoCA) and Consortium to Establish a Registry for Alzheimer's Disease plus Scale (Lulé et al., 2015; Poletti et al., 2016).

The Addenbrooke's Cognitive Examination (ACE-III) is a widely used dementia screening test in the UK (Jeyapaul and Kerwick, 2008). It is proven to have very good diagnostic accuracy for patients with memory complaints (Jubb and Evans, 2015); with greater accuracy than the MoCA, the Mini-Mental State Examination and the Memory Impairment Screen (Matías-Guiu et al., 2017). We chose the ACE-III to compare against the ECAS over other screening tests, because it is one of the most commonly used cognitive tests in the UK and beyond to diagnose dementia. It has been validated in a number of patient groups (Lees et al., 2017; Davies et al., 2008; McColgan et al., 2012). Furthermore, both the ACE-III and ECAS are multidomain and have similar assessment times (Velayudhan et al., 2014; Newman et al., 2018; Morris and Brookes, 2013). Although designed for the detection of different types of dementia, its sensitivity to detecting frontotemporal dementia and in particular the behavioural variant (bvFTD) is inconsistent (Yoshida et al, 2011; Bier et al, 2004; Elamin et al., 2015). Hsieh et al. (2013) showed that patients with bvFTD displayed a cognitive profile consisting of deficits in verbal memory, attention, fluency and language using the ACE-III. However, apart from verbal fluency, the ACE-III does not include an assessment of executive functions, the most prominent cognitive deficit in this type of dementia. Furthermore, the sensitivity and specificity of the given cut-off scores are for a general diagnosis of dementia that comprises Alzheimer's Disease, bvFTD and Primary Progressive Aphasia. They propose that fronto-temporal dementia should be confirmed with specific functional and behavioural inventories such as the Cambridge Behavioural Inventory, the Neuropsychiatric Inventory or the FTD Rating Scale FRS. Given the inclusion of tests of executive functions and an informant interview to detect abnormal behaviours, based on the most recent

diagnostic criteria for bvFTD (Rascovsky et al., 2011), the ECAS may be a more suitable test to assess this type of dementia.

The effect of demographic factors including age and education has been explored using local and/or translated versions in German, Italian, Chinese and Irish (Lulé et al., 2015; Poletti et al., 2016; Pinto-Grau et al., 2017; Loose et al., 2016; Ye et al., 2016) but not in a British population. Age has been found to significantly correlate with total ECAS scores in most studies (Lulé et al., 2015; Poletti et al., 2016; Pinto-Grau et al., 2017; Loose et al., 2016), with the exception of one (Ye et al., 2016). Although education was shown to correlate with ECAS scores across studies, the relation to measures of IQ has not been explored. Given the correlation between age and education found in the German, Italian and Irish studies, age and education adjusted local normative data have been produced.

This study had two primary aims:
Objective 1: Investigate the relationship between the ECAS and ACE-III.
Objective 2: Investigate the effect of age, education, and IQ on the ECAS in a healthy population to create appropriate adjusted cutoff scores to detect abnormality.

2.1.3 Methods

2.1.3.1 Relationship between the ECAS and the ACE-III

Participants
Healthy individuals (n=57) between the ages of 35 to 80 years old were recruited from the local population and the Psychology Volunteer Panel of the University of Edinburgh. Participants did not have any neurological illness in their medical history, or current psychiatric illness, or any learning disabilities. All were native English speakers.

A minimum of 55 participants was decided for this study, in order to predict a medium effect size (f^2= 0.15) (Cohen, 1988), with an alpha of 0.05 and a power of 0.80 in a linear regression of one predictor (Field, 2009). A sample size of 55 is also adequate for predicting a large effect size (*p*= 0.5), with an alpha of 0.05 and a power of 0.80 in a correlation (minimum sample size would have been of 21). Both calculations were done using G*Power (Faul et al., 2007).

Materials

ECAS. The ECAS is a short screening test (15-20 min) created to assess symptoms associated with cognitive and or behavioural impairment present in ALS. The ECAS is multidomain, providing subscores for language, fluency, executive, memory and visuospatial abilities. Language is evaluated by naming, comprehension and spelling. Fluency is measured by a free production of words beginning with the letter 's' and a restrained production of words beginning with the letter 't' but with only four letters. Executive functions are measured by a reverse digit span, alternation of letters and numbers, inhibitory sentence completion, and social cognition. Memory includes measurements of immediate recall, delayed percentage retention and delayed recognition. Visuospatial abilities are measured with dot and cube counting, and number location. The ECAS also includes a behaviour interview based on diagnostic criteria for bvFTD that is undertaken with an informant/carer (Abrahams et al. 2014, see http://ecas.psy.ed.ac.uk).

ACE-III. The ACE-III is a commonly used screening test for dementia. It assesses the abilities of attention, memory, fluency, language and visuospatial functions (Noone, 2015).

Wechsler Abbreviated Scale of Intelligence (WASI-II). The WASI-II is the brief version of the Wechsler Adult Intelligence Scale. We used the 15 minutes version with 2 subtests to obtain a measure of intelligence (Vocabulary and Matrix Reasoning) (Wechsler, 2011).

2.1.3.2 The Effect of Age and IQ on the ECAS

Participants

A total of 80 participants undertook this study. A total of 33 participants from the first study were included; and an additional 47 healthy individuals between the ages of 51-80, recruited from the local population and the Psychology Volunteer Panel of the University of Edinburgh. Participants did not have any neurological illness in their medical history, or current psychiatric illness, or learning disabilities. All were native English speakers. Social economical status was obtained based on the occupation of the participants. The classification was done according to the Standard Occupational Classification proposed by the Office for National Statistics (2010).

Participants were divided into 4 groups according to their age and education. Age: 51- to 65- and 66- to 80- years old; these age ranges were chosen to parallel typically used division for early versus late onset dementia. Education: secondary school or a technical degree vs university degree, or postgraduate degree. A minimum of 19 participants per group was decided in order to predict a large effect size (f= 0.40) (Cohen, 1988), this number of participants was obtained using an alpha of 0.05 and a power of 0.80 (Field, 2009) for a one-way ANOVA using G*Power (Faul et al., 2007), we included in some of the groups 1 or 2 more participants in case we needed to exclude some outliers.

2.1.3.3 Ethical Approval

This study was approved by The Psychology Research Ethics Committee of the University of Edinburgh.

2.1.3.4 Statistical Analysis

The data were analysed using SPSS statistics version 22. Pearson's correlations were used to assess the relationship between variables. ANOVA and t Tests were undertaken on parametric data to assess the difference between groups. ANOVA stepwise linear regression was used to find the

variables that predicted the final score of the ECAS. ANOVA linear regressions were done to find the effect of IQ on the ECAS and the ACE-III.

2.1.4 Results

2.1.4.1 Relationship between ECAS and ACE-III

The sample had 34 males and 23 females with a mean age of 56 years (±13.29, 35-80). The age of when they finished education was of 19.22 years (±3.20, 14-26), and their mean IQ was of 111.23 (±16.73, 75-156). Performance of participants on the ECAS and the ACE-III is presented in Table 1. The total scores of the ACE-III and the ECAS were significantly and moderately correlated (r = .538, p < 0.001). Memory (r = .368, p = 0.005), Fluency (r = .503, p < 0.001) and Language (r = .411, p = 0.002) correlated significantly between screens, however Visuospatial abilities (r = .197, p < 0.141) did not correlate between both tests.

As can be seen in Figure 1 the ACE-III suffered from more ceiling effects than the ECAS with some participants achieving full marks for the ACE-III, whereas none reached the maximum score for the ECAS. ANOVA linear regression models showed that 24% of the variance of the total score of the ECAS ($F(1,54)=17.292$, $p< .001$) was predicted by IQ (β=.492, t=4.15, p<.001), whereas 46% of the variance of the total score of the ACE-III ($F(1,54)=46.187$, $p< .001$) was predicted by IQ (β=.679, t=6.79, p<.001).

Overall, the scores of the domains of the ACE-III were more dependent on IQ than the domains in the ECAS. The percentage of the variance explained by IQ was higher in the ACE-III for the domains of Memory (29% vs 22%) and Visuospatial (7% vs 2%). Language was the same for both tests (30%). Fluency was more dependent on IQ for the ECAS (12% vs 21%). The

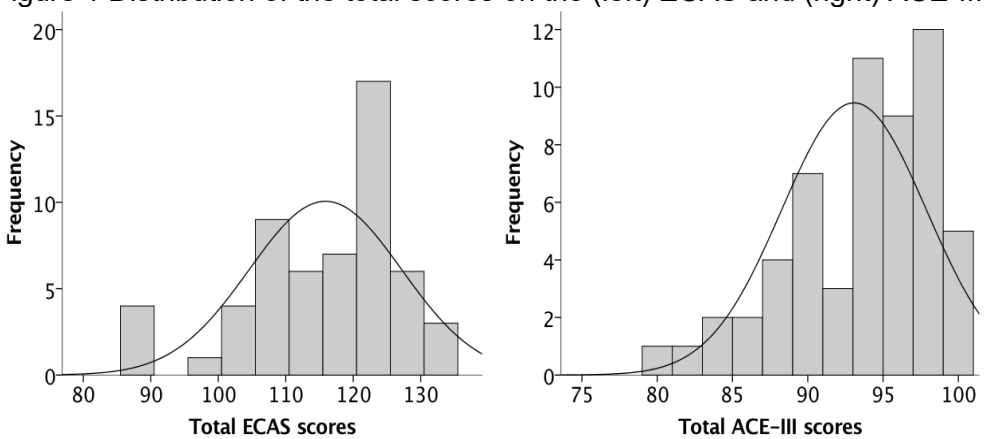
percentage of the variance explained by IQ was 16% for Attention on the ACE-III and 9% for the Executive domain on the ECAS.

Table 1: Performance on the ECAS and ACE-III:

N=57	(max)	Mean (SD)	Median (range)
ECAS total	136	115.87 (±11.30)	118 (88-134)
ECAS language	28	26.71 (±1.81)	27 (20-28)
ECAS fluency	24	19.40 (±3.46)	20 (10-24)
ECAS executive	48	39.71 (±4.69)	40 (22-47)
ECAS memory	24	19.22 (±3.57)	20 (7-24)
ECAS visuospatial	12	11.59 (±0.90)	12 (7-12)
ACE-III total	100	93.07 (±4.81)	94 (80-100)
ACE-III attention	18	17.01 (±1.10)	17 (13-18)
ACE-III memory	26	23.10 (±2.93)	24 (15-26)
ACE-III fluency	14	12.59 (±1.29)	13 (9-14)
ACE-III language	26	25.33 (±0.87)	26 (23-26)
ACE-III visuospatial	16	15.01 (±1.14)	15 (11-16)

Standard Deviation (SD), Edinburgh Cognitive and Behavioural ALS Screen (ECAS), Addenbrooke's Cognitive Examination (ACE-III). Maximum score (max)

Figure 1 Distribution of the total scores on the (left) ECAS and (right) ACE-III.



ECAS mean 115.88 (±11.303), ACE-III mean 93.07 (±4.81).

2.1.4.2 The effect of age, education and IQ.

Demographics of the full sample are presented in Table 2. There were no significant differences regarding IQ ($F(1,78)=0.681$, $p=0.412$) nor in socioeconomic status ($F(1,78)=1.084$, $p=0.301$). Three outliers (more than 2 standard deviations from the mean) in the ECAS total score were removed from the data in the further analyses. The remaining sample presents scores from 97 to 134 on the total score of the ECAS.

Table 2: Demographics of The effect of age, education and IQ.

Age group	Education group	Participants	Age	Age at finishing education	IQ
51-65	1	20 total (10 m)	58.3 (±4.64) 52-65	17.35 (±2.08) 15-24	108.30 (±14.56) 75-139
	2	21 total (11 m)	59.23 (±3.72) 51-65	22.52 (±1.36) 21-26	128.38 (±11.34) 103-156
66-80	1	19 total (9 m)	73.00 (±3.38) 67-78	16.94 (±1.95) 14-22	115.26 (±15.24) 87-141
	2	20 total (10 m)	72.20 (±4.00) 67-80	22.45 (±1.73) 19-26	127.25 (±10.12) 111-142

Education was divided between participants without a university degree (1) and participants with a university degree (2). m (presumably males). Results are presented Mean (Standard Deviation) Range.

An ANOVA stepwise linear regression model was undertaken including the variables of gender, age, education, and IQ. The most significant model predicted 32.5% of the variance of the ECAS Total Score ($F(3,73)=11.736$, $p< .001$). This model included the variables of IQ ($\beta=.557$, $t=5.54$, $p<.001$), age ($\beta=-2.82$, $t=-2.81$, $p=.006$) and gender ($\beta=.197$, $t=2.04$, $p=.045$). Education was not significant in the model since it could be sufficiently explained by IQ ($r = .514$, $p < 0.001$). Women scored slightly higher on the total score of the ECAS (119.16) in comparison to men (116.21).

2.1.4.3 Abnormality Cut-off scores

Education and age adjusted cut offs for abnormality are presented based on Education (those with and without a university degree) and age (below and above 65). Abnormality cut-offs were based on the 5 percentile (Table 3). Education was chosen over IQ to create the cut-off scores for the ease of use in association with the ECAS within the MND clinical services, since it is more easily available to than IQ.

Table 3: ECAS age and education adjusted cut-off scores to determine abnormality for ECAS Total Scores.

Age	Education	Mean (SD)	Range	Cut-off
≤65	1	119.650 (±8.628)	100-134	100
	2	123.381 (±7.221)	110-133	110
>65	1	117.000 (±8.062)	98-129	98
	2	120.895 (±6.315)	108-131	108

Education was divided between participants without a university degree (1) and participants with a university degree (2). Standard Deviation (SD)

2.1.5 Discussion

This study demonstrated that the ECAS has a good convergent validity with a commonly used dementia screening test, the ACE-III. A comparison of performance on the two assessments revealed that the ECAS has less ceiling effects overall in comparison with the ACE-III, since not one of the healthy participants scored full marks on the ECAS. Performance on the ECAS also seems to be less influenced by intelligence levels in comparison with the ACE-III, as IQ predicted 24% of the variance of the ECAS against 46% in the ACE-III. Visuospatial scores were more dependent on IQ in the ACE-III (7% as compared with the ECAS 2%) which is most likely related to the drawing component of the cube and the clock tasks. Fluency was more dependent on IQ in the ECAS (21%) as compared with the ACE-III (12%) which may be related to the inclusion of a constrained fluency in the ECAS and the more demanding lexical search for 4 letter words. Overall, IQ predicted more

variance in the ACE-III over the ECAS which is most likely related to the different demands of the tests. The ACE-III includes the drawing figures such as a cube, the repetition of complex words and phrases and the inclusion of general knowledge questions. It is likely that some if not all of these components, may be performed better in people with higher IQ.

All domains of the ECAS correlated with their counterparts in the ACE-III apart from visuospatial functions. The lack of correlation between the measurements of visuospatial abilities may be related to different methods used to assess these functions in the two tests. The ECAS was created for people with physical disability, and therefore does not include drawing, which is required for the ACE-III. For patients with motor dysfunction impairment on the visual task in the ACE-III could be due to motor problems (weakness, dyspraxia or rigidity, interfering with the quality of drawing), while the ECAS reflects visuospatial functions independently of motor skills. A more in depth comparison of the ECAS and ACE-III in measuring the cognitive decline with patients of different dementias, in particular Alzheimer's Disease and FTD, is needed to evaluate the utility of these tests in diagnosing and assessing change of the different pathologies. The ECAS may also be applied as a useful cognitive screening tool in other neurological disorders characterised by motor as well as cognitive dysfunction, such as Progressive Supranuclear Palsy (Colosimo et al., 2014) or Corticobasal Degeneration (Bak and Hodges, 2008).

The average IQ of some of our groups was higher than what you would expect in a normal population, which may be a limitation of the study. However, the literature indicates that when a sample comes from volunteers rather than randomly selected, the subjects tend to be healthier, have completed more years of education and have higher cognitive abilities (Ganguli et al., 1998; Henrich, Heine and Norenzayan, 2010; Arnett and Rikli, 1981; Wrights et al., 2015). We attempted to control for this during the recruitment process, by recruiting through churches, sport centres and outside schools; and successfully controlled for years of education. It is of note that most studies

which validate dementia screening tests, do not measure IQ but rely on education level as a group descriptor, and it is therefore likely that the samples used in these studies would have a higher IQ than average, similar to our study, since it is a characteristic of the volunteer sample.

IQ, age and gender were significant predictors of the total score of the ECAS. The correlation of the ECAS with age has been found previously in the German-Swiss versions of the ECAS (Lulé et al., 2015; Loose et al., 2016), the Italian version (Poletti et al., 2016), and the Irish version (Pinto-Grau et al., 2017). Education was not a significant predictor of the ECAS when IQ was included in the model because of their strong correlation. The influence of IQ on the ECAS has not been measured previously. Somewhat surprisingly in our sample, gender was also a significant predictor of performance on the ECAS, although much weaker than age and IQ. Gender was not reported to significantly affect ECAS performance in two previous studies (Poletti et al., 2016; Ye et al., 2016). In our study, women performed slightly better than men on ECAS Total Score. Within the ECAS domains, this effect was most pronounced in the Executive functions predicting 3% of the variance of the score but this difference did not reach significance.

Overall the cut-off scores for abnormality suggested from these findings were similar to those originally proposed (Abrahams et al. 2014), but nevertheless, may help to discern the impairment in cases where the score falls in the borderline range (Niven et al., 2015). In such situations, age and education can be taken into account; for example a score of 105 on the ECAS would not signify an impairment for someone in their 70's and without a university degree, whereas the same score would indicate a possible impairment for someone in their 50's with a university degree.

It is noted that our sample did not include people younger than 51 nor older than 80. People under 50 with a diagnosis of dementia represent 0.35% of the dementia population in Scotland (Prince et al., 2014), and it is advised in these

cases that the same cutoff as 51-65 could be used. Future studies could look at creating separate cut-off scores for those over the age of 80, as they represent a larger percentage of the population with dementia (Prince et al., 2014).

2.1.6 Conclusion

The ECAS shows good convergent validity with the ACE-III, but is less influenced by intelligence and presents less ceiling effects in comparison to the ACE-III. Therefore, the ECAS is a suitable screening tool in particular in those: where cognitive assessment is complicated by the presence of motor symptoms; with executive dysfunction symptoms; and those highly educated high-performers with mild cognitive impairment or early dementia. The inclusion of both assessments of executive functions and behaviour makes the ECAS an appropriate choice for the assessment of frontal lobes disorders.

2.1.7 Acknowledgements

The authors thank all the participants in this research.

2.1.8 Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

2.1.9 Funding

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2.2 Additional Section

In the section below I present additional data of a younger group that was collected but not reported in the article. I also include further figures from the results to provide a more in-depth analysis.

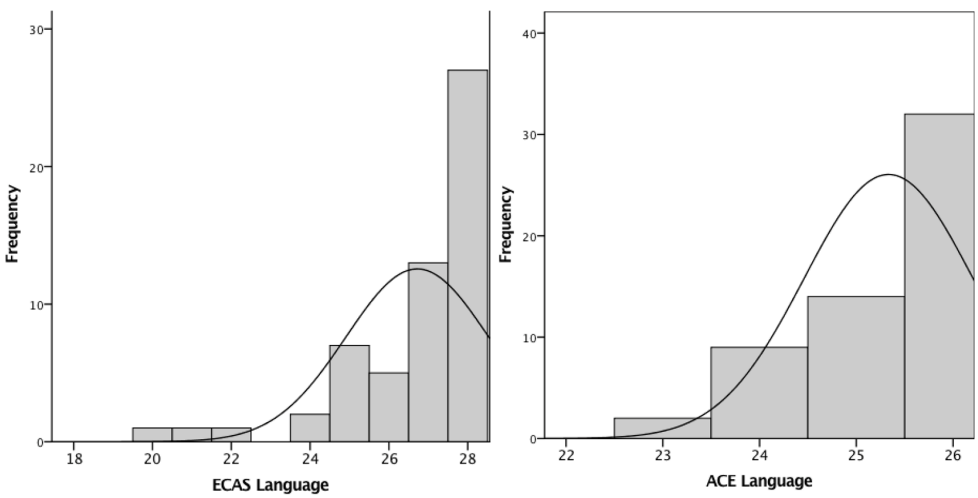
2.2.1 Eliminated younger group

In addition to the 80 participants recruited for study B (The effect of age, education and IQ), a further 40 participants were recruited between the ages of 35 to 50. Therefore, the experiment consisted of a total of 120 healthy individuals between the ages of 35 to 80, which were then divided into 6 groups according to their age and education. Age: 35-50, 51-65 years old and 66-80 years old; these age ranges were chosen to parallel the typically used division for early versus late onset dementia, plus a younger range for the rare cases in which dementia occurs in patients younger than 51. However, there was a large significant difference between groups regarding IQ ($F(2,112)=10.032$, $p<.001$) and socio-economical status ($F(2,113)=12.138$, $p<.001$). Post-hoc comparisons with the Tukey HSD test indicated that the mean of the youngest group (M=5.41, SD=2.42) in the socio-economical variable was significantly different ($p=.001$) in comparison to the middle age group (M=3.73, SD=1.97) and to the older group ($p<.001$) (M=3.30, SD=1.32). In the IQ variable, the young group (M=108.00, SD=15.05) was also significantly different to the middle age group ($p=.006$) (M=118.59, SD=16.38) and to the older group ($p<.001$) (M=123.03, SD=12.83). The middle age group mean was not significantly different from the older group in the socio-economical variable ($p=.613$) nor in the IQ variable ($p=.395$). Consequently, the youngest group was removed from all further analysis for study B. All analyses described below are with the same samples as the ones used in the article.

2.2.2 Relationship between ECAS and ACE-III

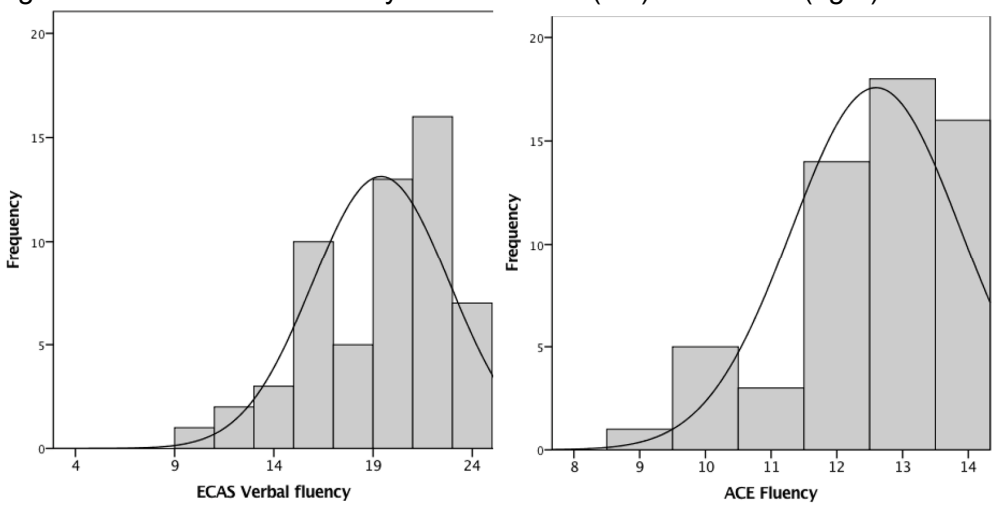
The article showed the ECAS was less prone to ceiling effects than the ACE-III overall. To expand on this issue, below I show a breakdown of the scores in the different domains. Figures 2 to 6 show the distribution of the domains scores on the ECAS and the ACE-III. The ECAS and the ACE-III present similar distributions on the language domain. The ECAS presents less ceiling effects than the ACE-III on the memory and fluency domains, while on the visuospatial domain the ACE-III presents less ceiling effects. The executive domain of the ECAS has a good distribution of scores with no ceiling effect, whereas the attention domain on the ACE-III presents a prominent ceiling effect.

Figure 2 Distribution of Language scores on the (left) ECAS and (right) ACE-III.



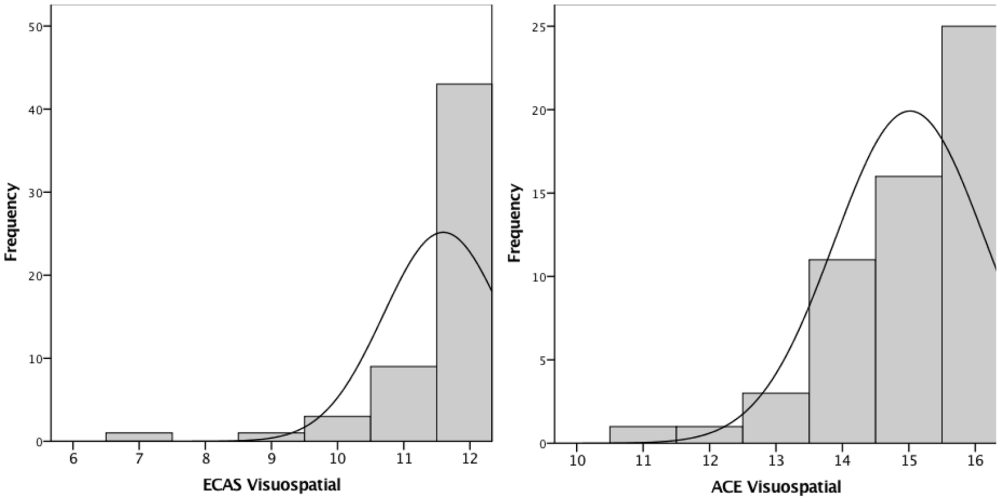
Edinburgh Cognitive and Behavioural ALS Screen (ECAS) mean 26.72 (±1.81), Addenbrooke's Cognitive Examination (ACE-III) mean 25.33 (±.87).

Figure 3 Distribution of Fluency scores on the (left) ECAS and (right) ACE-III.



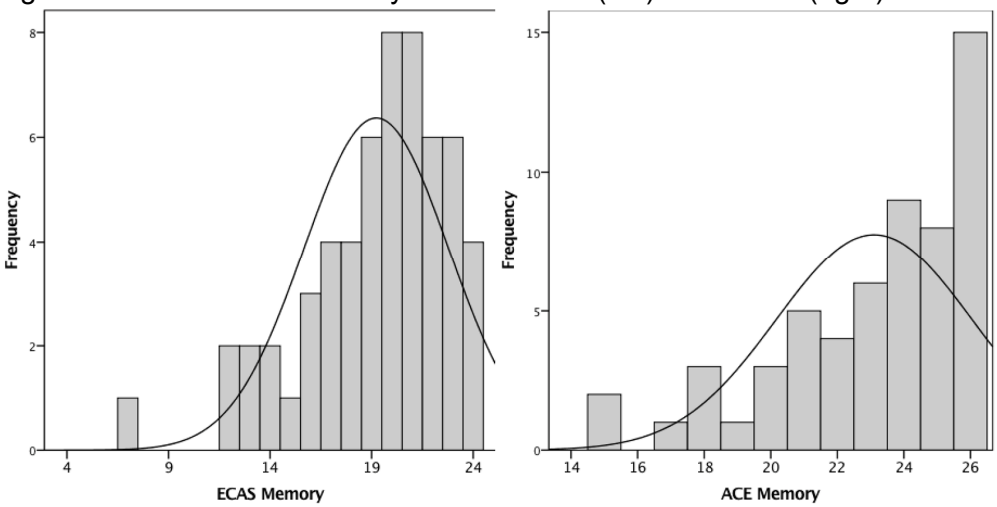
Edinburgh Cognitive and Behavioural ALS Screen (ECAS) mean 19.40 (±3.46), Addenbrooke's Cognitive Examination (ACE-III) mean 12.6 (±1.29).

Figure 4 Distribution of Visuospatial scores on the (left) ECAS and (right) ACE-III.



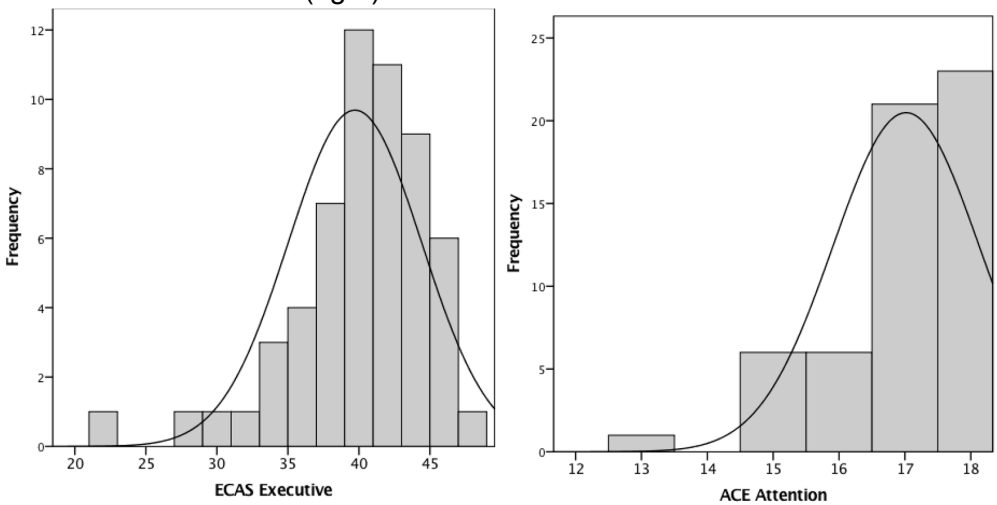
Edinburgh Cognitive and Behavioural ALS Screen (ECAS) mean 11.6 (±.904), Addenbrooke's Cognitive Examination (ACE-III) mean 15.02 (±1.14).

Figure 5 Distribution of Memory scores on the (left) ECAS and (right) ACE-III.



Edinburgh Cognitive and Behavioural ALS Screen (ECAS) mean 19.23 (±3.57), Addenbrooke's Cognitive Examination (ACE-III) mean 23.11 (±2.93).

Figure 6 Distribution of the Executive scores on the (left) ECAS and the Attention scores on the (right) ACE-III.



Edinburgh Cognitive and Behavioural ALS Screen (ECAS) mean 39.72 (±4.69), Addenbrooke's Cognitive Examination (ACE-III) mean 17.02 (±1.11).

2.2.3 The effect of age, education and IQ

ANOVA stepwise linear regression models were done to the domains of the ECAS, with the same 80 participants as the article, to investigate the predictors of each individual domain. IQ was the sole predictor of 29.5% of the Language score ($F(1,75)=31.369$, $p< .001$), 12.5% of the Fluency score ($F(1,75)=10.709$, $p= .002$) and 15.1% of the ALS specific score ($F(1,75)=13.308$, $p< .001$). IQ and gender predicted 11.2% of the variance of the Executive domain ($F(2,74)=4.649$, $p= .013$). IQ and age predicted 19.2% of the variance of Memory ($F(2,74)=8.820$, $p< .001$), 17.2% of the variance of Visuospatial ($F(2,74)=7.688$, $p= .001$) and 22.6% of the variance of the ALS non-specific ($F(2,74)=10.828$, $p< .001$).

2.2.4 Discussion

The additional data further expands on the distribution of scores in the domains of the ECAS and the ACE-III. I also added on the predictors of each individual domain of the ECAS. The ECAS has fewer ceiling effects than the ACE-III on the overall score and on the domains of memory and fluency; while the executive domain on the ECAS has less ceiling effects than the attention domain of the ACE-III. The ceiling effects on memory on the ACE-III could be the result of repeating the name and address while encoding, whereas the ECAS has no repetition (Verfaellie, LaRocque and Rajaram, 2010; English and Visser, 2013). It is also possible that the difference observed in this and other domains may be due to differences in the difficulty of the tasks, for example the memory test of the ECAS is a story recall task where a maximum score is achieved by remembering 10 distinct details. In contrast, the ACE-III includes the learning of a name and address with 7 small pieces of information.

As with the total score of the ECAS, IQ continued to be the most important predictor for the domains of the ECAS. The domain that was the most

dependent on IQ was Language, possibly because of the spelling component of the test (Milburn, et al., 2016; Preston et al., 2009). The finding in this research of IQ having an effect on fluency was consistent with the literature (von Stumm and Deary, 2013; Fritsch et al., 2007); furthermore, age influenced the score of Memory the most, which was also an expected result (van Geldorp et al. 2015).

2.3 Conclusions Chapter Two

The variables of IQ, age and gender were predictors of the total score of the ECAS. IQ was the most important predictor for the ECAS total score and most of its domains. The domain most dependent on IQ was Language, and age influenced the score of Memory the most. Education was not included as a predictor in the models as it strongly correlated with IQ. However, as IQ scores are obtained through a separate assessment, and the number of years of education is easily available, education was used alongside age to create abnormality cut-off scores for the clinical practice. Further research could expand to create abnormality cut-off scores for those younger than 50, and for those older than 80. Future research could also explore the effect of demographic factors on the ECAS on different populations, and in its different translations.

In this chapter, I demonstrated that the ECAS has a good convergent validity with the ACE-III; all domains correlated with their counterparts, with the exception of visuospatial functions. The ECAS had less ceiling effects on the overall score, and on the domains of memory and fluency than the ACE-III; and was also less influenced by IQ. These findings show the potential advantage of using the ECAS over the ACE-III as a short cognitive screen. Therefore, I thought the next step to further this research, was to analyse how effective would the ECAS be against the ACE-III in detecting cognitive impairment in a dementia population without ALS.

Chapter Three

Validation of The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) in behavioural variant Frontotemporal Dementia, Alzheimer's Disease, Primary Progressive Aphasia, Mild Cognitive Impairment, and Posterior Cortical Atrophy.

3.1 Introduction to article

Although the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) had been previously validated in ALS, it had not been validated for its use in other dementias against a comprehensive neuropsychological evaluation with a British population. As showed in the previous chapter, the ECAS had several advantages over the ACE-III when used in a healthy population. Following its successful validation in ALS, I wanted to explore if the ECAS would also be suitable as a cognitive screen in dementias without ALS, and how it would compare against the ACE-III in a clinical population. I also wanted to explore differences in the behaviours reported between the behavioural variant Frontotemporal Dementia (bvFTD) and Alzheimer's Disease (AD) patients on the ECAS behavioural screen.

In the following article, I analysed the validity of the ECAS in bvFTD and AD. This article was submitted as presented below to the International Journal of Geriatric Psychiatry in September 2020. It was published after some corrections in May 2021 (De Icaza Valenzuela, M.M., Bak, T.H., Thompson, H.E., Colville, S., Pal, S. and Abrahams, S. (2021) Validation of The Edinburgh cognitive and behavioural ALS screen (ECAS) in behavioural variant frontotemporal dementia and Alzheimer's disease*. International Journal of Geriatric Psychiatry*. 1-12. (DOI: 10.1002/gps.5566)). A final version of the

published article has been included in Appendix III. The additional information marked at the end of the paper was not included in the submitted manuscript, this includes further analyses made with the bvFTD and AD groups. I also explored in this chapter the validity of the ECAS in primary progressive aphasia, mild cognitive impairment and posterior cortical atrophy.

Research Article

Validation of The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) in behavioural variant Frontotemporal Dementia and Alzheimer's Disease

Short running title: Validation of screen in frontotemporal dementia

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3.1.2 Declaration of interest

The authors have no known conflict of interest in relation to the publication of this paper.

3.1.3 Abstract

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was developed to assess cognitive and behavioural changes in an anterior frontotemporal syndrome (executive functions, language, fluency and behaviour), common in Amyotrophic Lateral Sclerosis (ALS) and also assesses posterior cerebral dysfunction (memory and visuospatial abilities).

Objectives: To validate the ECAS in behavioural variant Frontotemporal Dementia (bvFTD) without ALS, as compared with Alzheimer's Disease (AD), against comprehensive neuropsychological assessment. Compare its sensitivity to that of the Addenbrooke's Cognitive Examination (ACE-III) and investigate behavioural changes in both types of dementia.

Methods: 16 people with bvFTD (without ALS), 32 with AD, and 48 healthy controls completed the ECAS, ACE-III and extensive neuropsychological assessment.

Results: The ECAS showed higher sensitivity and specificity (.938,.958) for both bvFTD and AD than the ACE-III. The anterior composite subscore was sensitive (.938,.917) for bvFTD; while the posterior composite subscore was sensitive (.969,.958) for AD. All bvFTD that were impaired on the ECAS total and anterior composite scores were also impaired on the anterior functions tests of the neuropsychological assessment. A cut-off of 4 or more

behavioural domains affected differentiated well between bvFTD and AD, while different themes emerged between the groups in a qualitative analysis of the behavioural interview.

Conclusions: The ECAS is a valid and sensitive assessment for bvFTD without ALS and for AD. Subscores of anterior and posterior cerebral functions were sensitive to bvFTD and AD respectively. The carer behavioural interview makes it particularly suitable to detect behavioural abnormalities related to frontal lobe disorders.

Key words: ECAS, ACE-III, frontotemporal dementia, Alzheimer's disease, screen, cognition, behaviour, dementia, neuropsychology, qualitative

Key points:

1. The ECAS showed higher sensitivity (94%) and specificity (96%) for both bvFTD and AD than the ACE-III.
2. The ECAS performed well against standard comprehensive neuropsychological assessment with perfect concordance between ECAS Total and Anterior functions composite scores, and performance on the anterior functions tests of the neuropsychological assessment for the bvFTD group. The ECAS total and posterior functions composite scores also showed good validity against the posterior functions tests of the neuropsychology assessment for the AD group.
3. The most recurrent abnormal behaviour for bvFTD was loss of sympathy/empathy (100%), while the most recurrent theme for AD was loss of interest in normal activities (56%). Important thematic differences between diagnoses were (26%) lack of awareness and (66%) lack of manners in bvFTD, while AD patients (33%) had a loss of self-confidence.

3.1.4 Introduction

Amyotrophic Lateral Sclerosis (ALS) is the most common form of Motor Neurone Disease and has been typically characterised as a rapid neurodegenerative disease affecting movement (Atkin and Turner, 2012). However, between 10-15% of people with ALS fulfil a diagnosis of frontotemporal dementia, most commonly the behavioural variant (bvFTD), and an additional 35% have milder and more specific cognitive impairment indicating a full spectrum of frontotemporal dysfunction (Goldstein and Abrahams, 2013; Strong et al., 2017). The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was developed to assess these cognitive and behaviour changes (Abrahams et al., 2014). It is designed to accommodate physical disability common in ALS, allowing for both written and spoken responses. As such, it is also well suited to assess cognitive functions in other diseases affecting motor functions, including Parkinson's Disease and Progressive Supranuclear Palsy (Foley et al., 2018).

The ECAS comprises a brief assessment of cognitive domains typically affected by anterior cerebral dysfunction: executive functions (including social cognition), language and verbal fluency, characteristically impaired in ALS. It also includes assessment of the domains which are typically affected by more posterior cerebral dysfunction: memory and visuospatial abilities. These were included to differentiate between the frontotemporal syndrome in ALS and cognitive deficits resulting from other disorders common in older adults, namely Alzheimer's Disease (AD) (Kourtesis et al., 2019). Furthermore, the ECAS includes a behavioural interview with carers which assesses five domains based on the diagnostic criteria for bvFTD (Rascovsky et al., 2011).

This brief assessment is sensitive in detecting mild cognitive impairment (without dementia) in ALS with impairments in executive, language and fluency (Abrahams et al., 2014). It has also been validated against comprehensive neuropsychological testing in ALS, showing good sensitivity and specificity

(Niven et al., 2015; Pinto-Grau et al., 2017) and convergent validity against other screening tests; the Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Consortium to Establish a Registry for Alzheimer's Disease plus Scale (CERAD plus) and Addenbrooke's Cognitive Examination (ACE-III) (Lulé et al., 2015; Poletti et al., 2016; De Icaza Valenzuela et al., 2018). A recent study demonstrated that both bvFTD with and without ALS were impaired on the ECAS against a healthy control group (Saxon et al., 2020). The study showed evidence of convergent validity with four standard neuropsychological tests of naming, spelling, cognitive inhibition (executive function) and social cognition. However, the study did not investigate the clinical utility of the test by validating performance against comprehensive clinical neuropsychology assessment or against more routinely used brief cognitive assessment/screening measures. The ACE-III is a commonly used cognitive screen, developed to assess different types of dementia; and was originally validated in both AD and FTD (Hsieh et al., 2013). However, its sensitivity in the detection of the bvFTD has been inconsistent (Yoshida et al., 2011; Bier et al., 2004; Elamin et al., 2015; Ruiz-Tangle et al., 2015). Although the ACE-III includes an assessment of fluency (letters and animals), it lacks other tests of executive functions, impairment of which form part of the diagnostic criteria of bvFTD.

In the early stages of both bvFTD and AD, deterioration typically follows a region-specific pattern with frontal lobe dysfunction beginning in the orbitofrontal cortex in bvFTD (Hornberger et al., 2010); and medial temporal and occipitoparietal regions in AD (Zhou et al., 2010; Sjogren et al., 2000). Recent studies have revealed that the ECAS composite score, compromising memory and visuospatial performance, was as sensitive to AD as the ACE-III (Kourtesis et al., 2020) and was effective at differentiating ALS from AD in a Greek population (Kourtesis et al., 2019).

This study aimed to validate the ECAS and further determine its clinical utility in detecting the cognitive and behavioural impairments in bvFTD in

comparison with AD. Specifically the aims were:

1. Determine whether the cognitive section of the ECAS is successful in detecting bvFTD without ALS, as compared with AD and healthy controls, and in comparison with the ACE-III. We hypothesize that the people with bvFTD would perform more poorly on the ECAS domains typically affected by anterior cerebral dysfunction (executive functions, fluency, language). In contrast people with AD would perform more poorly on those affected by more posterior cerebral dysfunction (memory and visuospatial).
2. Determine the validity of the ECAS total score, and composite scores against a comprehensive clinical neuropsychological assessment.
3. Investigate the utility of the behavioural interview and determine whether the themes reported differed between diagnostic groups.

3.1.5 Method

Participants

In this retrospective study we analysed data collected as part of routine clinical neuropsychological assessment from 16 people with bvFTD (9 males, mean age of 61 years (±9.38, 38-72) and education of 12.56 years (±3.24, 10-20)), and 32 with AD (16 males, mean age of 61.18 years (±5.87, 49-71) and education of 12.13 years (±2.17, 10-18)) from the Edinburgh Cognitive Diagnosis Audit Research and Treatment Register (DART), hosted by the Anne Rowling Regenerative Neurology Clinic and the University of Edinburgh. For the quantitative analysis of the behavioural data, we analysed data from a subgroup of 15 people with bvFTD and 24 with AD. Qualitative data was obtained from interviews with the carers/relatives of 15 people with bvFTD and 25 with AD (13 and 23 of which were included in the quantitative analyses of the behavioural interview).

Diagnoses were supported by magnetic resonance imaging (MRI) brain and HMPAO-SPECT imaging findings; measures of cerebrospinal (CSF) total Tau,

Phosphorylated Tau, and beta amyloid (Ab1-42); and/or disease-causing mutations identified following a neurodegenerative gene panel analysis. Diagnoses were made according to consensus criteria: Rascovsky et al. (2011) for bvFTD and McKhann et al. (2011) for AD.

Healthy participants (n=48, 29 males) matched in age (60.06 years (±11.92, 38-78)) and education (13.66 years (±3.03, 9-19)) were recruited from the local population and the Psychology Volunteer Panel of the University of Edinburgh. All were native English speakers without neurological illness or learning disabilities in their medical history.

Materials

Neuropsychological testing included the ECAS, both cognitive and behavioural sections (Abrahams et al., 2014) and the ACE-III (Hsieh et al., 2013). Impairments were determined using published abnormality cut-offs. The ECAS evaluates the domains of: memory, visuospatial, fluency, language and executive functions. In addition to the total score, the test also provides a composite score for more anterior cerebral functions (fluency, executive, and language, originally termed ALS-specific as these were the functions typically affected in ALS) and one for more posterior cerebral functions (memory and visuospatial, originally termed ALS non-specific). The ECAS also includes a short behavioural interview that is completed with a relative/carer of the patient. This interview includes 10 questions examining: disinhibition, apathy, loss of sympathy or empathy, perseveration, hyperorality or change in food preferences, and psychotic symptoms (Abrahams et al., 2014, see http://ecas.psy.ed.ac.uk). The carer is asked whether each behaviour occurs, to describe, and give examples of the behaviour.

Further extensive comprehensive neuropsychological assessment included a range of tests which are routinely clinically undertaken (see table 4). Impairment for each test was determined according to their published cut-off scores for abnormality or based on the 5th percentile of published normative data. To determine the validity of the ECAS anterior and posterior functions

composite scores against more extensive testing, the neuropsychological tests were grouped according to the cognitive domains which correspond with the ECAS (executive, language, fluency, memory, and visuospatial). Each domain was assessed by two or three neuropsychological tests, and an impairment in a domain was determined when performance on at least one of the tests was impaired. A deficit in anterior functions was classified when one of the following domains was impaired: fluency, language, and/or executive functions. A deficit in posterior functions was classified when either visuospatial and/or memory was impaired.

Table 4: Neuropsychological Tests

Cognitive Domain	Name of test	Reference
Cognitive Screen	Addenbrooke's Cognitive Examination (ACE-III)	Noone, 2015
Fluency	Controlled Oral Word Association (FAS)	Benton and Hamsher, 1983
	Category (Animal) Naming	Isaacs and Kennie, 1973
Language	The Graded Naming Test	Warrington, 1997
	Test of Reception of Grammar (TROG)	Bishop, 1989
Executive	Trail Making Test	Reitan and Wolfson, 1985
	The Sorting Test (The Delis-Kaplan Executive Function System)	Delis, Kaplan and Kramer, 2001
Memory	Free and Cued Selective Reminding Test (FSCRT)	Sarazin, et al., 2007
	BIRT Memory and Information Processing Battery Story and Figure Recall	Coughlan, Oddy and Crawford, 2007
Visuospatial	The Visual Object and Space Perception Battery	Warrington and James, 1991
	BIRT Memory and Information Processing Battery Figure copy	Coughlan, Oddy and Crawford, 2007

The tests are grouped into the cognitive domains which are assessed by the ECAS.

3.1.6 Ethical Approval

Patient data was collected from the Edinburgh Cognitive Diagnosis Audit Research and Treatment (DART) Register, South East Scotland A Research Ethics Committee approval 12/SS/0196, IRAS no 103819. The testing of healthy control participants was approved by The Psychology Research Ethics Committee of the University of Edinburgh.

3.1.7 Statistical Analysis

The data were analysed using SPSS statistics version 22. One-way between groups analysis of variance (ANOVA) were undertaken on parametric data to assess the difference between groups. Homogeneity of variance for all variables was unequal as determined by Levene's test, and we therefore used Welch's ANOVA with Games-Howell post hoc tests. ROC curves assessed the sensitivity and specificity of the ECAS to detect diagnosis of bvFTD and probable AD.

Transcripts of the behavioural interviews were analysed thematically using the Framework Analysis Method (Ritchie and Spencer, 1994), by two raters independently. The results of both analyses were subsequently discussed amongst the research group, and an agreement of the final themes was reached.

3.1.8 Results

3.1.8.1 Sensitivity of the ECAS in detecting bvFTD and AD as compared with the ACE-III

There was a significant difference between healthy controls and the two patient groups (bvFTD and AD) in the ECAS Total, composites and all domain scores, and in the ACE-III Total score (see Table 5), but the two patient groups did not significantly differ. Fifteen of sixteen (94%) of bvFTD group were impaired on the ECAS Total and the ECAS anterior functions composite score. Fourteen

of the bvFTD group also completed the ACE-III, of whom 11 (79%) scored within the abnormal range (82 or below) while a further patient scored within the borderline range (82-88). In the assessment of the AD group, 30/32 (94%) were impaired on the ECAS Total score, and 31 (97%) were impaired in the ECAS posterior functions composite score. Twenty-five of the AD group completed the ACE-III, of which 23 (92%) scored below the cut-off of 88; and 20 (80%) scored below the cut-off of 82. The frequency of impairment on the ECAS was identical when using abnormality cut-offs adjusted for age and education (De Icaza Valenzuela et al., 2018).

Table 5: Comparison of ECAS and ACE-III scores between bvFTD, AD, and control groups

	Welch's F	*p* value		Mean (SD) Range	*p* value patient group vs control	*p* value bvFTD vs AD
ECAS: bvFTD (n=16) AD (n=32) Controls (n=48)						
ECAS Total (max 136)	(2,29.47) = 89.63	<.001	bvFTD AD Controls	69.44 (±26.03) 20-108 71.84 (±21.58) 31-112 118.44 (±7.98) 102-134	<.001 <.001	=.946
Language (28)	(2,28.95) = 12.39	<.001	bvFTD AD Controls	22.50 (±5.06) 8-27 23.63 (±4.99) 8-28 27.02 (±1.49) 21-28	=.008 =.002	=.748
Fluency (24)	(2,31.41) = 40.36	<.001	bvFTD AD Controls	8.25 (±6.84) 0-20 12.00 (±6.44) 0-22 20.17 (±3.08) 10-24	<.001 <.001	=.180
Executive (48)	(2,29.51) = 52.11	<.001	bvFTD AD Controls	21.81 (±11.23) 2-37 22.97 (±11.12) 7-43 40.15 (±3.79) 32-47	<.001 <.001	=.939
Memory (24)	(2,33.37) = 159.72	<.001	bvFTD AD Controls	6.88 (±5.88) 0-17 4.28 (±4.51) 0-15 19.75 (±3.03) 12-24	<.001 <.001	=.287
Visuospatial (12)	(2,29.78) = 11.63	<.001	bvFTD AD Controls	10.00 (±2.28) 7-12 8.97 (±3.39) 1-12 11.56 (±0.94) 7-12	=.041 <.001	=.433
Composite score of Anterior functions (100)	(2,29.55) = 57.90	<.001	bvFTD AD Controls	52.56 (±20.05) 10-79 58.59 (±17.45) 28-90 87.13 (±6.42) 72-99	<.001 <.001	=.568
Composite score of Posterior functions (36)	(2,32.20) = 149.89	<.001	bvFTD AD Controls	16.88 (±7.39) 7-29 13.25 (±5.71) 3-25 31.31 (±3.30) 21-36	<.001 <.001	=.215

ACE-III: bvFTD (n=14) AD (n=25) Controls (n=44)						
ACE-III Total (100)	(2,23.68) = 39.84	<.001	bvFTD AD Controls	69.93 (±17.63) 22-90 69.92 (±15.24) 32-98 93.82 (± 4.26) 82-100	=.001 <.001	=1.000

behavioural variant Frontotemporal Dementia (bvFTD), Alzheimer's Disease (AD), Edinburgh Cognitive and Behavioural ALS Screen (ECAS), Addenbrooke's Cognitive Examination (ACE-III), Standard Deviation (SD)

The ECAS total cognitive score showed high and equal sensitivity and specificity (94%, 96% respectively) at detecting both bvFTD and AD using the established cut-off score of 105. In comparison, the ACE-III was less sensitive but had an equal specificity at detecting either diagnosis (bvFTD 79%,98%, AD 83%,98%) (see Table 6). The ECAS total score was the most sensitive measure in detecting bvFTD, followed closely by the ECAS anterior functions composite score (see Figure 7a). The ECAS posterior functions composite score was the most sensitive measure in detecting AD, followed by the ECAS total score (see Figure 7b).

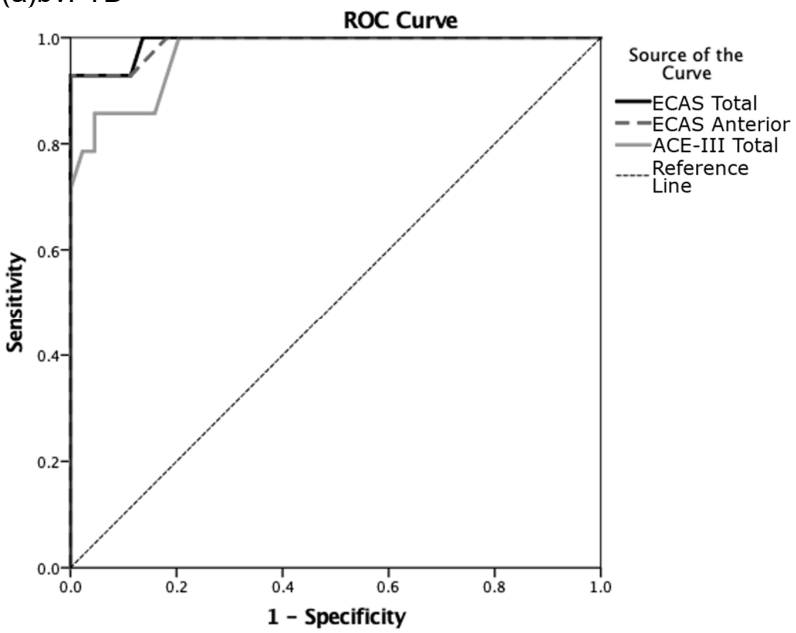
Table 6: Sensitivity and specificity of the ACE-III and ECAS tests scores in detecting bvFTD and AD vs controls

		bvFTD		AD	
	Abnormality Cut-off	Sensitivity	Specificity	Sensitivity	Specificity
ACE-III Total	82	.786	.977	.833	.977
ACE-III Total	88	.857	.864	.958	.864
ECAS Total	105	.938	.958	.938	.958
ECAS Total	110	1.000	.812	.969	.812
Language	26	.750	.750	.656	.750
Fluency	14	.875	.937	.594	.937
Executive	33	.813	.958	.844	.958
Anterior Composite	77	.938	.917	.844	.917
Memory	13	.750	.958	.906	.958
Visuospatial	10	.438	.917	.531	.917
Posterior Composite	24	.750	.958	.969	.958

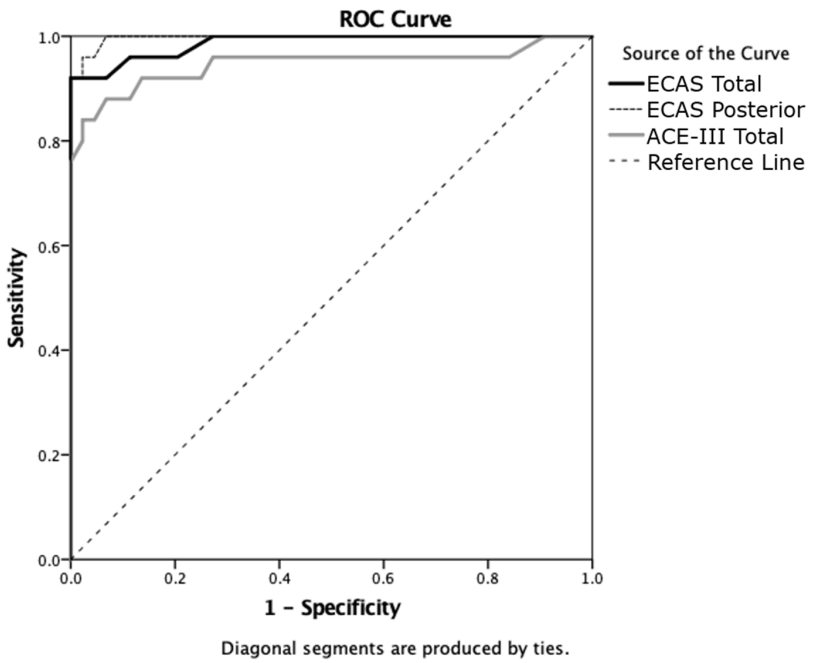
ECAS anterior composite (language, fluency, and executive) and ECAS posterior composite (memory and visuospatial), Abnormality cut-offs are both standard and borderline for both tests (Niven et al., 2015; Hsieh et al., 2013).

Figure 7: Comparison of the ECAS and the ACE-III in detecting bvFTD (a) and AD (b) against controls.

(a)bvFTD



(b)AD



ECAS Anterior composite (language, fluency, and executive), ECAS Posterior composite (memory and visuospatial)

3.1.8.2 Validation of the ECAS against Comprehensive Neuropsychological Assessment

Thirteen of the bvFTD group also completed the comprehensive neuropsychological assessment. Twelve (92%) were impaired on at least one of the anterior cerebral function domains of the full assessment (Fluency and/or Language and/or Executive), and all of these were also impaired on the ECAS Total and ECAS anterior functions composite scores giving perfect concordance, with 100% sensitivity and specificity. The ACE-III had a good sensitivity (82%, specificity 100%) to the anterior cerebral function domains of the neuropsychological assessment. One person with bvFTD was impaired only on the posterior functions of the full neuropsychological assessment, and was not impaired on either brief assessment, although fell in the borderline range on the ECAS Total score (scored 108). Of note this person had five behavioural domain changes. The profile of impairment across the tests are summarised in table 7.

Two AD participants did not undertake the neuropsychological assessment, but all who did were impaired in the posterior functions of the neuropsychological assessment (Memory and/or Visuospatial). However, the ACE-III did not detect five patients, the ECAS total score could not detect two patients, and the ECAS posterior composite score could not detect one patient who were impaired on the posterior functions of the full neuropsychological assessment. Therefore, the sensitivity of these brief assessments at detecting posterior cognitive dysfunction as determined by full neuropsychological assessment, was 93% ECAS Total score, 97% ECAS posterior score, and 79% ACE-III all with a specificity of 100%.

Table 7: bvFTD and AD patients impairment on the ECAS, ACE-III and anterior and posterior functions neuropsychological tests

Number of patients	ACE-III	ECAS total	ECAS Anterior Composite Score	ECAS Posterior Composite Score	Neuropsychology Anterior Domains	Neuropsychology Posterior Domains
bvFTD						
6	X	X	X	X	X	X
2	X	X	X	✓	X	X
1	X	X	X	X	X	✓
2	✓	X	X	X	X	X
1	✓	✓	✓	✓	✓	X
1		X	X	X	X	X
1	X	X	X	X		
1	X	X	X	✓		
1		X	X	X		
AD						
15	X	X	X	X	X	X
3	✓	X	X	X	X	X
2	X	X	✓	X	X	X
1	X	✓	✓	✓	X	X
1	✓	X	✓	X	X	X
1	✓	✓	✓	X	X	X
1	X	X	X	X		X
5		X	X	X	X	X
1		X	X	X		X
1	X	X	X	X		
1		X	X	X		

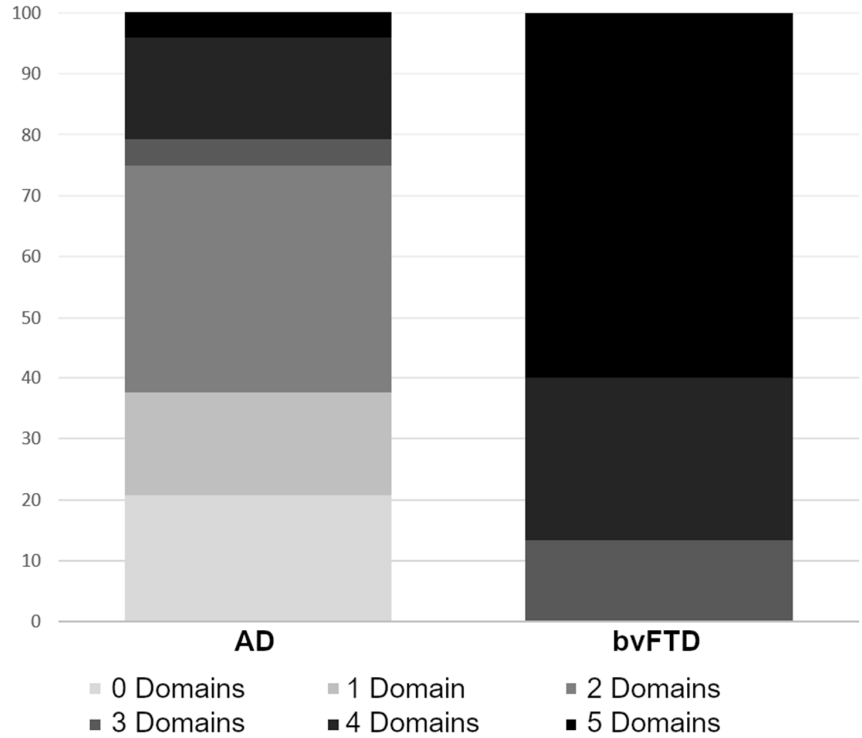
Normal Range (✓), Impaired Range (X), Neuropsychology Anterior Domains: X is marked for impairment on language and/or fluency and/or executive functions in the comprehensive neuropsychological assessment. Neuropsychology Posterior Domains: X is marked for impairment on memory and/or visuospatial functions in the comprehensive neuropsychological assessment.

3.1.8.3 Behavioural Interview

The carers/relatives of 15 people with bvFTD and 24 people with AD completed the behavioural interview. The majority of the bvFTD group had behavioural changes in five domains, whereas the majority of the AD group had behavioural changes in two domains (see Figure 8). The most common behavioural changes were disinhibition, apathy and loss of empathy in bvFTD

and apathy and perseverative in AD (see Table 8). The total number of behavioural domains impaired differentiated between bvFTD and AD with a sensitivity of 79%, specificity 87% using a cut-off of 4 or more behavioural domains affected.

Figure 8: Percentage of the number of behavioural domains affected



Alzheimer's Disease (AD) n=24, behavioural variant Frontotemporal Dementia (bvFTD) n=15

Table 8: Behavioural Changes on the ECAS behaviour screen.

AD (N=24) bvFTD (N=15)	AD	bvFTD
Disinhibition	33%	100%
Apathy and Inertia	58%	100%
Loss of Sympathy or Empathy	29%	87%
Perseverative	45%	80%
Hyperorality and Altered Food Preferences	25%	80%

Alzheimer's Disease (AD), behavioural variant Frontotemporal Dementia (bvFTD), Number of participants (n).

3.1.8.4Thematic Analysis of Carer Behavioural Interview

Several themes distinguished the bvFTD from the AD patients (see Table 9). The themes below were present in bvFTD only.

- Immediacy/ Impatience (66%) – "If he wants to do something in the moment he does, regardless of the circumstances. He just cannot stop himself".
- Manners (66%) – "Puts his feet up on the chair in restaurants. He eats off other people's plates and licks the plates in public"
- Loss of initiation of actions (33%) – Needs prompting for daily tasks.
- Egocentrism (33%) – "Only displays interest if it is related to him or when he is the center of attention, if not he switches off completely"
- Binge eating (46%) – "Eats non-stop…loses control"
- Strange beliefs (20%) – "Won't wash the front of her head because of her diagnosis of FTD"
- Lack of awareness (26%) – Upset about restrictions in his driver's license. Becomes verbally aggressive if he feels relative is suggesting that he has dementia
- Not the same person (46%) – "Not my mum. Used to be incredibly polite and now quite rude"
- Accidental oversights or Mistakes (60%) – "Exploded flask because he put it directly on the hob"

The themes reported for AD only were:

- Eating less or lost weight (32%) – "Doesn't eat well or the full meal"
- Avoids cooking (24%) – "…scared to touch something hot"
- Stopped reading (24%)
- Misplacing items (8%) – "Teapot in the fridge"
- Difficulties solving problems (20%) – "Couldn't figure out how to plough a field he did every year"
- Lost confidence (33%) – "Apologizes a lot"

Table 9: Themes from the analysis of the behavioural interview
bvFTD (n=15) AD (n=25)

bvFTD %	Themes	AD %
	Impulsivity and Disinhibition	
73	Buying Impulsively	12
66	Immediacy/Impatience	
66	Loss of manners or decorum	
60	Impulsive Decisions	33
60	Offensive/Inappropriate jokes or comments	33
46	Aggression	8
33	Hypersexual behaviour	8
	Apathy	
80	Loss of interest in normal activities/hobbies	56
33	Emotional flatness	24
33	Loss of initiation actions	
20	Neglect of self-care	12
	Social interactions	
100	Loss of sympathy/Empathy	32
80	Reduced social interest	32
33	Egocentrism	
	Perseverative Behaviour	
80	Simple repetitive movements	24
73	Compulsive behaviour	32
40	Hoarding	20
26	Fixed Routine	12
	Eating and preparing food	
80	Eats more carbs	24
46	Binge eating	
	Eats less/lost weight	32
	Avoids cooking	24
	Psychosis	
46	Paranoia	24
20	hallucinations	12
20	Strange beliefs	
	Other	
60	Accidental oversights/Mistakes	
46	Disorientated	20
46	Not the same person/Change personality	
26	Lack of awareness/Anosognosia	
	Lost confidence	33
	Stopped reading	24
	Solving problems	20
	Misplace items	8

Alzheimer's Disease (AD), behavioural variant Frontotemporal Dementia (bvFTD)

The most common themes in bvFTD were: loss of sympathy/empathy (100%)- “Always used to be caring and giving, but not so much anymore”, loss of interest in normal activities/hobbies (80%), reduced social interest, even with family and close friends (80%), simple repetitive movements (80%) (such as scratching and tapping), eating more carbohydrates (80%), buying impulsively (73%)- “cannot pass a shop without buying things immediately”, and compulsive behaviour (73%)- “Besotted with puzzles, does them obsessively”. The most common themes in AD were: loss of interest in normal activities/hobbies (56%), impulsive decisions (33%), offensive/inappropriate jokes or comments (33%), and lost confidence (33%)- “apologizes a lot”.

3.1.9 Discussion

The ECAS was successful in detecting the cognitive changes present in bvFTD and AD compared to healthy controls, although there were no significant group differences in scores between the two types of dementia. Using published abnormality cut-offs (Abrahams et al., 2014), the ECAS anterior functions composite score (sensitivity of 94% and a specificity of 92%) (which comprises the domains of Fluency, Executive Functions and Language) and the ECAS Total Score (sensitivity 94% and specificity 96%) were highly effective at detecting bvFTD when compared to healthy controls. The percentage of impairment on the ECAS in the bvFTD group in our sample (94%) was similar to what has been previously reported (91%) (Saxon et al., 2020). The composite score of more posterior functions (Memory and Visuospatial domains) (sensitivity 97% and specificity 96%) and the ECAS Total Score (sensitivity 94% and specificity 96%) were highly effective at detecting AD when compared to healthy controls. In contrast the ACE-III had a lower sensitivity although relatively equal specificity at detecting both bvFTD (79%, 98%) and AD (85%, 98%).

The ECAS also showed strong validity at detecting cognitive impairments as compared with the gold standard of neuropsychological assessment.

There was a perfect concordance of the ECAS scores and impairment on the anterior functions tests of the neuropsychological battery for the bvFTD group with 100% sensitivity, and 100% specificity. The only bvFTD patient that was unimpaired on the ECAS was also not impaired in the anterior functions' tests of the neuropsychological battery but showed changes in the five behavioural domains of the ECAS. The presentation of behaviour change without cognitive impairment in FTD has been previously demonstrated (Koriath et al., 2017). There was also good concordance between the deficits detected on the ECAS Total and posterior functions composite scores and impairments in posterior functions tests in the comprehensive neuropsychological assessment for the AD group. The ECAS Total score failed to detect two AD patients, while the ECAS posterior functions composite score failed to detect one patient only and the ACE-III failed to detect five patients with cognitive impairments as determined by the neuropsychological assessment.

These findings indicate the possible utility of the ECAS in a broader clinical setting for the screening of the dementias. The ECAS has already been shown to be an effective cognitive screen for movement disorders of ALS (Abrahams et al., 2014), Parkinson's Disease, and Progressive Supranuclear Palsy (Foley et al., 2018). Since the total score of the ECAS was more sensitive to bvFTD and AD than the ACE-III; and it includes a behavioural interview, the ECAS could be used as an alternative for the ACE-III for a cognitive screen in the clinical setting. The ECAS also has the additional advantage of being less prone to ceiling effects and is less influenced by IQ than the ACE-III (De Icaza Valenzuela et al., 2018); and therefore, very useful for a young onset population in a dementia clinic.

In the analysis of the behavioural data, most bvFTD patients tended to have behavioural changes in the five domains, whereas AD patients had behavioural changes in two domains. A cut-off of 4 or more behavioural domains affected had a 79% sensitivity and 87% specificity to differentiate

between the diagnoses of bvFTD and AD. Apathy was the most prevalent behaviour in both patient groups, which is consistent with the literature (Radakovic et al., 2020; Radakovic et al., 2014; Landes, Sperry and Strauss, 2005). This was followed by disinhibition in the bvFTD group, and perseverative behaviour in the AD group, which is congruent with the literature (Mendez et al., 2008; Ossenkoppele et al., 2015). Identifying apathy as a behavioural change in the screening process could help orientate the carers and clinicians to manage this symptom.

The qualitative thematic analysis of the behavioural interview uncovered a number of themes which differentiated between the two patient groups. Themes present in bvFTD only were centred around loss of control (immediacy, loss of manners, binge eating), changes in personality (egocentrism and not being the same person), loss of initiation actions, strange beliefs, anosognosia, and accidental oversights/mistakes. The most common theme found in bvFTD patients was loss of sympathy/empathy which was an expected behavioural change (Saxon et al., 2017), followed by compulsions which have been reported for bvFTD previously (Ducharme et al., 2015; Mendez et al, 2005; Wylie et al., 2013). Of note both these themes were also present in ~a third of people with AD and therefore of relevance to clinical management rather than for diagnostic purposes. The most common themes present in AD but absent in bvFTD were eating less or lost weight, avoids cooking, lost confidence and stopped reading. Weight loss in Alzheimer's has been widely reported (Soto et al., 2012; Wolf-Klein and Silverstone, 1994). Weight loss was not reported in this group of bvFTD. However, it should be noted that ALS develops in 12.5% of bvFTD, in whom weight loss may be a symptom (Van Es et al., 2017). It is therefore advised that all patients with suspected bvFTD undergo a neurological examination. Avoidance of cooking observed in the AD group seem to emerge from fear of having an accident. Awareness of diagnosis in AD unlike the lack of awareness in bvFTD could play a role in whether people avoid certain activities and the loss in self-

confidence. The findings demonstrate that certain behaviours may help in differential diagnosis.

It should be noted that the clinic where the research took place is a tertiary referral centre which reviews diagnostically challenging cases, in particular complex differential diagnosis of AD vs bvFTD in people with behavioural symptoms; therefore, the AD patients reported here may have had more behavioural symptoms than the typical population. Nevertheless, despite this complexity of presentation, distinctive behavioural features were present which distinguished between the two groups. In addition, the clinic focusses on younger adults, and a study investigating an older population and with a larger group of bvFTD patients is warranted. Strengths of this study were its thorough investigation of the clinical validity of the ECAS with these dementia groups and the inclusion of well characterised patients (diagnoses supported by imaging, CSF, and/or genetic analysis). The validation against comprehensive neuropsychology reinforces the use of the ECAS as a useful screening tool for the cognitive assessment of patients with and without a motor disorder.

The findings demonstrate that the ECAS could be used by clinicians to evaluate suspected frontal lobe disorders and AD. Using the ECAS as a first line screen for cognitive impairment where there is a suspicion of bvFTD could speed up the process of assessment, diagnosis and treatment for this disease. Behavioural interviews with the carers add to the utility of the cognitive screens and may bring to light possible changes which may be important for clinical management. The ECAS could also heighten awareness in carers of the possible behavioural changes the patients could experience, which may facilitate reporting to their health professional in the future (Hodgins, Mulhern and Abrahams, 2019).

3.1.10 Conclusions

The ECAS was successful in assessing the profile of cognitive and behavioural impairment in both bvFTD and AD. The combined score for memory and visuospatial assessment was particularly sensitive to AD, while the combined score for executive, fluency and language functions was sensitive to bvFTD. The ECAS also shows strong validity against full neuropsychological assessment and was more successful than the ACE-III at detecting impairment in both bvFTD and AD. The inclusion of a behavioural interview in the ECAS makes it particularly suitable to aid in the diagnosis of behavioural abnormalities related to frontal lobe disorders, and can aid in distinguishing between bvFTD and AD.

Additional Section

The remainder of this chapter reports on data which was not present in the manuscript above.

In the section below I present additional detailed information regarding the neuropsychological assessment, and figures and tables from the results that were not included in the article regarding the groups of bvFTD and AD to provide a more in-depth analysis. I also looked at the ECAS in other groups of patients (MCI, PPA and PCA) that were not reported in the article as the sample sizes were too small.

3.2 Additional information on bvFTD and AD

3.2.1 Objectives

- To expand on the comparison of the ECAS domains with the ACE-III domains.
- To explore the sensitivity of the domains of the ECAS and the ACE-III to bvFTD and AD.
- To explore the sensitivity of the subtests of the ECAS to bvFTD and AD.
- To explore the sensitivity of the ECAS and the ACE-III to a mixed group of dementia.
- To explore the sensitivity of the ECAS versus the ACE-III in differentiating between diagnoses of bvFTD and AD.
- To expand on the validation of the ECAS against a comprehensive neuropsychological assessment.

3.2.2 Methods

This section was done with the same participants and materials as those in the article above.

3.2.3 Results

3.2.3.1 Sensitivity of the ECAS versus the ACE-III in detecting bvFTD and AD

For further comparison of the ECAS and ACE-III, a breakdown of the ACE-III into subdomain scores revealed that both patient groups were significantly worse than the control group in all scores, other than the attention and visuospatial subscores on which the AD group were impaired only (see Table 10). There were also no significant differences between the two patient groups.

In the article I focused on the sensitivity of the ECAS and ACE-III total scores and composite functions scores to each type of dementia. I decided to expand on this to investigate how sensitive the individual domains and subtasks of each tests were sensitive to bvFTD and AD. The ECAS total score was the most sensitive measure to detect bvFTD, followed closely by the composite score of the anterior functions (language, fluency and executive). However, the executive domain was the most sensitive domain to bvFTD, while the visuospatial domain was the measure with the lowest sensitivity for bvFTD (see Figure 9). In the ACE-III, the domain of fluency and the total score of the test were the most sensitive measures to detect bvFTD; while attention and visuospatial were the least sensitives (see Figure 10).

Table 10: Comparison of ECAS and ACE-III scores between bvFTD, AD, and control groups

	Welch's F	*p* value		Mean (SD) Range	*p* value patient group vs control	*p* value bvFTD vs AD
ACE-III: bvFTD (n=14) AD (n=25) Controls (n=44)						
ACE-III Total (100)	(2,23.68) = 39.84	<.001	bvFTD AD Controls	69.93 (±17.63) 22-90 69.92 (±15.24) 32-98 93.82 (± 4.26) 82-100	=.001 <.001	=1.000
Attention (18)	(2,23.85) = 17.60	<.001	bvFTD AD Controls	15.07 (±3.93) 3-18 13.33 (±3.10). 8-18 17.11 (±1.10) 13-18	=.171 <.001	=.349
Memory (26)	(2,25.37) = 57.70	<.001	bvFTD AD Controls	15.07 (±7.14) 2-26 11.75 (±5.18) 4-25 23.43 (±2.70) 15-26	=.002 <.001	=.301
Fluency (14)	(2,23.57) = 32.64	<.001	bvFTD AD Controls	6.07 (±3.89) 0-13 8.54 (±3.72) 2-14 12.75 (±1.10) 10-14	<.001 <.001	=.154
Language (26)	(2,22.68) = 11.92	<.001	bvFTD AD Controls	20.42 (±4.65) 11-25 22.58 (±4.66). 8-26 25.43 (±0.81) 23-26	=.004 =.018	=.367
Visuospatial (16)	(2,24.35) = 8.69	=.001	bvFTD AD Controls	13.28 (±3.14) 5-16 12.41 (±3.36) 7-16 15.09 (±1.17) 11-16	=.126 =.002	=.706

behavioural variant Frontotemporal Dementia (bvFTD), Alzheimer's Disease (AD), Addenbrooke's Cognitive Examination (ACE-III), Standard Deviation (SD)

Figure 9: Sensitivity of ECAS total score and domains to bvFTD.

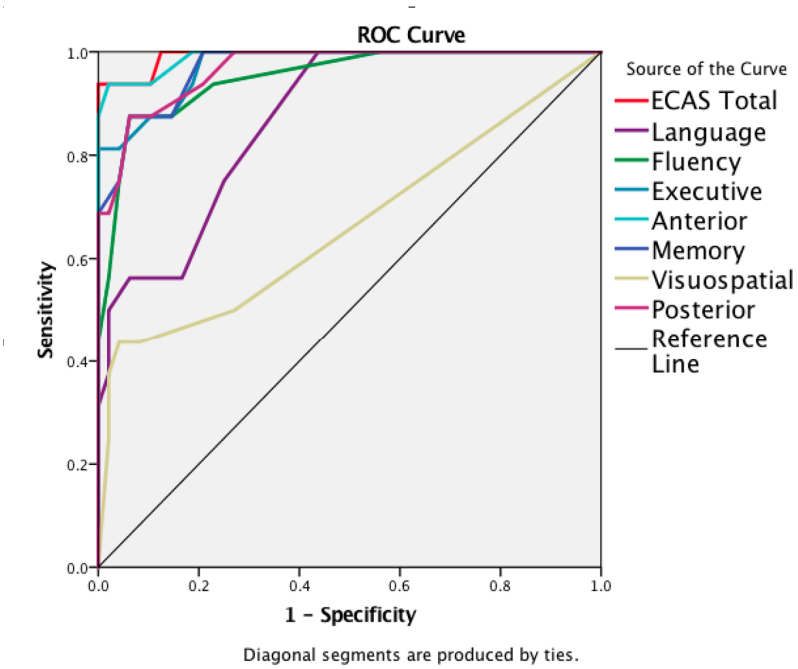
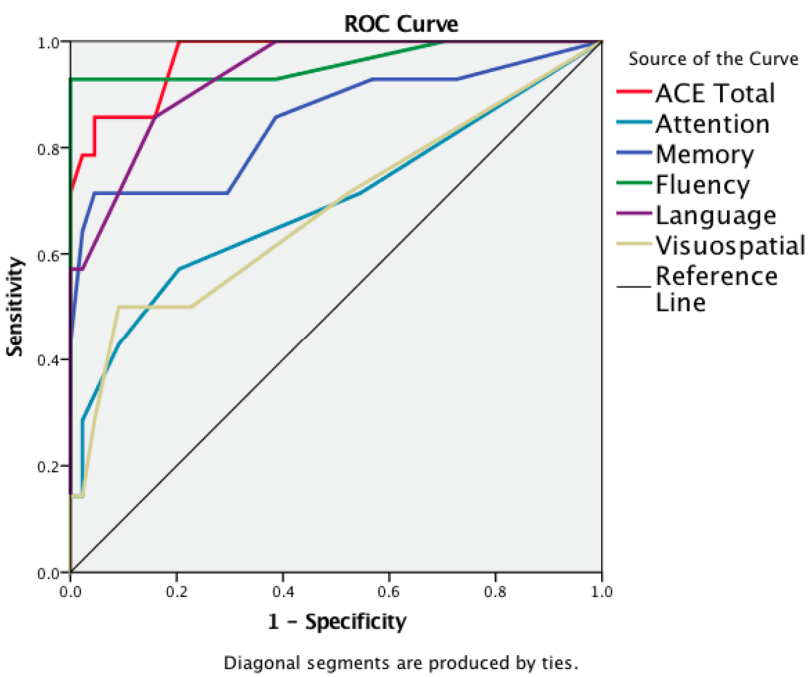


Figure 10: Sensitivity of ACE-III total score and domains to bvFTD.



The composite ECAS score of the posterior functions (memory and visuospatial) was the most sensitive measure to detect AD, followed by the memory domain and the total score of the ECAS. Language and the Visuospatial domain were the least sensitive to detect AD (see Figure 11). In the ACE-III, the domain of memory and the total score were the most sensitive to detect AD, while the visuospatial domain was the least sensitive (see Figure 12). From the ROC curves in these four figures it can be observed that the ECAS total score and the composite score for anterior functions were more sensitive in detecting bvFTD than the ACE-III total score and the fluency domain. The composite score for posterior functions and the ECAS total score were also more sensitive in detecting AD than the ACE-III total score and the memory domain.

Figure 11: Sensitivity of ECAS total score and domains to AD.

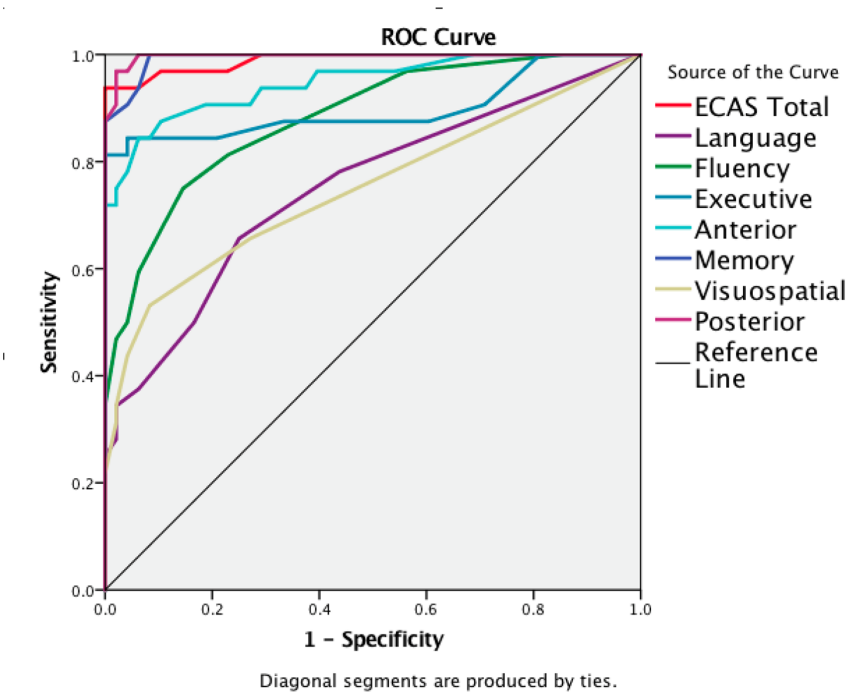
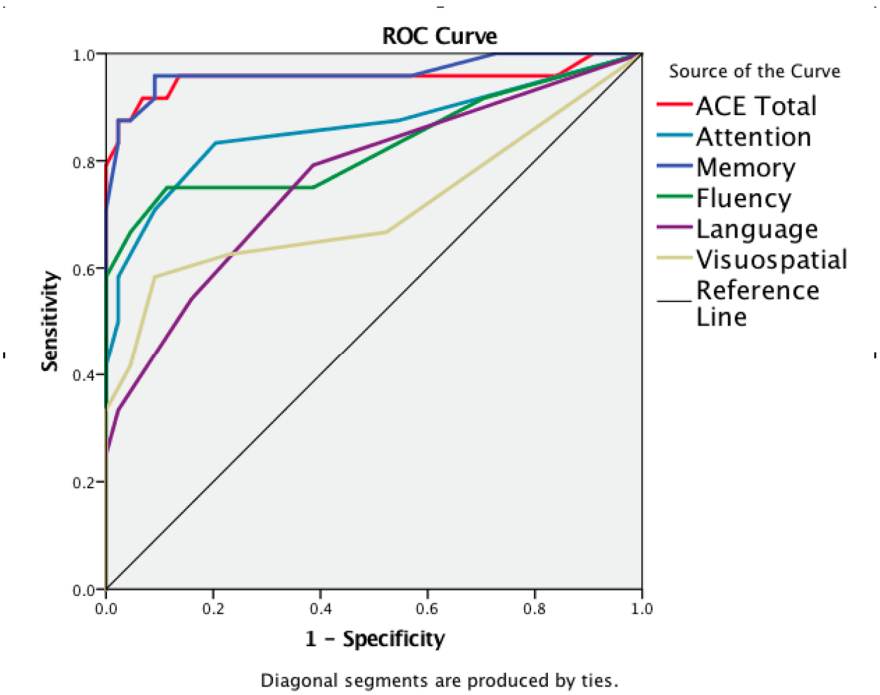


Figure 12: Sensitivity of ACE-III total score and domains to AD.



I additionally explored how sensitive were the individual subtests of the ECAS to each diagnosis (Figure 13). Unfortunately, I did not have the raw scores for the subtests on the ACE-III, therefore, I was unable to do a comparison between them. The immediate recall and recognition subtests were the most sensitive to bvFTD; followed closely by the fluency subtests, and the sentence completion and reverse digit span subtests. The least sensitive subtests for bvFTD were the three visuospatial. In Figure 14 it can be observed the ROC curves of all the individual subtests of the ECAS for the diagnosis of AD. The three memory subtests seem to be the most sensitive to discern this disease; whereas the subtests of comprehension, naming, dot counting, and number location seem to be the least sensitive.

Figure 13: Sensitivity of ECAS subtests to bvFTD.

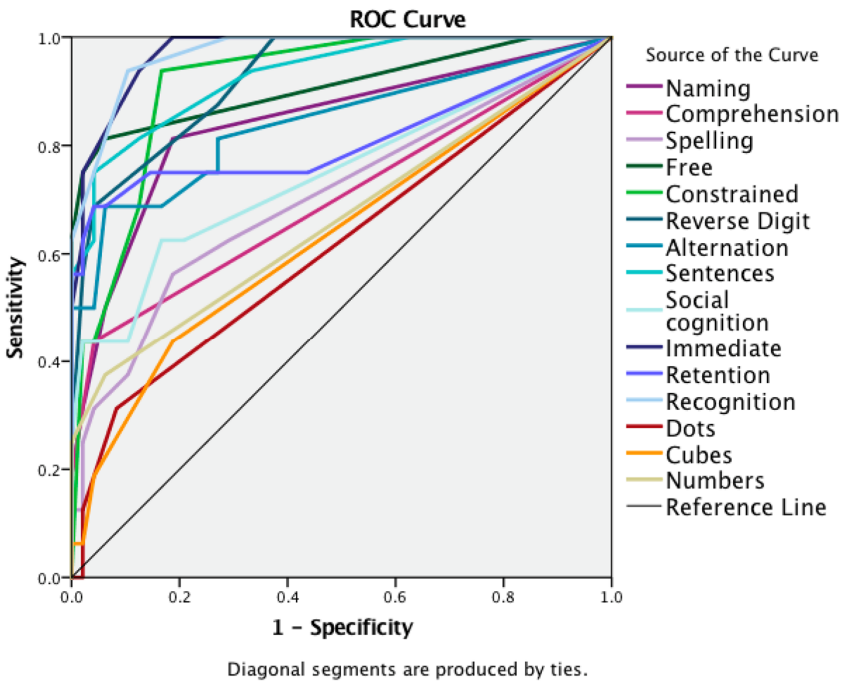
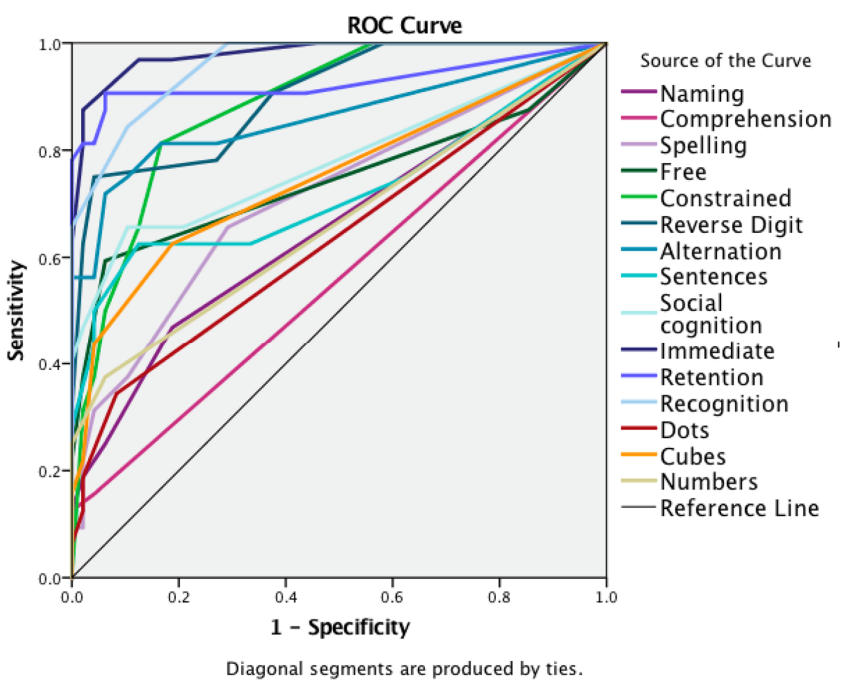
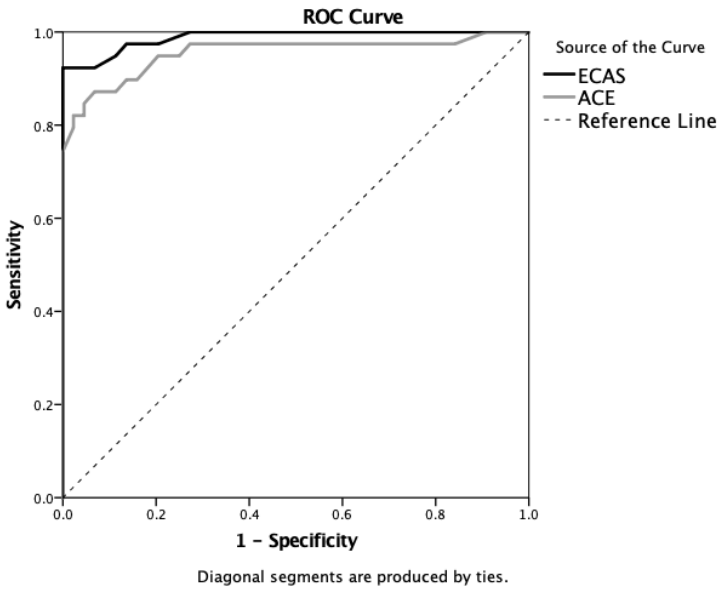


Figure 14: Sensitivity of ECAS subtests to AD.



Some of the standardised abnormality cut-offs in screening tests, such as the ACE-III, have been done with a mixed group of dementia instead of providing sensitivity to values to each diagnosis (Hsieh et al., 2013). To provide a comparison I therefore decided to explore the ECAS total score versus the ACE-III in detecting dementia as a mixed group (combined group of bvFTD and AD). The ECAS total cognitive score showed excellent sensitivity and specificity (94%, 96% respectively) to detect dementia in comparison to healthy controls using the established cut-off score of 105. Whereas the ACE-III had a lower sensitivity (90%) and specificity (86%) to detect dementia using the cut-offs scores of 88, and 82 (sensitivity 80%, specificity 98%) (figure 15).

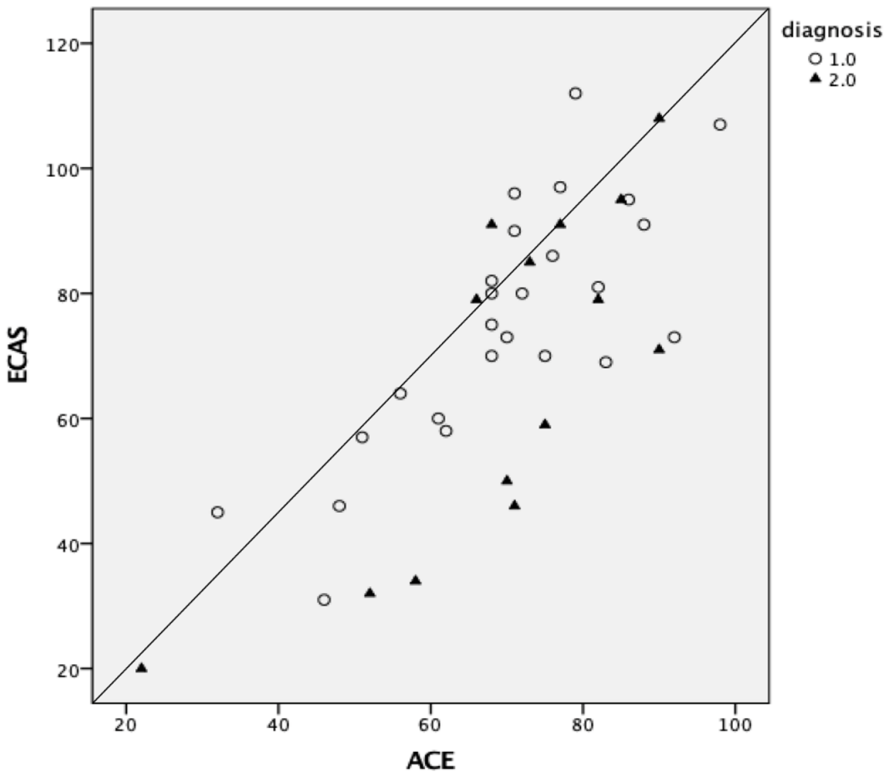
Figure 15: Sensitivity of the ECAS and the ACE-III total scores to dementia.



3.2.3.2 Sensitivity of the ECAS versus the ACE-III in differentiating between diagnoses

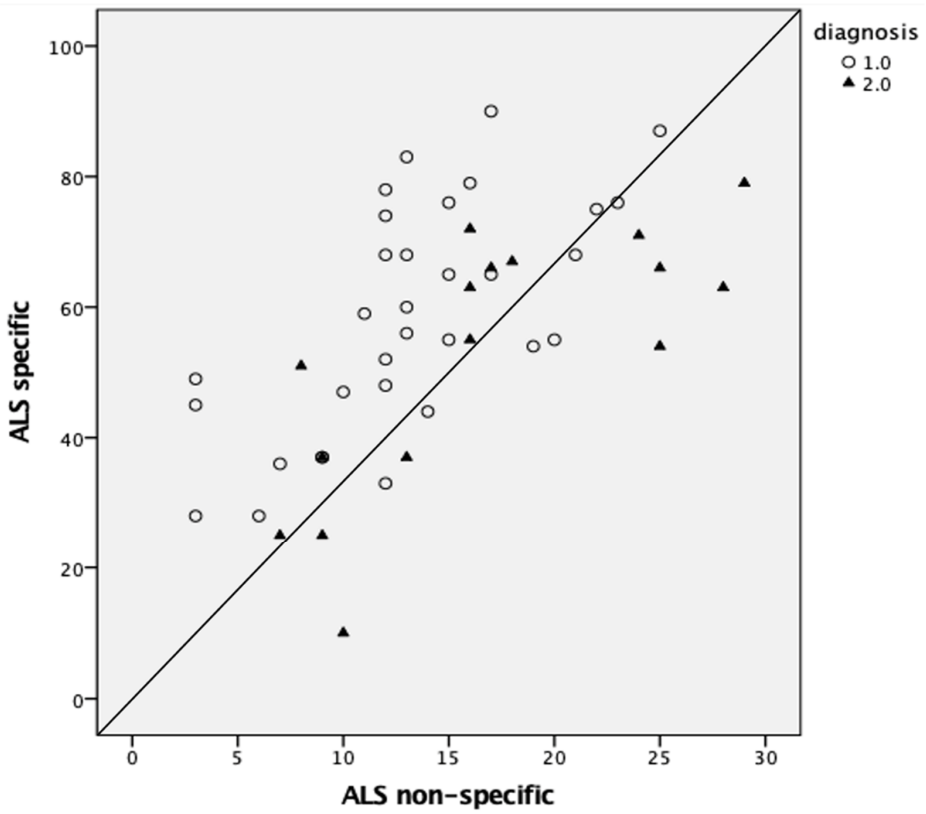
Although there was a good correlation between the ECAS and the ACE-III scores, bvFTD patients scored slightly lower on the ECAS than on the ACE-III, while AD patients scored similarly between tests (see Figure 16). I decided to explore the sensitivity of the ECAS and the ACE-III at differentiating between diagnoses, with the hypothesis that the composite scores of the ECAS might be effective at differentiating between the two types of dementia. This hypothesis was based on the differences of typical clinical profiles of impairment between bvFTD and AD patients, and the finding in Kourtesis et al. 2019 were the posterior composite score of the ECAS was sensitive to differentiate between ALS and AD patients. However, bvFTD patients had similar scores for both composite scores, while the majority of AD cases scored lower in the composite posterior and higher in the composite anterior (see Figure 17). Although neither of the composites scores reached a significant difference between these groups (as stated in the article). I decided to explore the sensitivity of these scores at differentiating diagnoses compared to the total score of the ECAS and the ACE-III (Figure 18). The composite scores of the ECAS had slightly better sensitivity for differentiating between groups than the total score of both tests; however, specificity was too low to accurately differentiate diagnoses. As seen in Table 11, the total score of the ECAS was more sensitive than the ACE-III; however, the best score to differentiate between diagnoses was the Composite Posterior score (with a high sensitivity but a poor specificity). In contrast, the number of behavioural domains affected was clearly better than any of the cognitive measures at differentiating between the two groups, as stated in the article (see Figure 19).

Figure 16: Individual patient Total scores on the ECAS and the ACE-III in bvFTD and AD groups.



Addenbrooke's Cognitive Examination (ACE-III), Edinburgh Cognitive and Behavioural ALS Screen (ECAS), 1 (○) represents AD patients, 2 (▲) represents bvFTD patients.

Figure 17: Individual patient Anterior (ALS-Specific) and Posterior (ALS Non-Specific) ECAS composite scores in bvFTD and AD



Anterior composite score (language, fluency, and executive) is represented here by the title ALS Specific and the Posterior composite score (memory and visuospatial) is represented here by the title ALS non-specific. 1 (○) represents AD patients, 2 (▲) represents bvFTD patients.

Figure 18: ACE-III vs ECAS at differentiating between bvFTD and AD

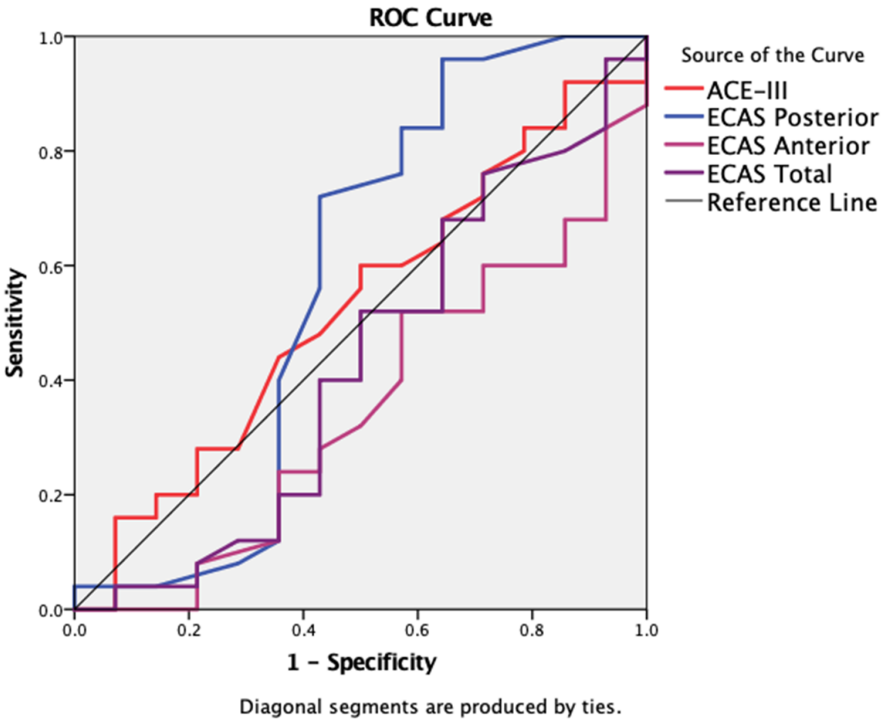
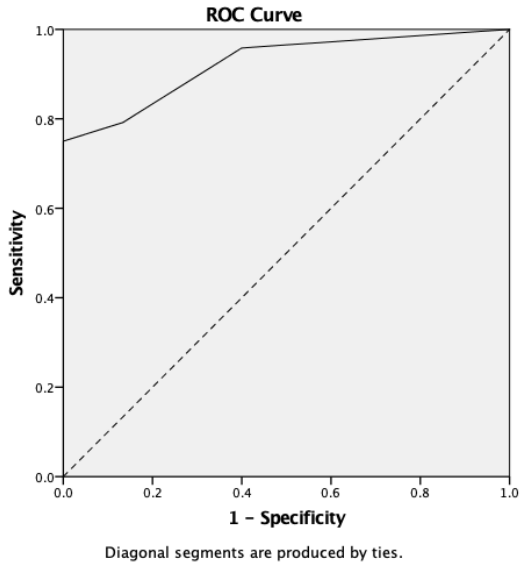


Table 11: Cut-offs sensitivity and specificity at differentiating bvFTD and AD

	Cut-off	Sensitivity	Specificity
ACE-III Total	73	.600	.500
ECAS Total	91	.760	.286
Composite Anterior	62	.520	.429
Composite Posterior	23	.960	.357

Composite scores of anterior (language, fluency, and executive) and posterior (memory and visuospatial), Edinburgh Cognitive and Behavioural ALS Screen (ECAS) and Addenbrooke's Cognitive Examination (ACE-III). The cut-off would mean that the lower than scores would be given to the AD diagnosis for the ACE-III total, ECAS total and Composite Posterior, while the lower than score of the Composite Anterior would be given to the bvFTD diagnose.

Figure 19: ROC curve bvFTD vs AD on total of behavioural domains impaired



In the bvFTD group, 94% were impaired on the ECAS total score, 94% were impaired on the anterior score, and 75% were impaired on the posterior score. In the AD group, 94% were impaired on the ECAS total score, 84% were impaired on the anterior score, and 97% were impaired on the posterior score. Even though most bvFTD patients were impaired on the anterior functions, and most AD patients were impaired on the posterior functions, both patient groups were impaired on both types of functions. Therefore, the composite scores were not effective at differentiating between these diagnoses.

To further explore if there was a difference between bvFTD and AD groups, I created ratios of impairment by changing the anterior and posterior composite scores to percentage values. The average ratio between the anterior and posterior composites scores for bvFTD was of 1.19 (±.43, .36-2.29), where 3 patients scored =1 (equal ratio), 5 patients scored <1 (ratio for anterior impairment) and 8 patients scored >1 (ratio for posterior impairment). The average ratio between the anterior and posterior composites scores for AD was of 1.89 (±1.09, 1-5.88), where 3 patients scored =1 (equal ratio), no patients scored <1 (ratio for anterior impairment) and 29 patients scored >1

(ratio for posterior impairment). Therefore, most AD patients had a greater impairment in posterior functions; while bvFTD patients had mixed presentations of impairments, with some having a greater anterior impairment and some having a greater posterior impairment. However, the average ratio was significantly different (p=.018) between diagnoses.

To explore further the lack of significant difference between patient groups on the ECAS posterior functions subscore, I calculated power analyses in G*Power (Faul et al., 2007). The current comparison of the bvFTD group with the healthy control group had a large effect size (d= 2.52) and a power of .99 when using an alpha of 0.05; however, the comparison of the bvFTD group and the AD group had a medium effect size (d= 0.55) and a much reduced power of .55 when using an alpha of 0.05. Therefore, power may have been an issue in detecting a difference between bvFTD and AD patients on the ECAS composite scores.

3.2.3.3 Validation against Full Neuropsychological Assessment

I decided to include in this section the neuropsychological assessment data of each patient to expand on table 7 (see tables 12 and 13) to show the impairment of each patient on each individual test of the neuropsychological assessment. In the bvFTD group, 46% of patients were impaired in the three anterior domains of the neuropsychological assessment (fluency, language and executive), 31% were impaired in only two, and 15% were impaired in only one. The domains with the highest frequency of patients impaired in the neuropsychological assessment for the bvFTD group were memory and fluency (see table 14). The test with the highest frequency of patients impaired in the bvFTD group was the FSCRT, followed by the FAS and Animal Fluency. All AD patients who undertook the neuropsychological assessment were impaired on memory, whereas only 68% of those patients were impaired on visuospatial functions. The domains with the highest frequency of patients impaired for the AD group were memory and executive. The test with the

highest frequency of patients impaired in the AD group was the FSCRT, followed by the BIRT Story Recall, the Trail Making Test and VOSP number location.

Table 12: Neuropsychological data by patient for the bvFTD group

					Neuropsychology Assessment											
					Neuropsychology Anterior Domains						Neuropsychology Posterior Domains					
					Fluency		Language		Executive		Visuospatial			Memory		
	ACE-III	ECAS Anterior	ECAS Posterior	ECAS Total	FAS	Animal Fluency	Naming	TROG	Trail	Sorting	Dot	Number Location	Figure Copy	Story Recall	Figure Recall	FSCRT
1	✓	X	X	X	✓	✓	X		✓	✓			✓	✓	✓	X
2		X	X	X												
3	X	X	X	X												
4	X	X	✓	X	X	X	X		✓	✓			X	✓	X	X
5	X	X	X	X	X	X	✓	X	X	X			X	X	✓	X
6	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	X	✓	✓	X
7	X	X	✓	X												
8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	✓	X
9	X	X	X	X	X	✓	X		X	X	✓	X	X	X	✓	✓
10	X	X	X	X	X		X		X	X			✓	X	✓	X
11	X	X	X	X	X	X	✓		✓	X			✓	X	X	X
12	X	X	X	X	X	X	X	✓	X	✓	✓	✓	✓	X	✓	X
13	✓	X	X	X	X	X	✓	X	X	X	✓	X	✓	X	✓	X
14		X	X	X	X	X			X	X			✓	✓	✓	X
15	X	X	X	X					X				✓		✓	
16	X	X	✓	X	X	X	✓	✓	X	✓	✓	✓	✓	X	✓	X

Addenbrooke's Cognitive Examination-III (ACE), Edinburgh Cognitive and Behavioural ALS Screen (ECAS), ECAS Anterior (language, fluency, and executive domains), ECAS Posterior (memory and visuospatial domains), Controlled Oral Word Association (FAS), The Graded Naming Test (Naming), Test of Reception of Grammar (TROG), Trail Making Test (Trail), The Sorting Test (Sorting), VOSP Dot counting (Dot), VOSP Number location, BIRT Memory and Information Processing Battery Story Recall (Story Recall), BIRT Memory and Information Processing Battery Figure Recall (Figure Recall), Free and Cued Selective Reminding Test (FSCRT). Impaired Range (X) and Normal range (✓). Blank spaces are missing data. Coloured in red are the abnormal scores for the ACE-III, ECAS Total, ECAS composite scores and neuropsychology domains. Coloured in green are the ACE-III, ECAS Total, ECAS composite scores and neuropsychology domains in the normal range.

Table 13: Neuropsychological data by patient for the AD group

					Neuropsychology Assessment											
					Neuropsychology Anterior Domains						Neuropsychology Posterior Domains					
					Fluency		Language		Executive		Visuospatial			Memory		
	ACE-III	ECAS Anterior	ECAS Posterior	ECAS Total	FAS	Animal Fluency	Naming	TROG	Trail	Sorting	Dot	Number Location	Figure Copy	Story Recall	Figure Recall	FSCRT
1		X	X	X	✓	✓	✓	X		X	X	X	X	✓	X	X
2	X	X	X	X	X	X	✓		X	✓			✓	X	✓	X
3	X	X	X	X	✓	✓	✓		X	✓			✓	X	X	X
4	X	X	X	X	✓	X	✓	✓	X	✓	✓	X	X	X	✓	✓
5	X	X	X	X	✓	X	✓	X	X	X			X	X	X	X
6		X	X	X	X	X	X		X		✓	X	X	X	✓	X
7		X	X	X	X	X	✓				X		X	X	X	
8	X	X	X	X	X	X	✓	X	✓				✓	X	✓	X
9		X	X	X	X	X							X	X	X	
10	X	X	X	X	✓	✓	✓		X	✓	✓	X	X	X	✓	X
11	X	X	X	X	✓	X	✓	X	X		✓	X	X	X	X	X
12	X	X	X	X												
13	X	X	X	X	X	X								X		
14	✓	X	X	X	✓	X	X	✓	X	✓			✓	X	✓	X
15		X	X	X												
16	X	X	X	X									✓	X	X	X
17	X	✓	X	X	✓	X	✓	✓	X	✓	✓	✓	✓	X	X	X
18	X	X	X	X	✓	X	X		X	X			X	X	X	X
19	X	X	X	X	X	X			X	X			X	X	X	
20		X	X	X										X		X

21		X	X	X	X	X	X	X	X	✓	✓	X	✓	X	✓	X
22	X	X	X	X	X	X	✓		X	X	✓	X	X	X	✓	X
23	X	✓	X	X	✓	X	X	✓	✓	✓	✓	X	✓	✓	✓	X
24	X	X	X	X	X	X	✓		X				X	X	✓	X
25	X	X	X	X	✓		✓	X	X		✓	X	X	X	✓	X
26	X	✓	✓	✓	✓	X	X		X	✓	✓	X	✓	X	✓	X
27	X	X	X	X	✓	✓	✓	X	X	✓	X	X	X	X	✓	X
28	✓	✓	X	X	✓	✓	✓	X	✓	✓	✓	✓	✓	X	✓	X
29	X	X	X	X	✓	✓	✓	✓	X	✓			X	✓	X	X
30	✓	X	X	X	✓	✓	✓	X	X	✓	✓	X	✓	X	✓	X
31	✓	X	X	X	✓	X	✓	✓	X	✓	✓	✓	✓	X	X	X
32	✓	✓	X	✓	✓	✓	✓	✓	X	✓			✓	X	✓	X

Addenbrooke's Cognitive Examination-III (ACE), Edinburgh Cognitive and Behavioural ALS Screen (ECAS), ECAS Anterior (language, fluency, and executive domains), ECAS Posterior (memory and visuospatial domains), Controlled Oral Word Association (FAS), The Graded Naming Test (Naming), Test of Reception of Grammar (TROG), Trail Making Test (Trail), The Sorting Test (Sorting), VOSP Dot counting (Dot), VOSP Number location, BIRT Memory and Information Processing Battery Story Recall (Story Recall), BIRT Memory and Information Processing Battery Figure Recall (Figure Recall), Free and Cued Selective Reminding Test (FSCRT). Impaired Range (X) and Normal range (✓). Blank spaces are missing data. Coloured in red are the abnormal scores for the ACE-III, ECAS Total, ECAS composite scores and neuropsychology domains. Coloured in green are the ACE-III, ECAS Total, ECAS composite scores and neuropsychology domains in the normal range.

Table 14: Percentage impaired on each test of the full Neuropsychological Assessment

Test	bvFTD% of impaired scores	AD% of impaired scores
Fluency	83	68
FAS	83	36
Animal Fluency	73	70
Language	73	58
The Graded Naming Test	54	24
TROG	50	56
Executive	77	88
Trail Making Test	69	87
The Sorting Test	58	25
Visuospatial	46	68
VOSP dot counting	17	19
VOSP number location	67	80
BIRT Figure copy	38	53
Memory	92	100
BIRT Story Recall	67	90
BIRT Figure Recall	15	43
FSCRT	92	96

Controlled Oral Word Association (FAS), Test of Reception of Grammar (TROG), Free and Cued Selective Reminding Test (FSCRT). Impairment for each test was determined according to their published cut-off scores for abnormality or based on the 5th percentile of published normative data. Each domain was assessed by two or three neuropsychological tests, and an impairment in a domain was determined when performance on at least one of the tests was impaired

3.2.4 Discussion

The ECAS domains were sensitive to bvFTD and AD as expected. The domain most sensitive to bvFTD was executive functions while the domain most sensitive to AD was memory. Impairments in both of these functions are part of the diagnostic criteria for each of these diseases (Rascovsky et al. 2011; McKhann et al. 2011) and are extensively reported in the literature (Elderkin-Thompson et al., 2004; Johns et al. 2009; Parra et al., 2009). Fluency was the most sensitive domain to bvFTD in the ACE-III; this finding was expected and has been previously reported (Elderkin-Thompson et al., 2004; Johns et al.

2009). As on the ECAS, the domain most impaired by AD in the ACE-III was memory. Visuospatial functions were the least sensitive domain for both diagnoses and in both tests, which was unexpected for AD. There have been some contradictions in the literature regarding visuospatial functions being impaired (Quental et al., 2013; Salimi et al., 2019) or not (Binetti et al., 1998) in early stages of AD. The sample in this study was of a younger onset and with low levels of impairment in visuospatial functions for the AD group, further studies may investigate whether there is a similar profile in older AD patients. The bvFTD group was slightly more impaired in executive functions than the AD group; however, the AD group was also quite impaired in the executive functions' domain on the ECAS and more so than in the language and visuospatial domains. These results were similar in the neuropsychological assessment, where more AD patients were impaired in the executive tests than in the visuospatial ones. Previous research has suggested that perhaps executive functions should not contribute to differentiate between diagnoses as both patient groups have been shown to have impairments (Reul et al., 2017).

The most sensitive subtests of the ECAS to bvFTD were immediate memory and recognition. Studies have reported memory impairments in bvFTD to be quite prevalent, less pronounced than in AD, but with a significant difference than controls (Poos et al., 2018). It is to be noted that this memory impairment in the bvFTD group of this sample was also replicated in the neuropsychological assessment, where all but one patient were impaired in the memory assessment. These results are supportive of the hypothesis that neural degeneration in mediotemporal areas could contribute to memory loss in bvFTD (Irish et al., 2013; de Souza et al, 2013). However, an alternative explanation could be that there is an overlap of functions where an impairment on executive functions has an effect on memory performance due to the cognitive demands of using a strategy and holding attention (Saxon et al., 2020).

The ECAS total score had an identical level of sensitivity and specificity to a general group of dementia (94%, 96%) than to the individual diagnosis of bvFTD and AD. The ECAS was also more sensitive to detect dementia than the ACE-III. In this sample the ACE-III had less sensitivity (80%, specificity 98%) to detect dementia than the previous published values (93%, specificity 100%) (Hsieh et al., 2013). I also found that the best measure to differentiate the diagnoses of bvFTD and AD with the ECAS is with the amount of behavioural changes in the five domains of the behavioural screen, as stated in the article. This measure was more sensitive than the composite scores of the ECAS.

3.2.5 Conclusions bvFTD and AD

As shown in the article above and in this chapter, the ECAS was a successful cognitive screen for bvFTD and AD groups when compared to healthy controls, but there were no significant differences in cognitive scores between these two patient groups. The ECAS total score and the anterior composite score were the most sensitive measures to detect impairment in bvFTD patients, while the posterior composite score and the ECAS total score were the most sensitive measures to detect impairment in AD patients. Nevertheless, both composite scores were sensitive to both diagnoses albeit to a different degree. The ratio analysis showed that while the vast majority of AD patients were more impaired on posterior functions, some bvFTD patients were more impaired on anterior functions and some were more impaired on posterior functions. There was, however, a significant difference between the ratios of these groups. The power analyses showed that a larger patient sample would be needed to explore if there is a difference on the posterior composite score between groups. The most sensitive ECAS domains for each diagnosis were executive functions for bvFTD and memory for AD. The ECAS had a higher sensitivity and a marginally lower specificity than the ACE-III for the screening of both diagnoses. Therefore, the ECAS could be potentially used instead of the ACE-III for the screening of AD, but even more so for the screening of bvFTD due

to its inclusion of executive functions, the behavioural interview, and the ACE-III's inconsistencies at detecting dementia in bvFTD (Elamin et al., 2015).

The ECAS showed to be valid at detecting cognitive changes in bvFTD and AD patients when compared to an extensive neuropsychological assessment; with concordance between impairment shown on the anterior and posterior composite scores on the ECAS, with the impairment shown on anterior and posterior functions' tests on the neuropsychological assessment. The ECAS behavioural screen showed to be sensitive to differentiate between the bvFTD and AD groups. In addition, different themes were found between the groups in the behavioural screen. Future work could explore the ECAS in other dementia diagnoses; as done with the PPA, MCI and PCA groups in the next section of this chapter. The ECAS could also be compared to other dementia screening tools in patient populations. If the ECAS was to be developed into a future version, the behavioural screen could be changed to include more questions relevant to the themes found in this study for the AD group.

3.3 MCI, PPA and PCA on the ECAS

3.3.1 Introduction

In addition to the bvFTD and AD data used for the article, I was also able to obtain data from some patients with Mild Cognitive Impairment (MCI), Primary Progressive Aphasia (PPA) and Posterior Cortical Atrophy (PCA) from the database obtained from the Edinburgh Cognitive Diagnosis Audit Research and Treatment Register (DART), hosted by the Anne Rowling Regenerative Neurology Clinic and the University of Edinburgh. These groups were not included in the main article as the number of participants for each group were small.

Previous studies have determined the sensitivity of different translations of the ACE-III to MCI. One study using the Chinese version reported a sensitivity of 97.3% and specificity of 90.7% (cut-off of 85) (Wang et al., 2019), while another study using a different Chinese version of the ACE-III found a sensitivity of 75% and specificity of 89% using a cut-off of 88/89 (Li et al., 2019). The Spanish version reported a sensitivity of 76.6% and specificity of 75% for a cut-off of 73/74 (Matias-Guiu et al., 2017), and the Japanese version found a sensitivity of 80% and specificity of 86% (cut-off of 88/89) (Senda et al. 2020). There have not been studies on the sensitivity of the ACE-III to PPA and PCA individually. Instead, the original ACE-III validation study (Hsieh et al., 2013) included PPA patients in a bigger patient group to determine sensitivity to dementia. Another study included both PPA and PCA patients to obtain the sensitivity of the ACE-III to early-onset dementia (Elamin et al., 2015).

The aim of this study was to determine whether the ECAS is an appropriate assessment to detect MCI, PPA and PCA against healthy controls, and determine its validity against a full neuropsychological assessment. I hypothesised that the MCI group would perform worse than the control group,

but better than the other dementia groups on the total scores of the ECAS and the ACE-III. I expected that the PPA group would perform lower than the other groups in the domains of language and fluency. I also expected the PCA group to perform lower than the other groups primarily in the visuospatial domains, but perhaps they would additionally score lower in the memory domain, as it has been a finding reported previously and is consistent with the Alzheimer pathology of this group, although initial presentation is atypical (Ahmed et al., 2016 b). In this study, PCA patients were impaired on the memory domain of the ACE-R.

The study below was exploratory and would need validation in future studies as the number of participants for each group were small.

3.3.2 Method

Participants

In this retrospective study I analysed data collected as part of routine clinical neuropsychological assessment from 12 people with MCI, 13 people with PPA (5 logopenic, 3 nonfluent/agrammatic, 2 semantic, 3 unclear at time of testing), and 6 people with PCA from the Edinburgh Cognitive Diagnosis Audit Research and Treatment Register (DART), hosted by the Anne Rowling Regenerative Neurology Clinic and the University of Edinburgh.

Diagnoses were supported by magnetic resonance imaging (MRI) brain and HMPAO-SPECT imaging findings; measures of cerebrospinal (CSF) total Tau, Phosphorylated Tau, and beta amyloid (Ab1-42); and/or disease-causing mutations identified following a neurodegenerative gene panel analysis. Diagnoses were made according to consensus criteria including: Albert et al. (2011) for MCI, Gorno-Tempini et al. (2011) for PPA and Crutch et al. (2017) for PCA.

Healthy participants (n=48, same sample as the article) matched in age and education to the MCI, PPA and PCA groups were recruited from the local population and the Psychology Volunteer Panel of the University of Edinburgh.

All were native English speakers without neurological illness or learning disabilities in their medical history.

Materials

The materials used on these participants were the same as those described in the article included on this chapter.

3.3.3 Ethical Approval

Ethical approval was obtained for the collection and analyses of the patient data in the DART Register 12/SS/0196 Edinburgh Cognitive Diagnosis Audit Research and Treatment Register IRAS no 103819. Healthy control collection was approved by The Psychology Research Ethics Committee of the University of Edinburgh.

3.3.4 Statistical Analysis

The data were analysed using SPSS statistics version 22. One-way between groups analysis of variance (ANOVA) were undertaken on parametric data to assess the difference between groups. Since the groups had such a difference in sample size, homogeneity of variances for all variables was violated per the Levene test, I provide the Welch adjusted values with Games-Howell post hoc tests.

ROC curves assessed the sensitivity and specificity of the ECAS to detect diagnoses of MCI, PPA and PCA.

3.3.5 Results

Demographics for the three patient groups and the healthy controls can be found in Table 15.

Table 15: Demographics of the sample

Group	Number of participants	Gender	Age	Education
MCI	12	7 males 5 females	61.33 (±6.40, 51-69)	12.28 (±2.28, 10-16)
PPA	13	8 males 5 females	64.38 (±6.00, 57-77)	12.50 (±2.67, 9-21)
PCA	6	2 males 4 females	58.50 (±5.95, 50-67)	11.60 (±2.70, 9-16)
controls	48	29 males 19 females	60.06 (±11.92, 38-78)	13.66 (±3.03, 9-19)

Results for age and education are presented: mean (standard deviation, range)

3.3.5.1 Sensitivity of the ECAS versus the ACE-III in detecting MCI, PPA and PCA

There was a significant difference between the control group and the three patient groups (MCI, PPA, and PCA) in the total score of the ECAS, both composite scores and the domain of memory; as well as the total score of the ACE-III (see Table 16). MCI patients scored significantly lower than controls in the domains of memory for both tests and fluency in the ACE-III. PPA patients scores were significantly different from controls in all domains of the ECAS except the visuospatial domain, while in the ACE-III they only differed in the domains of memory and fluency. PCA patients scores were significantly different than controls in all domains of the ECAS except the fluency domain; in contrast, only the visuospatial domain was impaired in the ACE-III.

Table 16: Comparison of the ECAS and ACE-III scores with MCI, PPA, PCA and control groups
MCI (n=12) PPA (n=13) PCA (n=6) Controls (n=48)

	Welch's F	Sig		Mean (SD) Range	Sig vs Cont.
ECAS Total	(3,14.52) = 31.35	**<.001**	MCI PPA PCA Controls	99.33 (±9.61) 79-119 63.38 (±31.33) 19-119 60.50 (±25.64) 18-87 118.44(±7.98) 102-134	**<.001** **<.001** **=.009**
ECAS Language	(3,14.09) = 11.40	**<.001**	MCI PPA PCA Controls	25.25 (±2.45) 20-28 18.92 (±6.97) 8-27 18.17 (±5.41) 11-25 27.02 (±1.49) 21-28	=.128 **=.006** **=.036**
ECAS Fluency	(3,14.25) = 15.30	**<.001**	MCI PPA PCA Controls	16.33 (±5.31) 2-20 6.62 (±7.32) 0-18 11.33 (±10.17) 0-24 20.17 (±3.08) 10-24	=.126 **<.001** =.263
ECAS Executive	(3,14.25) = 16.24	**<.001**	MCI PPA PCA Controls	35.42 (±6.50) 23-47 22.77 (±13.17) 2-41 19.83 (±9.28) 3-29 40.15 (±3.79) 32-47	=.122 **=.002** **=.011**
ECAS Memory	(3,14.43) = 26.38	**<.001**	MCI PPA PCA Controls	11.42 (±4.99) 3-17 4.54 (±7.88) 0-22 8.33 (±6.74) 1-16 19.75 (±3.03) 12-24	**<.001** **<.001** **=.031**
ECAS Visuospatial	(3,14.70) = 41.10	**<.001**	MCI PPA PCA Controls	10.92 (±1.73) 7-12 10.54 (±1.56) 7-12 2.83 (±1.83) 1-5 11.56 (±0.94) 7-12	=.610 =.155 **<.001**
ECAS Composite score of Anterior functions	(3,14.21) = 17.81	**<.001**	MCI PPA PCA Controls	77.00 (±9.89) 59-93 48.31 (±24.90) 10-85 49.33 (±21.08) 14-69 87.13 (±6.42) 72-99	**=.022** **<.001** **=.025**
ECAS Composite score of Posterior functions	(3,14.50) = 33.61	**<.001**	MCI PPA PCA Controls	22.33 (±4.49) 15-28 15.08 (±8.64) 9-34 11.17 (±8.32) 3-21 31.31 (±3.30) 21-36	**<.001** **<.001** **=.007**
ACE-III Total	(3,12.24) = 21.93	**<.001**	MCI PPA PCA Controls	85.73 (±4.98) 77-92 67.50 (±17.76) 44-97 62.00 (±12.93) 43-79 93.82 (± 4.26) 82-100	**=.001** **=.016** **=.006**
ACE-III Attention	(3,10.83) = 2.90	=.084	MCI PPA PCA Controls	16.90 (±1.57) 14-18 14.25 (±3.41) 8-18 14.40 (±2.88) 10-17 17.11 (±1.10) 13-18	=.976 =.172 =.292

ACE-III Memory	(3,11.06) = 13.72	**<.001**	MCI PPA PCA Controls	18.27 (±3.28) 13-22 13.50 (±6.34) 7-26 15.00 (±6.36) 7-21 23.43 (±2.70) 15-26	**=.002** **=.012** =.128
ACE-III Fluency	(3,10.67) = 17.69	**<.001**	MCI PPA PCA Controls	10.18 (±1.94) 7-13 6.50 (±2.92) 3-11 7.40 (±3.84) 2-12 12.75 (±1.10) 10-14	**=.006** **=.002** =.112
ACE-III Language	(3,10.58) = 3.86	=.043	MCI PPA PCA Controls	24.90 (±1.22) 23-26 19.50 (±6.30) 11-26 20.00 (±5.78) 11-26 25.43 (±0.81) 23-26	=.553 =.117 =.293
ACE-III Visuospatial	(3,11.09) = 29.54	**<.001**	MCI PPA PCA Controls	14.63 (±1.36) 12-16 13.75 (±4.86) 2-16 4.80 (±2.28) 2-8 15.09 (±1.17) 11-16	=.743 =.863 **=.002**

This table shows the total score of the ECAS and the composite scores of anterior (language, fluency, and executive) and posterior (memory and visuospatial) functions and the domains. Abbreviations on table are: mild cognitive impairment (MCI), primary progressive aphasia, (PPA), posterior cortical atrophy (PCA), Number of participants (n), Edinburgh Cognitive and Behavioural ALS Screen (ECAS), Addenbrooke's Cognitive Examination (ACE-III) Significance (Sig.), Standard Deviation (SD), Controls (Cont.)

The ECAS total cognitive score showed excellent sensitivity and specificity to detect MCI (91%, 95%), PPA (87%, 98%), and PCA (100%, 95%) using the established cut-off score of 105 (see Table 17). There was no difference in the number of patients impaired from the PPA and PCA groups when using the adjusted age and education cut-offs (De Icaza Valenzuela et al., 2018); however, MCI patients differed from 10 out of 12 impaired with the original 105 abnormality cut-off, to 5 out of 10 impaired based on age and education abnormality cut-offs, with 2 patients without education data. The cut-off of 82 in the ACE-III was not sensitive to MCI (18%, 98%). However, the cut off of 88 showed a good sensitivity and specificity to MCI (73%, 86%), although it was less sensitive than the ECAS. The ECAS total score was also more sensitive to PPA (87%, 95%) than the ACE-III (75%, 98%). The ECAS and the ACE-III had similar sensitivity to detect PCA (100%, 95% and 100%, 98% respectively) and detected all individuals with this diagnosis. The Posterior composite score of the ECAS had the same sensitivity towards PPA and PCA as the ECAS total

score. Figure 20 shows the ROC curves for the scores of the ECAS and the ACE-III for the diagnosis of MCI and Figure 21 shows the ROC curves for the diagnosis of PPA. I do not present a figure of the ROC curve for the PCA diagnosis as both tests had a sensitivity of 100% towards the diagnosis.

Table 17: Sensitivity and specificity of tests scores in detecting MCI, PPA, and PCA vs controls

		MCI		PPA		PCA	
	Cut-off	Sens.	Spec.	Sens.	Spec.	Sens.	Spec.
ACE-III Total	82	.182	.977	.750	.977	1.000	.977
ACE-III Total	88	.727	.864	.875	.864	1.000	.864
ECAS Total	105	.909	.955	.875	.955	1.000	.955
ECAS Total	110	.909	.818	.875	.818	1.000	.818
Language	26	.636	.727	1.000	.727	1.000	.727
Fluency	14	.182	.955	.750	.955	.500	.955
Executive	33	.455	.977	.625	.977	1.000	.977
Anterior	77	.545	.909	.875	.909	1.000	.909
Memory	13	.455	.955	.875	.955	.667	.955
Visuospatial	10	.273	.909	.375	.909	1.000	.909
Posterior	24	.545	.955	.875	.955	1.000	.955

Mild cognitive impairment (MCI), primary progressive aphasia, (PPA), posterior cortical atrophy (PCA), composite scores of anterior (language, fluency, and executive) and posterior (memory and visuospatial), Edinburgh Cognitive and Behavioural ALS Screen (ECAS) and Addenbrooke's Cognitive Examination (ACE-III). Established cut-offs for the tests are 82 for ACE-III and 105 for ECAS; however, I decided to include the sensitivity of other values which determine borderline cases.

Figure 20: ROC curve MCI vs Controls on ECAS and ACE-III Total Scores

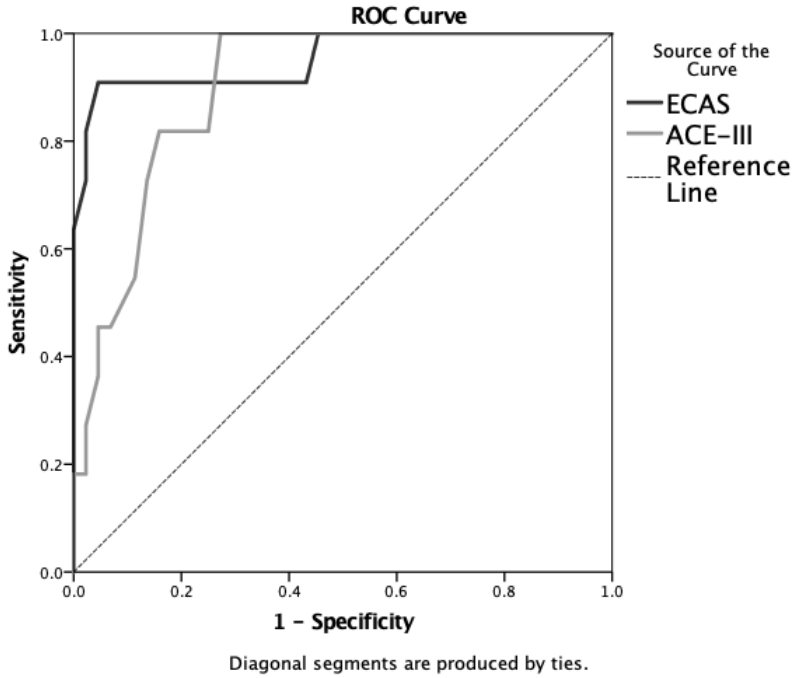
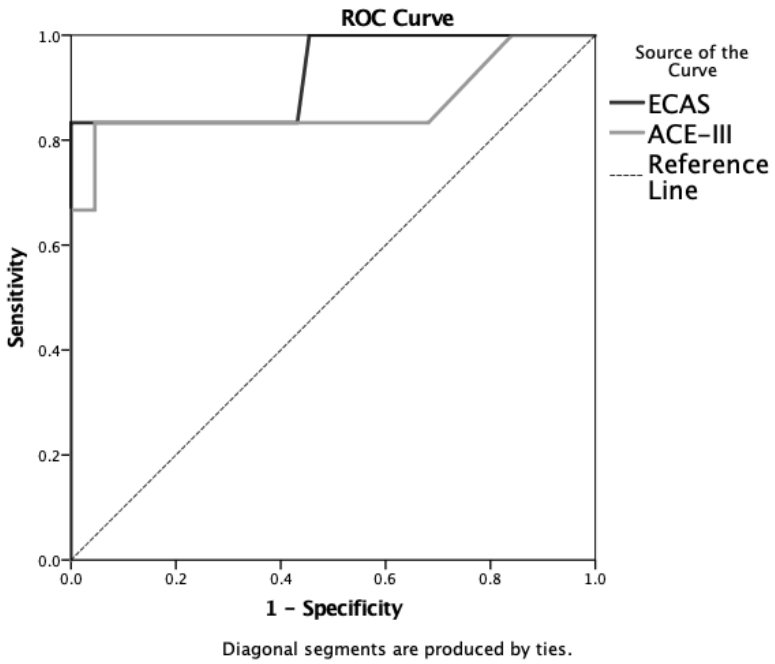
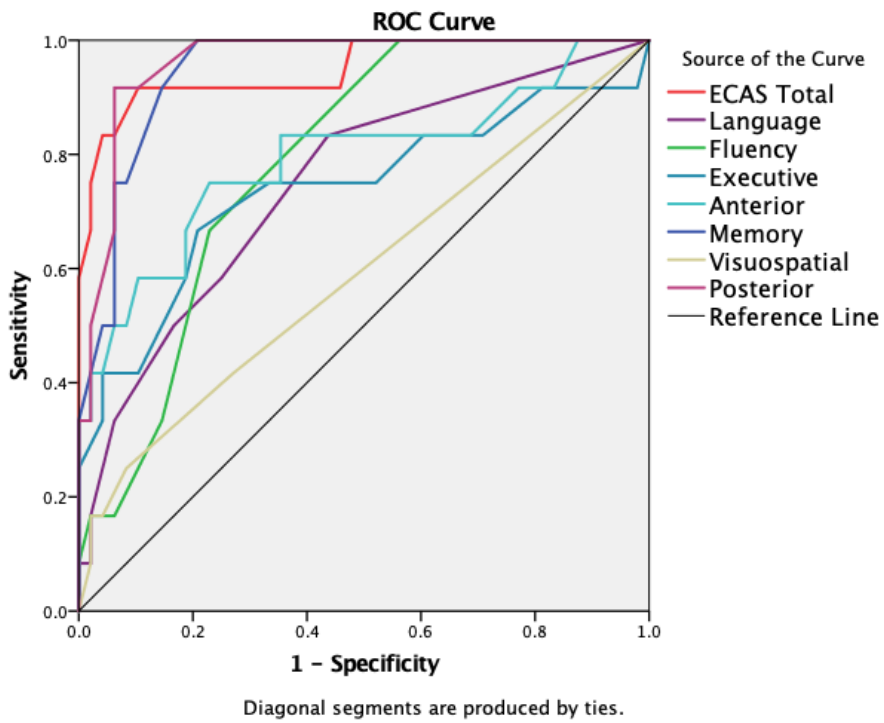


Figure 21: ROC curve PPA vs Controls on ECAS and ACE-III Total Scores



The ECAS total score and the composite ECAS score of the posterior functions (memory and visuospatial) were the most sensitive measure to detect MCI, followed by the memory domain (see Figure 22). The fluency domain was the most sensitive measure to detect PPA, followed by the composite ECAS score of the anterior functions (language, fluency and executive) and the language domain (see Figure 23). The ECAS total score, the executive domain, the composite ECAS score of the anterior functions, and the visuospatial domain had 100% sensitivity to detect PCA (see Figure 24). The most sensitive subtest for MCI was the Immediate memory score, followed by retention and recognition (see Figure 25). The most sensitive subtest for PPA was free fluency, followed by constrained fluency and reverse digits (see Figure 26). The most sensitive subtest for PCA was number location, followed by dot counting and immediate memory (see Figure 27).

Figure 22: ROC curve MCI vs Controls on ECAS domains



ECAS Anterior (language, fluency, and executive domains), ECAS Posterior (memory and visuospatial domains).

Figure 23: ROC curve PPA vs Controls on ECAS domains

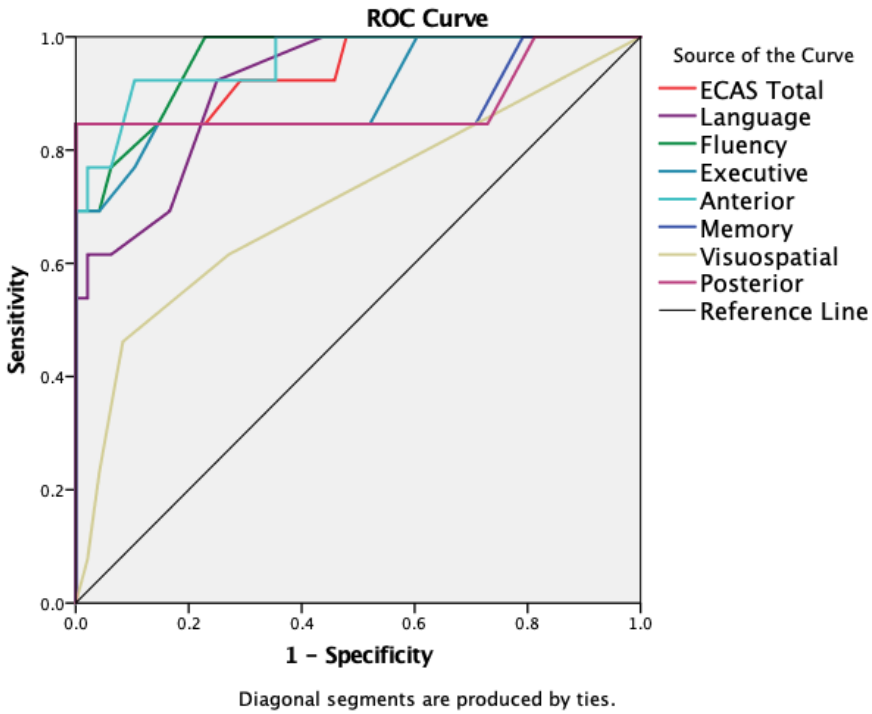


Figure 24: ROC curve PCA vs Controls on ECAS domains

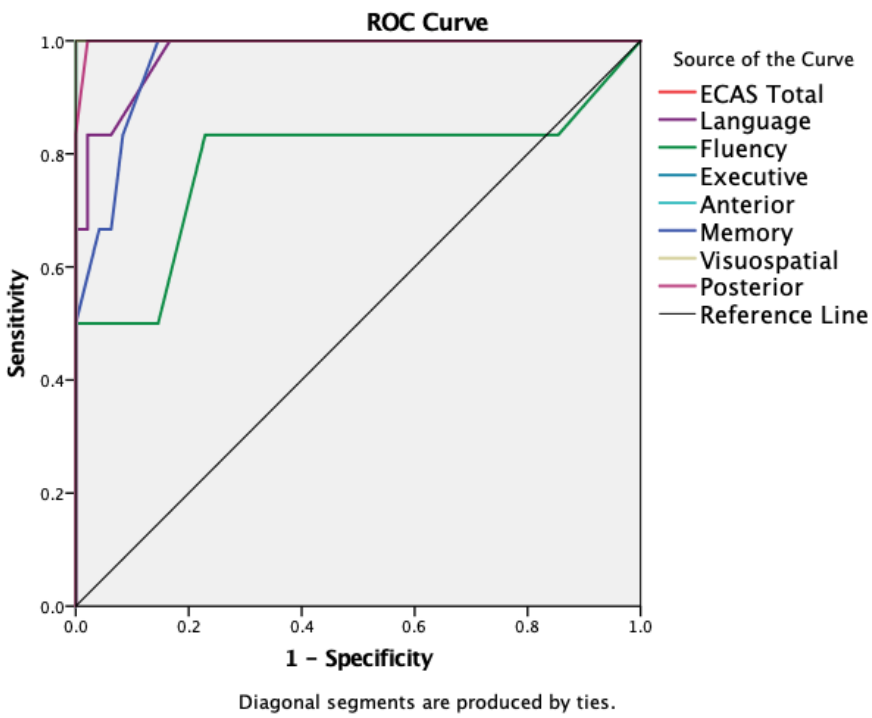


Figure 25: ROC curve MCI vs Controls on ECAS subtests

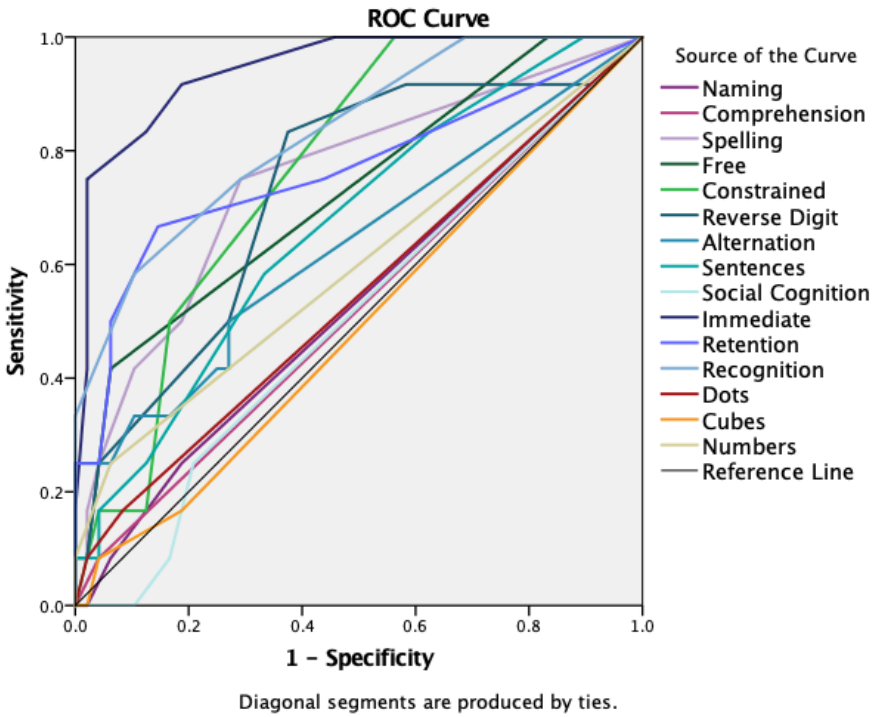


Figure 26: ROC curve PPA vs Controls on ECAS subtests

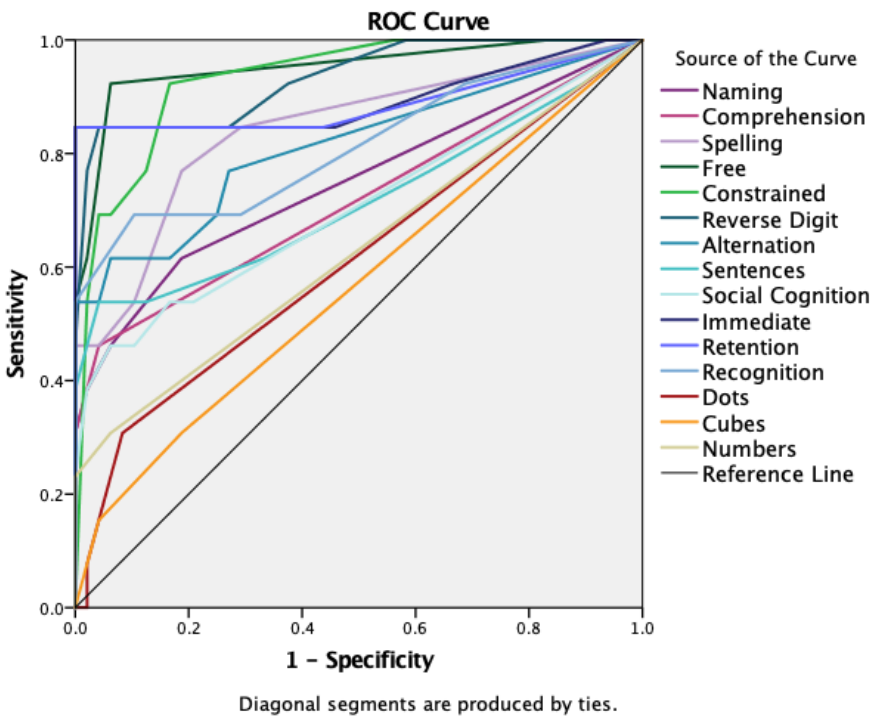
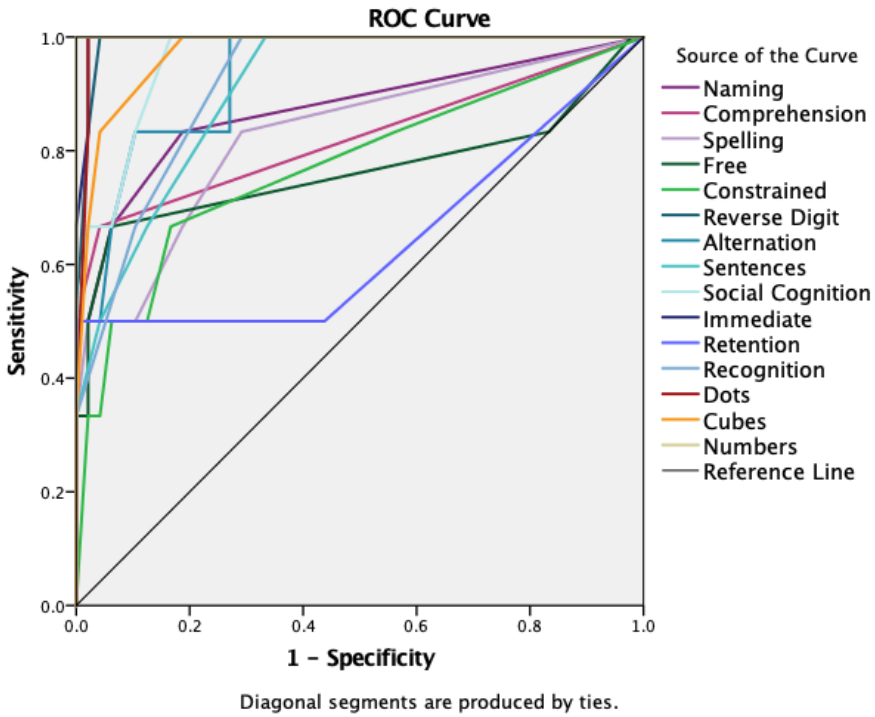
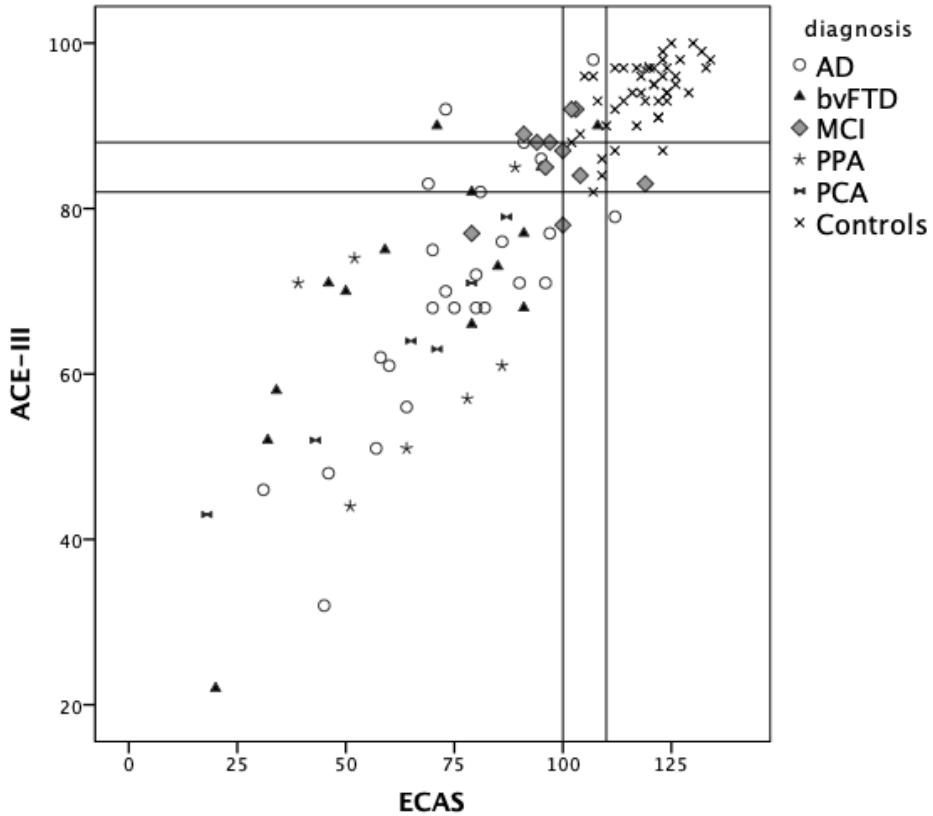


Figure 27: ROC curve PCA vs Controls on ECAS subtests



I have included a scatterplot of the scores on the ECAS and the ACE-III by diagnosis in figure 28 together with the AD and bvFTD groups for comparison. As expected, the control group scored mostly above the cut-offs of both tests; while the MCI group scored mostly around the borderline ranges for both tests and the dementia groups scored lower than the cut-offs.

Figure 28: Scatterplot of ECAS and ACE-III scores by diagnosis



The lines for each test mark the borderline range for abnormality

3.3.5.2 Validation of the ECAS against Full Neuropsychological Assessment

Results of the patients on the neuropsychological assessment can be found in table 18. Ten (83%) of MCI patients were impaired on the ECAS total score. Eleven patients completed the ACE-III, from which 8 (73%) scored below the cut-off of 88 and only 2 (18%) scored below the cut-off of 82. Nine of the MCI patients undertook the full Neuropsychological Assessment, from which eight (88%) were impaired. Two (22%) were impaired exclusively in posterior cerebral function domains, six (67%) were impaired in both anterior and posterior cerebral function domains and one (11%) was not impaired in any domain. Eleven (85%) of PPA patients were impaired on the ECAS total score. Eight patients completed the ACE-III, from which 7 (87%) scored below the

cut-off of 88 and 6 (75%) scored below the cut-off of 82. Twelve of the PPA patients undertook the full Neuropsychological Assessment. One PPA patient was not impaired on the ECAS total score nor in the composite scores, nor on any of the domains of the neuropsychological assessment. All other PPA patients (92%) were impaired in the fluency domain of the neuropsychological assessment. All 6 PCA patients were impaired in the ECAS total score, both composite scores, the ACE-III and the visuospatial domain of the neuropsychological assessment. Tables 19-21 include the detailed results per patient of the validation data using the 105-original cut-off.

Table 18: MCI, PPA and PCA patients impairment (yes/no) in the ACE-III, ECAS and full neuropsychological assessment.

Number of patients	ACE-III	ECAS total	ECAS Anterior	ECAS Posterior	Neuro Total	Neuro Anterior	Neuro Posterior
MCI							
2	✓	X	X	X	X	X	X
1	✓	X	X	✓	X	X	X
1	✓	X	X	✓	✓	✓	✓
1	X	X	✓	X	X	X	X
1	✓	X	✓	X	X	✓	X
1	✓	X	✓	X	X	X	X
1	✓	✓	✓	✓	X	X	X
1		✓	✓	X	X	✓	X
1	X	X	X	X			
1	✓	X	✓	✓			
1	✓	X	X	✓			
PPA							
5	X	X	X	X	X	X	X
1	X	X	X	X	X	X	✓
1	✓	X	X	X	X	X	X
2		X	X	X	X	X	X
1		✓	✓	✓	✓	✓	✓
2		X	X	X	X	X	✓
1	✓	✓	✓	✓			
PCA							
6	X	X	X	X	X	X	X

Addenbrooke's Cognitive Examination (ACE-III), Edinburgh Cognitive and Behavioural ALS Screen (ECAS), Neuropsychological Assessment (Neuro), Normal Range (✓), Impaired Range (X).

Table 19: MCI impairment in tests

					Neuropsychology Assessment											
					Neuropsychology Anterior Domains						Neuropsychology Posterior Domains					
					Fluency		Language		Executive		Visuospatial			Memory		
	ACE-III	ECAS Anterior	ECAS Posterior	ECAS Total	FAS	Animal Fluency	Naming	TROG	Trail	Sorting	Dot	Number Location	Figure Copy	Story Recall	Figure Recall	FSCRT
1	84	81	23	104	✓	✓	✓	X	✓	✓	✓	✓	✓	X	✓	✓
2	83	93	26	119	✓	X	✓	✓	✓	✓	✓	✓	✓	X	✓	✓
3	89	67	24	91	✓	✓	✓	X	X	✓	✓	✓	X	✓	✓	✓
4	88	69	28	97	✓	X			✓	✓			✓	✓	✓	X
5	85	80	16	96	✓	✓	✓	✓	✓	✓	✓	X	X	✓	✓	✓
6	88	71	23	94	✓	✓	X	X		✓	✓	X	✓	X	✓	✓
7	78	85	15	100	✓	X	X		✓	X			✓	X	✓	X
8	77	59	20	79												
9	92	78	25	103												
10		91	16	107	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	X
11	87	74	26	100												
12	92	76	26	102	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓

Addenbrooke's Cognitive Examination-III (ACE), Edinburgh Cognitive and Behavioural ALS Screen (ECAS), ECAS Anterior (language, fluency, and executive domains), ECAS Posterior (memory and visuospatial domains), Controlled Oral Word Association (FAS), The Graded Naming Test (Naming), Test of Reception of Grammar (TROG), Trail Making Test (Trail), The Sorting Test (Sorting), VOSP Dot counting (Dot), VOSP Number location, BIRT Memory and Information Processing Battery Story Recall (Story Recall), BIRT Memory and Information Processing Battery Figure Recall (Figure Recall), Free and Cued Selective Reminding Test (FSCRT). Impaired Range (X) and Normal range (✓). Blank spaces are missing data. Coloured in red are the abnormal scores for the ACE-III, ECAS Total, ECAS composite scores and neuropsychology domains. Coloured in green are the ACE-III, ECAS Total, ECAS composite scores and neuropsychology domains in the normal range.

Table 20: PPA impairment in tests

					Neuropsychology Assessment											
					Neuropsychology Anterior Domains						Neuropsychology Posterior Domains					
					Fluency		Language		Executive		Visuospatial			Memory		
	ACE-III	ECAS Anterior	ECAS Posterior	ECAS Total	FAS	Animal Fluency	Naming	TROG	Trail	Sorting	Dot	Number Location	Figure Copy	Story Recall	Figure Recall	FSCRT
1	85	77	12	89	X	X	✓	X	X	✓	✓	✓	✓	X	✓	X
2	57	64	14	78	X	X			X	✓			X	X	✓	
3		10	9	19		X							✓		X	
6	74	43	9	52	X	X	X	X	X	✓	✓	X	✓	X	✓	X
7		25	10	35		X			X	✓			✓		✓	
4	97	85	34	119												
11		34	16	50	X	X	X		X	✓			✓		✓	
12		20	10	30	X	X	✓		X	✓	X	X	X		✓	
10	61	73	13	86	✓	X			X				✓		✓	
13	51	52	12	64	X	X			X				✓	X	✓	
5		78	34	112	✓	✓	✓		✓	✓			✓	✓	✓	✓
8	71	29	10	39	X	X	✓			✓			✓	X	✓	✓
9	44	38	13	51	X	X	X	X	X	X			✓	X	✓	

The PPA patients are divided by diagnostic as logopenic (blue), nonfluent/agrammatic (orange), semantic (yellow) and unclear at time of diagnosis (purple). Addenbrooke's Cognitive Examination-III (ACE), Edinburgh Cognitive and Behavioural ALS Screen (ECAS), ECAS Anterior (language, fluency, and executive domains), ECAS Posterior (memory and visuospatial domains), Controlled Oral Word Association (FAS), The Graded Naming Test (Naming), Test of Reception of Grammar (TROG), Trail Making Test (Trail), The Sorting Test (Sorting), VOSP Dot counting (Dot), VOSP Number location, BIRT Memory and Information Processing Battery Story Recall (Story Recall), BIRT Memory and Information Processing Battery Figure Recall (Figure Recall), Free and Cued Selective Reminding Test (FSCRT). Impaired Range (X) and Normal range (✓). Blank spaces are missing data.

Coloured in red are the abnormal scores for the ACE-III, ECAS Total, ECAS composite scores and neuropsychology domains. Coloured in green are the ACE-III, ECAS Total, ECAS composite scores and neuropsychology domains in the normal range.

Table 21: PCA impairment in tests

					Neuropsychology Assessment											
					Neuropsychology Anterior Domains						Neuropsychology Posterior Domains					
					Fluency		Language		Executive		Visuospatial			Memory		
	ACE-III	ECAS Anterior	ECAS Posterior	ECAS Total	FAS	Animal Fluency	Naming	TROG	Trail	Sorting	Dot	Number Location	Figure Copy	Story Recall	Figure Recall	FSCRT
1	71	62	17	79	✓	X				X	X	X	X	X	✓	✓
2	64	44	21	65	X		X		X	✓	X	X	X	✓	✓	✓
3	63	67	4	71	✓	X	X	X			X		X	X	X	✓
4	79	69	18	87	✓	✓			X		X	X		✓		✓
5	52	40	3	43	✓	X	✓				X	X		X		✓
6	43	14	4	18	X	X					X		X	X	X	X

Addenbrooke's Cognitive Examination-III (ACE), Edinburgh Cognitive and Behavioural ALS Screen (ECAS), ECAS Anterior (language, fluency, and executive domains), ECAS Posterior (memory and visuospatial domains), Controlled Oral Word Association (FAS), The Graded Naming Test (Naming), Test of Reception of Grammar (TROG), Trail Making Test (Trail), The Sorting Test (Sorting), VOSP Dot counting (Dot), VOSP Number location, BIRT Memory and Information Processing Battery Story Recall (Story Recall), BIRT Memory and Information Processing Battery Figure Recall (Figure Recall), Free and Cued Selective Reminding Test (FSCRT). Impaired Range (X) and Normal range (✓). Blank spaces are missing data. Coloured in red are the abnormal scores for the ACE-III, ECAS Total, ECAS composite scores and neuropsychology domains. Coloured in green are the ACE-III, ECAS Total, ECAS composite scores and neuropsychology domains in the normal range.

3.3.6 Discussion

This section explored how well the ECAS detected different types of dementia and MCI in comparison with the ACE-III and as compared to a full neuropsychological assessment. As expected, the MCI group scored in the borderline ranges for both the ECAS and the ACE-III, while most of the control group scored higher than the cut-offs and the dementia groups scored lower than the cut-offs. I expected the MCI group to score in between these borderline ranges as they would not be as impaired as the other dementia patients. The ECAS had a similar sensitivity at detecting impairment in MCI, PPA and PCA as the full neuropsychological assessment.

3.3.6.1 MCI

The ECAS was more sensitive than the ACE-III at detecting cognitive changes in MCI patients. The published cut-off of 82 in the ACE-III (Hsieh et al., 2013) was not sensitive in detecting MCI (sensitivity 18%, specificity 98%). But although the ACE-III cut-off of 88 had a better sensitivity (73%, 86%), it was not as high as the ECAS Total Score (91%, 96%) when compared to healthy controls. Therefore, the ECAS Total was better than the ACE-III at screening for impairment in MCI. The sensitivity of the ACE-III towards MCI has been previously reported to vary from 75% to 97%, while specificity has varied from 5% to 77% (Beishon et al. 2019). In our sample sensitivity of the ACE-III was slightly lower than those values but with a higher specificity.

Although the typical MCI presentation is that of a memory impairment (Petersen, 2004), the patients that get referred to the Anne Rowling Regenerative Neurology Clinic often are referred for differential diagnosis and present symptoms with either a frontal impairment or a mixed presentation. The MCI sample in this study presented more impairment in tests of posterior functions (memory and visuospatial) (88%) in the neuropsychological assessment than in the tests regarding the anterior functions (executive,

fluency and memory); however, a large percentage (67%) were also impaired in one or more anterior functions. This difference in sample might have had an effect in the difference between sensitivity values observed in the ACE-III. Of 8 MCI patients impaired on the neuropsychological assessment, 6 were also impaired on the ECAS total score, and 7 were impaired in one of the composite scores of the ECAS. One patient was impaired on the ECAS total score and on the ECAS anterior composite score but was not impaired on the neuropsychological assessment.

3.3.6.2 PPA

The ECAS was more sensitive than the ACE-III to detect cognitive changes in PPA patients. The ACE-III (75%, 98%) was not as effective at detecting PPA as the ECAS total score (88%, 96%), nor as the composite scores for anterior (88%, 91%) and posterior (88%, 96%) functions. Of two PPA patients who were not impaired on the ECAS, one of those did not have a neuropsychological assessment and the other one was not impaired in the neuropsychological assessment. All patients that were impaired on the neuropsychological assessment were also impaired on the ECAS total score and on both composite scores. Therefore, the ECAS was sensitive to the impairment found on the neuropsychological assessment in PPA patients.

Most PPA patients (77%) were impaired on the fluency domain of the ECAS (slightly more on free fluency than constrained fluency); and with the exception of the one patient, all other PPA patients (91%) were impaired in fluency in the neuropsychological assessment. Most PPA patients were also impaired on the language domain of the ECAS (92%), and in some executive subtasks such as reverse digits. Unfortunately, there was missing data on the language tests of the neuropsychological assessment to make a true comparison of impairment on this domain with the ECAS for this patient group. PPA patients presenting an impairment in fluency was expected and congruent with previous literature (van den Berg et al., 2017) and the clinical presentation of the disease. The ECAS was therefore sensitive to cognitive impairment on the

fluency domain as per the neuropsychological assessment, and on language as expected based on the typical clinical presentation of the disease.

3.3.6.3 PCA

The ECAS and the ACE-III sensitivity towards detecting PCA were very similar to one another. The ECAS (sensitivity 1.000 and specificity .955) and the ACE-III (sensitivity 1.000 and specificity .977) were no different at screening for PCA; as all PCA patients were impaired in both tests. Although an impairment of memory is commonly found in PCA (as the most common underlying pathology of PCA is AD (Galton et al., 2000)), in this sample the PCA group was only impaired in the memory domain of the ECAS and not in the memory domain of the ACE-III. This finding is contradictory to what has been previously found with PCA patients and the ACE-R (Ahmed et al., 2016 b). Nevertheless, 67% of PCA patients in our sample were impaired on the memory assessment of the full neuropsychological examination and on the memory domain of the ECAS, which is a similar percentage of the ones impaired in memory in Ahmed et al. (2016 b) study. The patients that were impaired on the memory domain of the neuropsychological assessment were also impaired on the memory domain of the ECAS. As expected, all PCA patients were impaired in the Visuospatial section of the neuropsychological assessment and on the visuospatial domain of the ECAS.

3.3.6.4 General Discussion

The ECAS total score has shown to have a good sensitivity and specificity to screen for bvFTD, AD, MCI, PPA and PCA. The combined anterior score was particularly sensitive to bvFTD, while the combined posterior score was particularly sensitive to AD. The ECAS has also shown consistently to be equal and in some cases better than the ACE-III at screening for bvFTD, AD, MCI, PPA and PCA. The domains of the ECAS most sensitive for each of the diagnoses were: executive for bvFTD, memory for AD and MCI, fluency for PPA and visuospatial for PCA.

The ECAS showed a strong validity against a full neuropsychological assessment for bvFTD, AD, MCI, PPA and PCA. All bvFTD patients impaired on the anterior domains of the neuropsychological assessment were also impaired on the ECAS anterior composite score. Almost all (86%) AD patients who were impaired on the memory domain of the neuropsychological assessment were also impaired on the ECAS posterior composite score. Most (87%) MCI patients who were impaired on the neuropsychological assessment were also impaired on one of the ECAS composite scores, while all PPA patients impaired on the neuropsychological assessment were also impaired the ECAS total score and both composite scores. All PCA patients were impaired on the visuospatial domain of the neuropsychological assessment and on the visuospatial domain of the ECAS. Therefore, the ECAS was able to detect cognitive impairment as found on the neuropsychological assessment for these diagnoses. The ECAS can provide profiles of impairment that could aid with diagnosis and identifying potential targets for rehabilitation.

The inclusion of a behavioural interview in the ECAS makes it particularly suitable to aid in the diagnosis of behavioural abnormalities related to frontal lobe disorders, and can aid in distinguishing between bvFTD and AD. The ECAS is a very promising tool in detecting MCI, future studies should expand on the utility of the ECAS and its behavioural screen on anterior and posterior presentations of MCI. An important limitation of this study is that our groups have a small sample size. Therefore, these findings are exploratory and hypotheses forming. Future studies should determine whether the results are replicated in a bigger sample to be representative of the patient population.

Chapter Four

Longitudinal assessment using the ECAS. Relationship to dementia severity and functional assessments.

4.1.1 Introduction

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (Abrahams et al., 2014) was shown to have good sensitivity and specificity to different dementia diagnoses (see Chapter 3; Foley et al., 2018; Kourtesis et al., 2020), and it has been validated against numerous screening tests (Abrahams et al., 2014; Niven et al., 2015; De Icaza Valenzuela et al., 2018). However, its relationship with functional assessments and severity disease scales has not been explored in people with dementia without ALS. Likewise, the ECAS behavioural interview has not been previously compared to other frontal behavioural questionnaires in samples without ALS.

In addition to the neuropsychological assessment of cognition, it is important for clinicians to understand how each individual patient is able to function in their everyday life. Impairments in everyday functional abilities have been linked to cognitive deficits (Lau et al., 2015; Vermeersch et al., 2015; Giebel and Challis, 2017). Functional decline has been shown to start at least 10 years before a dementia diagnosis, with the decline occurring more rapidly in the 2 years that precede a diagnosis (Pérès et al., 2008). In AD and vascular dementia, basic activities such as eating and getting dressed show little decline in the early stages of dementia, while instrumental activities such as driving and using a telephone can be impaired in the early stages (Boyle et al., 2002; Martyr, Nelis and Clare 2014). Functional impairment in dementia has been associated with an increase of mortality rate (Mitchell et al., 2004) and it can predict caregiver burden (Razani et al., 2007). By inquiring about the possible impairments in activities of daily living, clinicians can refer patients and carers to the appropriate resources and give much more personalised

advice in how to manage their condition at home. Furthermore, severity ratings can be created based on functional decline, which are useful for communicating the patient's condition between health professionals and selecting pharmacological options (O'Bryant et al., 2008). Stages of dementia severity are also widely used in research for comparing patient populations and monitoring progression (Perneczky et al., 2006).

The Clinical Dementia Rating Scale (CDR) (Hughes et al., 1982; Morris, 1993) is a widely used instrument for rating severity in dementia. The clinician assesses patients' cognitive and functional levels to assign them to impairment categories. Patients' impairments are rated as absent, questionable, mild, moderate or severe in each individual domain. The six domains included are: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. For example, in the memory domain, patients are awarded 0 points if there is no memory loss, 0.5 when there is consistent slight forgetfulness, 1 when memory loss interferes with everyday activities, 2 when new material is rapidly lost, and 3 when only fragments of memory remain. The overall score is obtained with an algorithm; however, some studies use instead the sum of scores (Miyagawa et al., 2020; O'Bryant et al., 2008). A total score of 0 in the CDR indicates no cognitive nor functional impairment. A total score of 0.5 indicates consistent forgetfulness, slight impairment in solving problems, or struggling slightly both at home and work or social environments. A score of 1 (Mild) is marked by memory loss that interferes with everyday activities; difficulties with time, and unable to function independently in complicated tasks, often needing prompting for self-care. A score of 2 (Moderate) indicates severe memory loss where the patient is often disoriented to place, social judgment is impaired, and only very simple tasks are preserved; requiring assistance at personal care. In a total score of 3 (Severe), only fragments of memory remain, the person might be too ill to be taken outside the home and requires significant help for personal care.

Although the CDR has demonstrated to have a high validity and reliability

(Morris, 1993), it requires a lot of information to be given by caregivers, who might not always be available or might not always be reliable or well informed (Perneczky et al., 2006). Another disadvantage of the CDR is that as it was created for AD, it lacks language and behavioural domains, and the scoring algorithm places memory above other domains; therefore, FTD patients' severity might be underrepresented (Miyagawa et al., 2020). The CDR-FTLD was created to increase sensitivity to FTD patients by including the domains of language and behaviour (Knopman et al., 2008; Knopman et al., 2011). The CDR-FTLD has been shown to measure dementia severity in FTD and AD (Mioshi, Flanagan and Knopman, 2016).

A study using the original CDR, found that 17% of the total score of the ACE-III was predicted by the CDR in patients with bvFTD, and 49% in patients with PPA (So et al., 2018). This study also provided severity cut-offs of mild, moderate and severe for the ACE-III for individual diagnoses; however, the authors recognised that statistical assumptions were violated in the creation of these cut-offs. The authors have not explained which statistical assumptions were violated, however it is very probable that one of the statistical assumptions violated would pertain to the number of patients for each diagnoses in each severity level used (4 in total), as their total sample size per diagnosis was of 67 bvFTD, 54 AD, 27 SD, 23 PNFA and 23 LPA. In addition, the authors indicate that future studies with FTD should be done with the CDR-FTLD instead of the CDR. The relationship between the ECAS and the CDR, in particular the CDR-FTLD version, has not been explored previously. However, the Norwegian version of the ECAS is planning to include the CDR as part of their validation study (Taule et al. 2019).

The Frontal Behavioral Inventory (FBI) (Kertesz et al., 1997) was created to assess the behavioural changes in patients with bvFTD and help to differentiate diagnosis from PPA. The questionnaire is done with the caregiver of the patient. It contains 24 items divided between negative behaviours and positive behaviours; which were based on the Lund/Manchester consensus

(The Lund and Manchester Groups, 1994). These items are included in table 22, each item is rated on a 4-point scale. The FBI has been used previously to differentiate correctly 92% of patients between bvFTD and other diagnoses (AD, vascular dementia, depression and PPA) (Kertesz et al., 2000). Its sensitivity to differentiate between bvFTD and AD has been of 75% (specificity 77%) (Blair et al., 2007). Another study found the FBI to discriminate with a sensitivity of 97% and a specificity of 95% between bvFTD and AD and vascular dementia (Milan et al., 2008). The FBI has also shown to have a small correlation (r=0.237, p=0.013) with the Addenbrooke's Cognitive Examination -Revised (ACE-R) (Cao et al., 2015). In the validation of the Italian version of the ECAS, the FBI was used to support convergent validity of the ECAS behavioural screen (Poletti et al., 2016). In this study, a moderate correlation (r=0.630, p<0.0001) was found between the FBI and the ECAS behavioural screen (Poletti et al., 2016). The FBI and the ECAS behavioural screen naturally share items, as both were made to assess behavioural changes associated with frontotemporal dementia. However, the FBI is time consuming (Tippett et al., 2017) and could be considered outdated in comparison to the ECAS behavioural screen, which is based on the current diagnostic criteria for bvFTD (Rascovsky et al. 2011).

The Frontotemporal Dementia Rating Scale (FRS) (Mioshi et al., 2010) is a behavioural and functional instrument for measuring severity stages and tracking disease progression in FTD. It was developed to detect differences between the variants of FTD and rate their progression separately. It contains questions regarding the patient's behaviour, finances, household chores and telephone, meal preparation and eating, medications, outing and shopping, and self-care and mobility. The FRS has previously shown to have a strong correlation (r=-0.713, p<0.001) with the CDR (Mioshi et al., 2010). However, opposite results have been found with regards to the ACE-R as one study found a moderate correlation (r=0.695, p<0.05) between the FRS and the ACE-R with a progressive nonfluent aphasia group (Mioshi et al., 2010), and another study found no significant correlation between the tests with a mixed

group of dementias (Hsieh et al., 2012).

Table 22: FBI Items by negative and positive behaviours

Negative behaviours	Positive behaviours
apathy	aggression
aphasia	excessive jocularity
apraxia	hoarding
aspontaneity	hyperorality
disorganization	hypersexuality
inattention	inappropriateness
indifference	incontinence
inflexibility	irritability
logopenia	perseveration
loss of insight	poor judgment and impulsivity
personal neglect	restlessness
semantic deficit	utilization behaviour

There has not been a longitudinal study on the ECAS in populations without ALS yet. Therefore, I decided to explore if there was a change of ECAS scores overtime, and in comparison with the CDR-FTLD in a dementia population. Alternative versions of the ECAS are available for measuring change overtime (Crockford et al., 2018a) and were used accordingly in this study. Versions B and C were equivalent to the original version of the ECAS as performances were not significantly different between versions and they had a similar distribution of scores (Crockford et al., 2018a). I also followed the recommended values to assess for a reliable change in ECAS scores across alternative versions (Crockford et al., 2018b). A previous longitudinal study was done with the Italian ECAS albeit with an ALS population in which no cognitive nor behavioural decline were found across time, though a single version of the ECAS was administered on the four assessments (Poletti, 2018). This study had an attrition problem as all patients were invited for the follow up assessments, but of the 168 patients that started the study, 48

participated on the second assessment, 18 on the third and only 5 on the fourth (Poletti, 2018). In contrast, a longitudinal study with the ACE-R found that on average 10 points were lost on the ACE-R total score over 12 months in patients with PPA, and 5 points in patients with AD (Hsieh et al., 2012). Another study also found a significant decline of ACE-R total scores and FRS in a bvFTD population (Devenney et al., 2015).

Objectives:

1. Analyse the relationship of the ECAS and the ECAS behavioural screen with the CDR-FTLD, FBI and FRS. I hypothesised that the ECAS would correlate with the CDR-FTLD; while the ECAS behavioural screen would correlate with the FBI.
2. Assess if there is a change of scores on the ECAS overtime in a dementia population.
3. Explore which variables can predict attrition.

4.1.2 Methods

Participants

I assessed 56 patients from the Anne Rowling Regenerative Neurology Clinic. Twenty-nine of those patients were assessed a second time, and 13 patients were assessed three times. There was a difference of 6 to 11 months in between assessments for each patient. The average between the first and second assessment was of 8.55 months (±1.42, 7-11), while the average between assessments two and three was of 8.15 months (±1.51, 6-11). The data collection for this study started in October 2015 and ended in January 2018.The data of eight patients was removed as they had other diagnoses in addition to dementia that could interfere with the results; such as psychiatric disorders, learning disabilities and epilepsy. Therefore, our final dataset included 48 patients between the ages of 38 to 81 years old (29 males) for the first assessment, 25 patients for the second assessment and 10 patients for the third assessment.

The patients included for the 1st Assessment had Alzheimer's disease (n=18); behavioural variant frontotemporal dementia (n=7, from which one patient also had ALS); logopenic primary progressive aphasia (n=6); mild cognitive impairment (n=5); and "other" category which included Parkinson's (n=3), posterior cortical atrophy (n=2), behavioural variant Alzheimer's disease (n=1), progressive supranuclear palsy (n=1), Lewy Bodies dementia (n=2), subjective cognitive impairment (n=1), and vascular Alzheimer's disease (n=2). Demographics of the sample can be found in figures 29-33 and table 23. The age of the "other" category was significantly different to the diagnosis of MCI (p = .028), however as no further analyses were done between diagnoses this difference is inconsequential for this study. This difference can be observed in figure 32, as the other group is the oldest and the MCI group is the youngest. Nevertheless, all other groups are matched in age and FIQ (see figure 33). The patients IQ was assessed with an estimation of their premorbid IQ, using the Test of Premorbid Functioning (TOPF) (Wechsler, 2011b).

The assessment of premorbid IQ in dementia can be difficult, as it requires tasks that accurately represent IQ, while at the same time withstand the effects of dementia. The TOPF is one of the most common tests used for this purpose as it was developed and standardized with the WAIS-IV (Stott et al, 2017). It is important to note that the IQ measurement in this study is therefore a premorbid estimation, while the IQ measurement in chapter two with a healthy population was obtained with a test for current IQ.

Table 23: Demographics

Full sample Demographics		
	Age	FIQ
n=83	62.67 (±7.50) 38-81	100.45 (±9.46) 75-123
Demographics per Assessment		
Assessment	Age	FIQ
1 (n=48)	62.72 (±7.81) 38-81	99.76 (±9.41) 75-123
2 (n=25)	62.00 (±7.31) 39-76	100.72 (±9.47) 85-123
3 (n=10)	64.10 (±6.95) 57-77	102.80 (±10.22) 93-123
Demographics per diagnosis (assessment 1)		
Diagnoses	Age	FIQ
AD (n=18)	61.50 (±4.75) 55-71	97.76 (±10.54) 75-123
bvFTD (n=7)	62.14 (±12.32) 38-75	100.66 (±9.62) 85-111
PPA (n=6)	64.67 (±9.87) 54-76	99.16 (±10.47) 87-117
MCI (n=5)	56.00 (±4.95) 50-62	95.00 (±4.35) 90-98
Other (n=12)	66.75 (±6.83) 52-81	104.00 (±7.45) 92-114

Mean (SD) Range

Figure 29: Diagnoses per Assessment

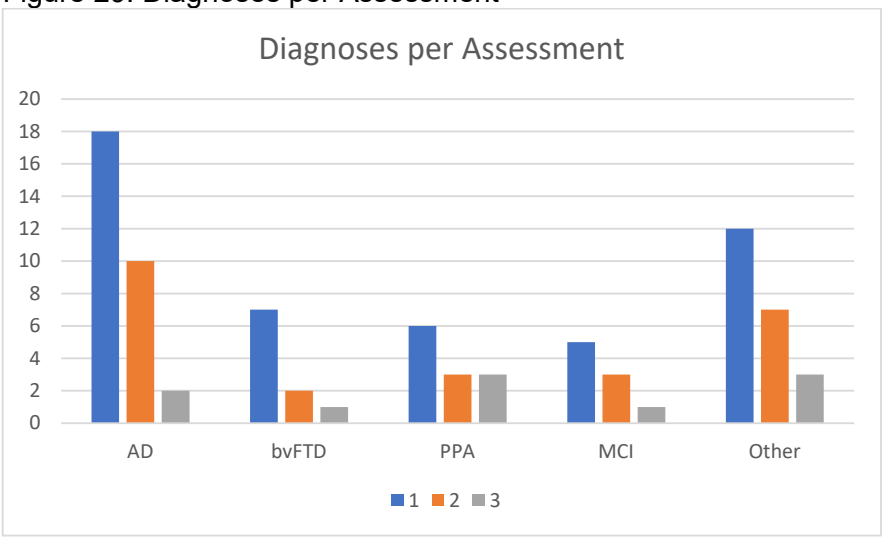


Figure 30: Age distribution of the full sample with normality curve

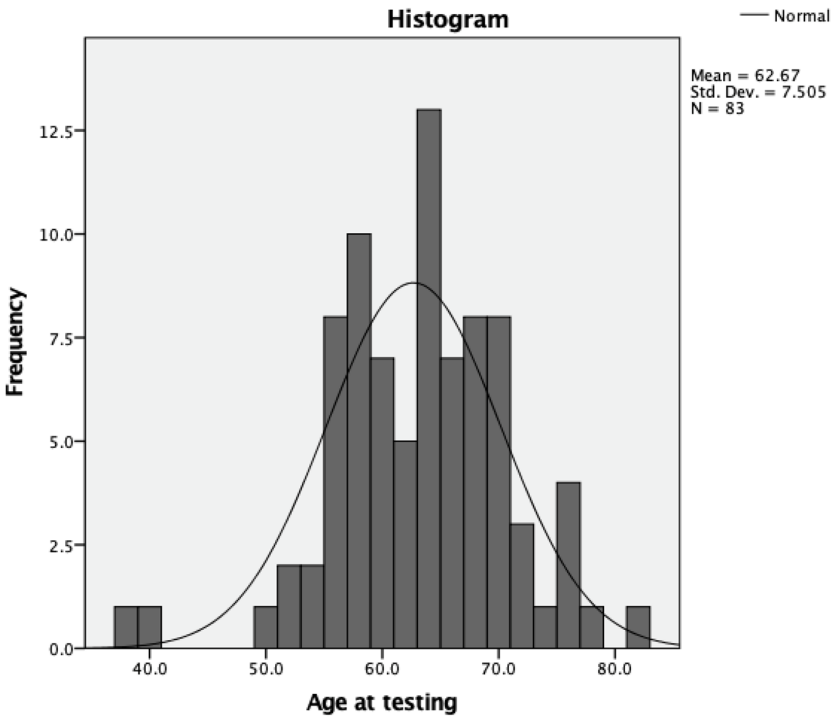


Figure 31: FIQ distribution of the full sample with normality curve

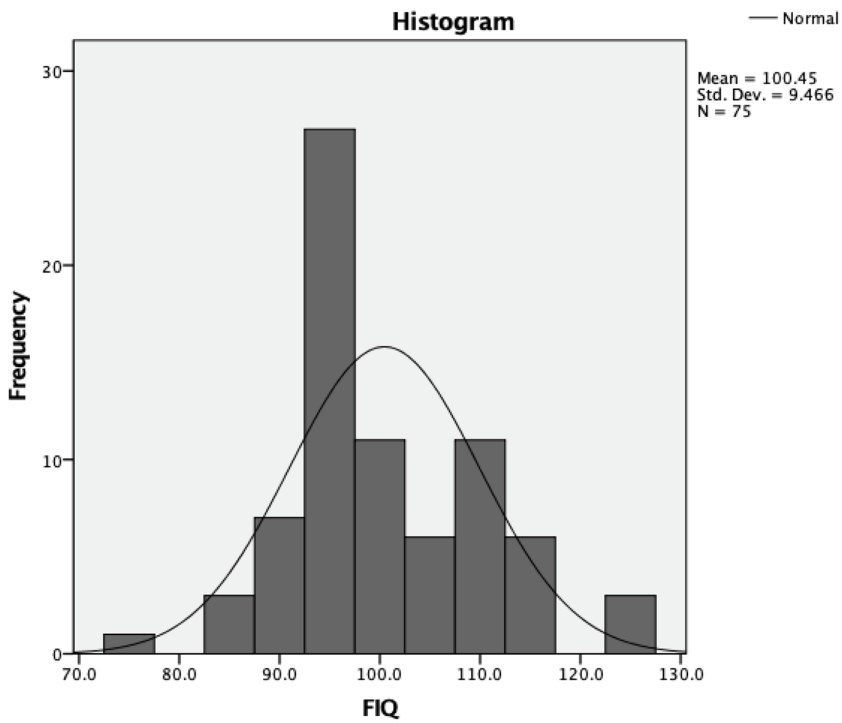


Figure 32: Distribution of age on the first assessment per diagnosis

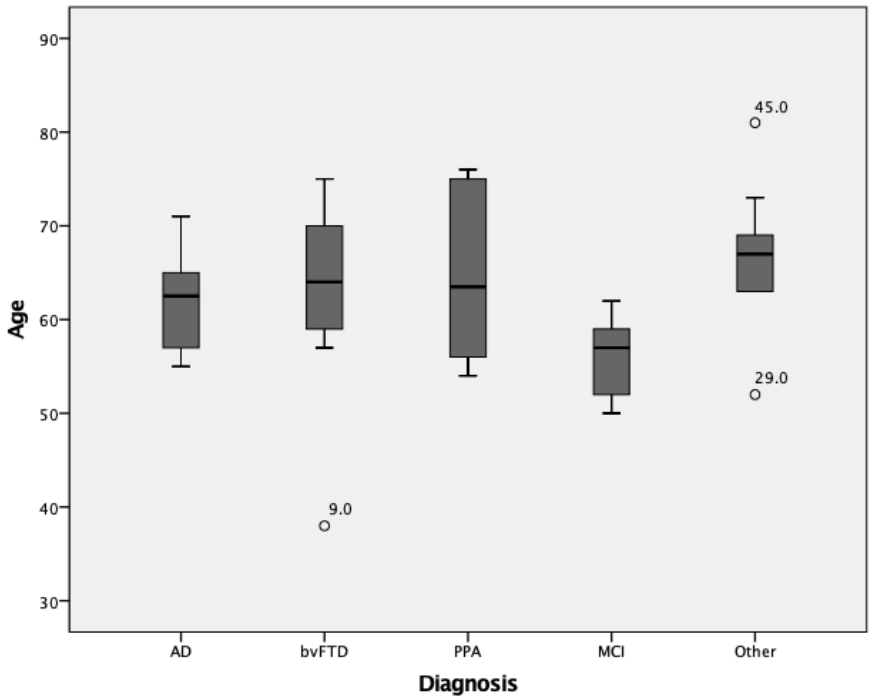
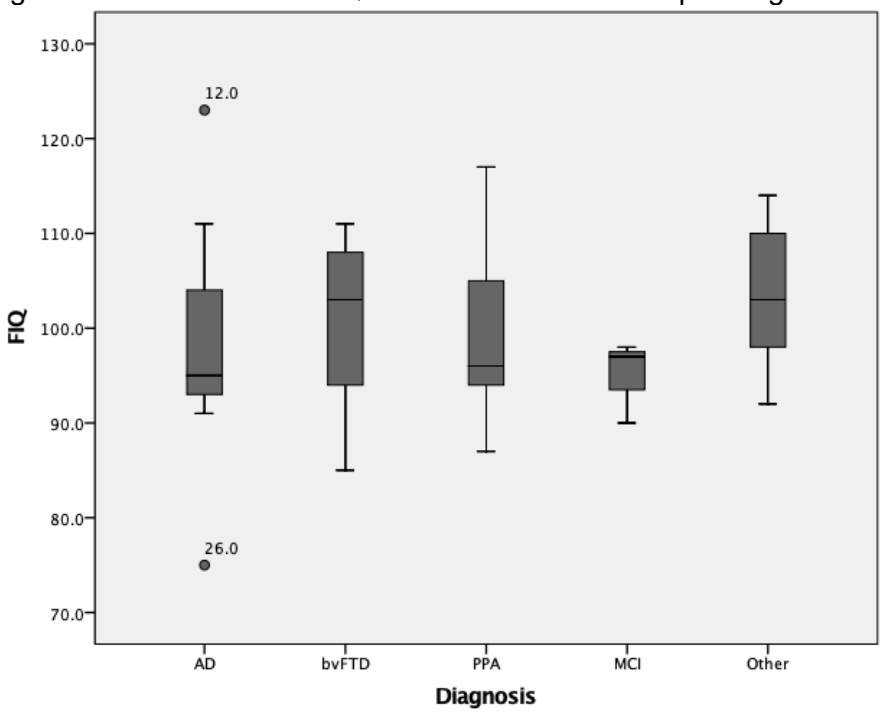


Figure 33: Distribution of FIQ on the first assessment per diagnosis



Materials

The ECAS in its original version (Abrahams et al., 2014) was used for the first assessment, while the alternative version B was used for the second assessment and the alternative version C was used for the third assessment (Crockford et al., 2018). The behavioural interview of the ECAS, alongside the FBI (Kertesz et al., 1997) and FRS (Mioshi et al., 2010) were done with the patients carer/family member. The CDR-FTLD (Knopman et al., 2008; Knopman et al., 2011) was done in accordance with the results of both the patient's cogntive assessment and the interview with the patients carer/family member.

4.1.2.1 Ethical Approval

Patient data collection was approved within the Edinburgh Cognitive Diagnosis Audit Research and Treatment (DART) Register, South East Scotland A Research Ethics Committee approval 12/SS/0196, IRAS no 103819.

4.1.2.2 Statistical Analysis

The data were analysed using SPSS statistics version 22. Data included repeated assessments of the same patients. Pearson's correlations were used to assess the relationship between variables. One-way between groups analysis of variance (ANOVA) were undertaken on parametric data to assess the difference between impairment groups (healthy, questionable, mild, moderate and severe) based on the CDR-FTLD. Homogeneity of variance for all variables was unequal as determined by Levene's test, and I therefore used Welch's ANOVA with Games-Howell post hoc tests. One-way between groups analysis of variance (ANOVA) were also undertaken on parametric data to assess the difference between assessments. Homogeneity of variance for the variables of FRS was unequal as determined by Levene's test on the analysis of 2 assessments, and I therefore used Welch's ANOVA with Games-Howell post hoc tests for those variables. All other variables used Tukey HSD post hoc tests. ANOVA stepwise linear regression was used to find the variables that predicted the final score of the ECAS, ECAS ALS-Specific score, ECAS

ALS non-specific score, ECAS behavioural total and attrition. ROC curves assessed the sensitivity and specificity of the ECAS to differentiate between questionable and mild dementia.

4.1.3 Results

4.1.3.1 Relationship between the ECAS, the CDR-FTLD, FBI and FRS.

The total score of the ECAS significantly correlated with the CDR-FTLD, FBI and FRS (see table 24), having the strongest correlation to the CDR-FTLD (see figure 34). The ECAS behavioural screen also correlated significantly with the CDR-FTLD, FBI and FRS, but more so with the FBI (see figures 35-37). As expected, the MCI group was overall the least impaired in both the ECAS total and the CDR. While the bvFTD group scored the highest in the amount of behavioural changes in the ECAS.

Table 24: Correlation between ECAS and other assessments

(n=83)	CDR-FTLD	FBI	FRS
ECAS total score	*r* = -.629 ***p* < .001**	*r* = -.233 ***p* = .050**	*r* = -.413 ***p* < .001**
ECAS behavioural screen	*r* = .606 ***p* < .001**	*r* = .842 ***p* < .001**	*r* = .624 ***p* < .001**
CDR-FTLD		*r* = .699 ***p* < .001**	*r* = .821 ***p* < .001**
FBI			*r* = .745 ***p* < .001**

Figure 34: Correlation ECAS Total score and CDR-FTLD

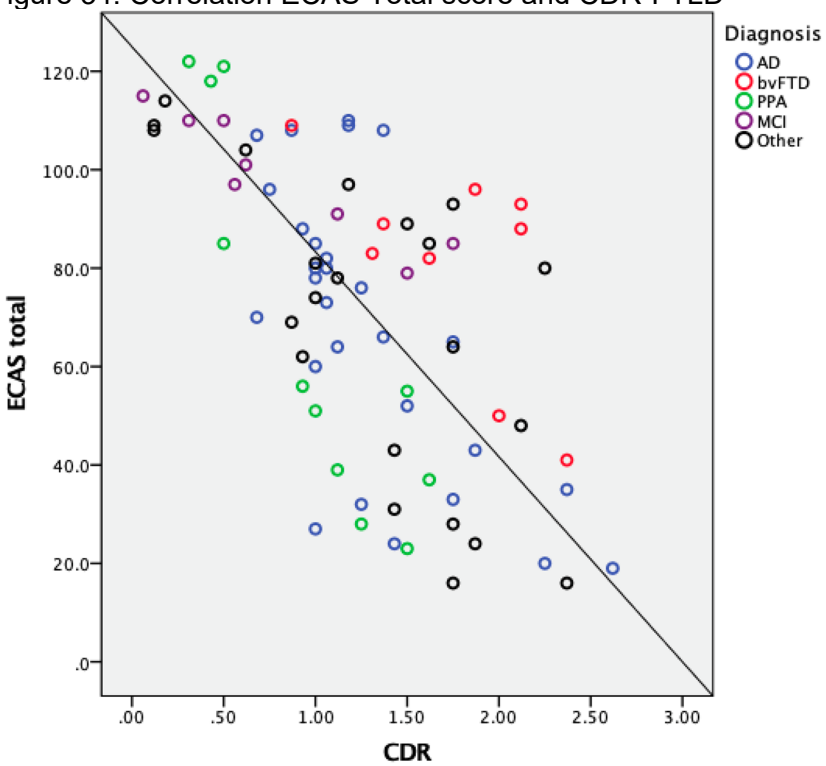


Figure 35: Correlation ECAS Behavioural score and CDR-FTLD

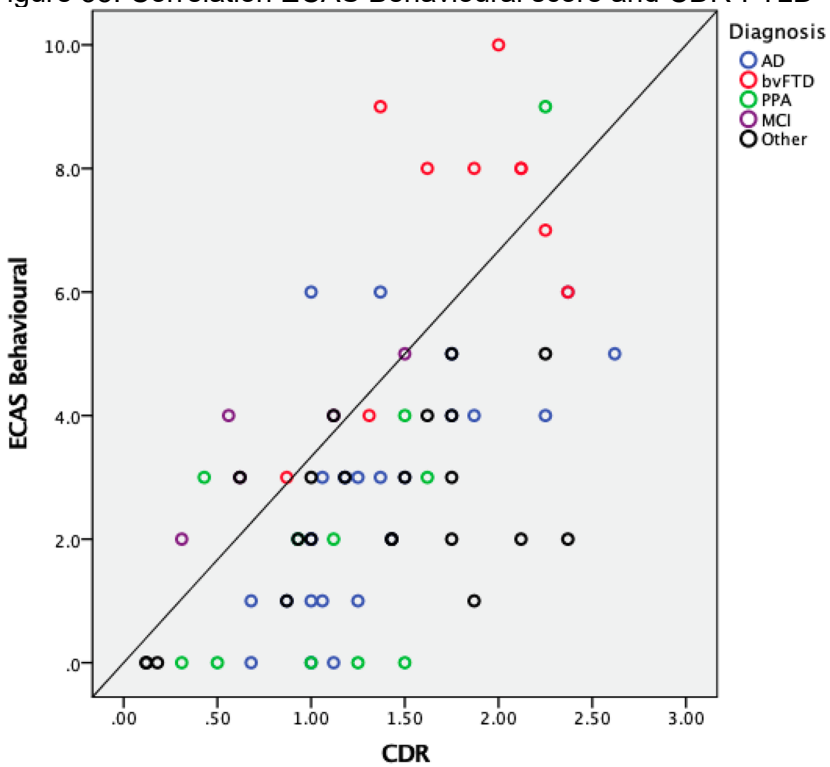


Figure 36: Correlation ECAS Behavioural score and FBI

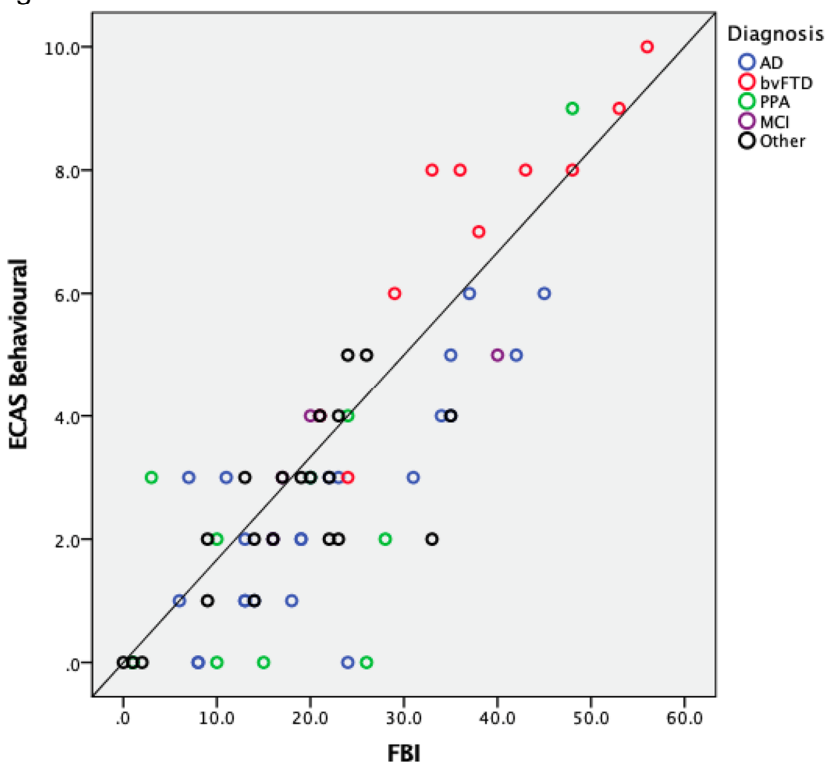
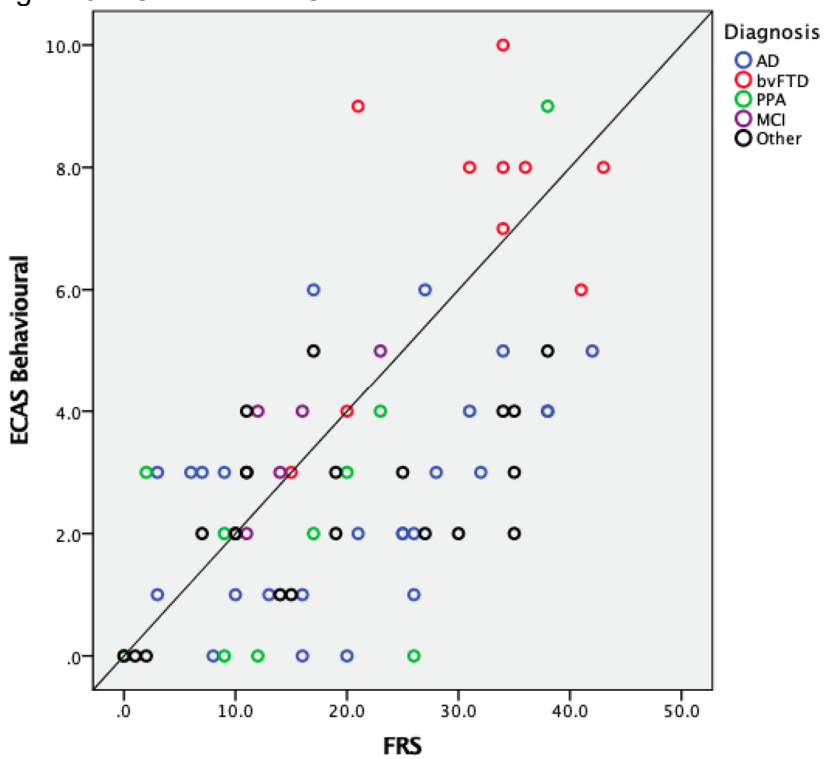


Figure 37: Correlation ECAS Behavioural score and FRS



4.1.3.2 Severity on the ECAS

The patients were divided by the severity of their dementia according to the CDR-FTLD. I compared the results of the ECAS on the severity classification to explore the possibility of creating severity cut-off scores in addition to the original abnormality cut-off score (see tables 25 and 26). Unfortunately, the severe category only included one patient, therefore it was not included. There was a significant difference on all ECAS scores between the severity classification of the CDR-FTLD; however, post hoc analyses revealed that the only groups that differed were questionable versus mild in all variables. The best sensitivity and specificity cut-off to determine the difference between questionable dementia and mild dementia was a total score of 96 (sensitivity 84%, specificity 90%) (see figure 38). Distribution of the ECAS scores by severity groups are presented in figures 39-47.

Table 25: ECAS scores by CDR-FTLD Severity classification

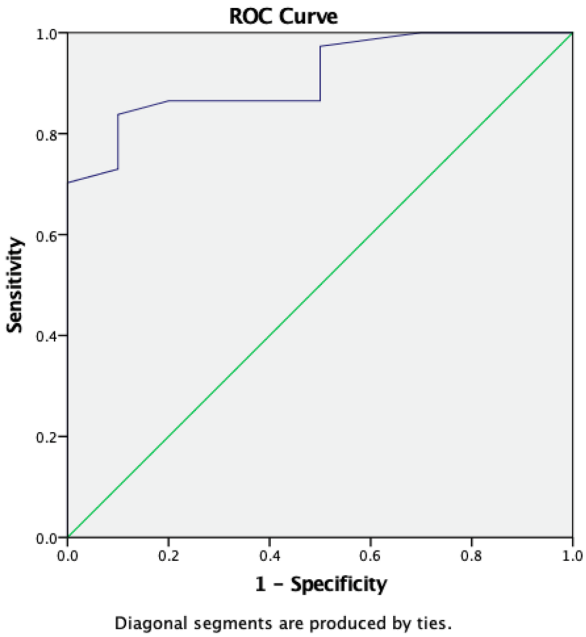
	Healthy (n=4)	Questionable (n=10)	Mild (n=37)	Moderate (n=26)	Full sample (n=77)
ECAS Total	111.50 (±3.51) 108-115	107.50 (±11.48) 85-122	70.83 (±26.01) 24-110	57.53 (±26.98) 16-96	73.22 (±29.91) 16-122
ALS Specific (Anterior)	85.00 (±4.96) 79-90	80.80 (±10.98) 55-90	55.73 (±21.27) 17-94	44.81 (±21.36) 12-79	56.82 (±23.39) 12-94
ALS non Specific (Posterior)	26.50 (±1.73) 25-29	26.70 (±6.32) 17-35	14.70 (±6.56) 1-30	12.69 (±8.21) 1-28	16.19 (±8.53) 1-35
Language	27.25 (±0.95) 26-28	27.00 (±0.94) 26-28	21.78 (±5.92) 10-28	19.74 (±6.84) 5-27	22.02 (±6.23) 5-28
Fluency	21.00 (±1.15) 20-22	18.40 (±4.50) 6-22	10.43 (±7.97) 0-22	6.34 (±7.46) 0-20	10.63 (±8.41) 0-22
Executive	36.75 (±4.34) 33-41	35.40 (±6.97) 23-43	23.51 (±11.81) 3-44	18.69 (±10.72) 0-35	24.11 (±12.07) 0-44
Memory	15.00 (±1.41) 14-17	15.10 (±6.15) 6-23	5.56 (±5.25) 0-18	5.88 (±6.06) 0-18	7.40 (±6.56) 0-23
Visuospatial	11.50 (±0.57) 11-12	11.60 (±0.69) 10-12	9.13 (±3.18) 0-12	7.00 (±3.33) 1-12	8.83 (±3.33) 0-12

Results are presented Mean (SD) Range

Table 26: Significance of table 25 with Post Hoc Tests

	Welch's ANOVA sig.	Healthy vs Questionable	Questionable vs Mild	Mild vs Moderate
ECAS Total	**< .001**	=.757	**< .001**	=.218
ALS Specific (Anterior)	**< .001**	=.761	**< .001**	=.200
ALS non Specific Posterior)	**< .001**	=1.000	**=.001**	=.729
Language	**< .001**	=.968	**< .001**	=.600
Fluency	**< .001**	=.371	**= .002**	=.173
Executive	**< .001**	=.971	**= .002**	=.342
Memory	**< .001**	=1.000	**= .003**	=.996
Visuospatial	**< .001**	=.992	**< .001**	=.060

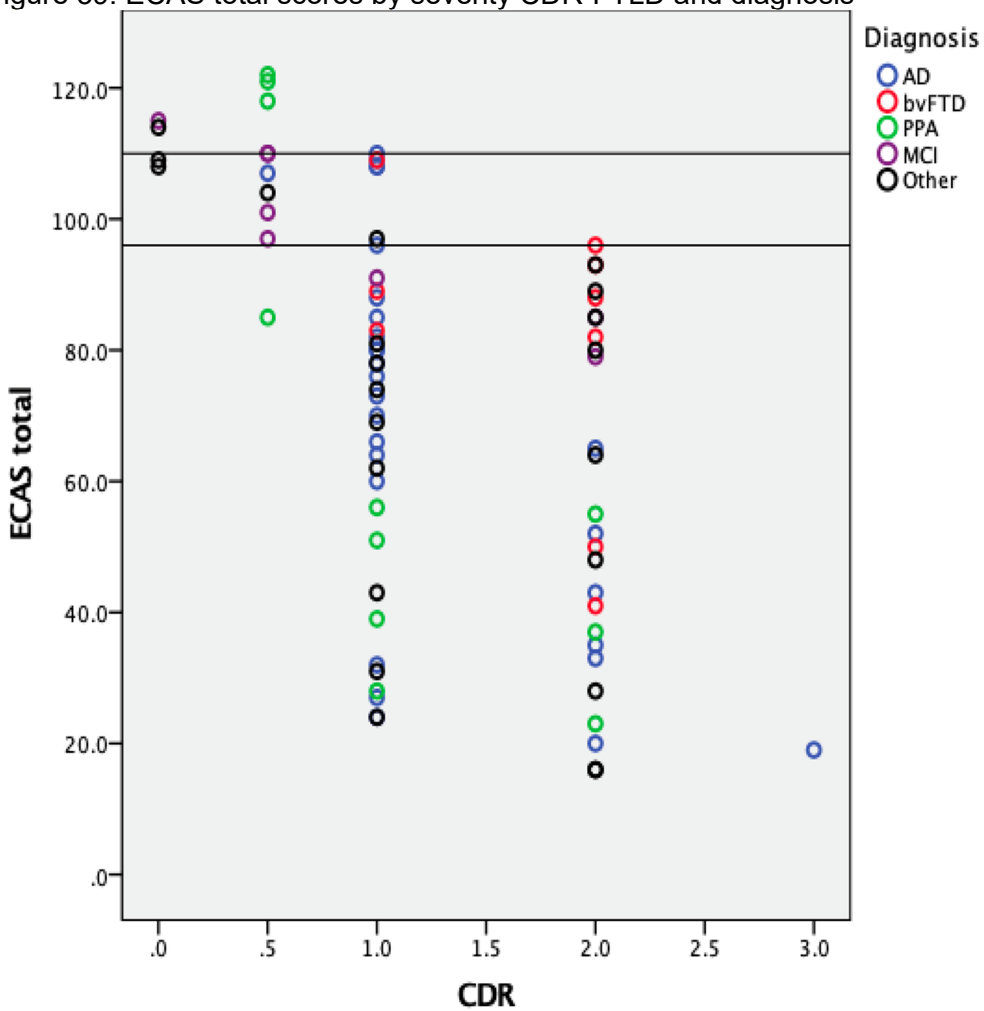
Figure 38: Sensitivity of the ECAS total score at detecting questionable versus mild dementia



As expected, the group with a “healthy” score on the CDR-FTLD scored above the original cut-off of 105 (see figures 39 and 40). The majority (60%) of the questionable group scored in between the range of the borderline cut-off scores, 110 (Niven et al. 2015) and 96 (our proposed cut-off). The mild group scored equal or below the borderline score of 110, while all the moderate patients scored below the 96 abnormality cut-off score. On the ALS Specific composite score (Anterior), ALS non-Specific composite score (Posterior), and the executive domain, all patients of the healthy group scored above the abnormality cut-off; similarly the questionable group scored in its majority above the abnormality cut-off, while most of the patients in the mild and moderate groups scored below the abnormality cut-off (see figures 41, 42 and 45). On the Language and Fluency domains all the healthy and questionable patients scored above the abnormality cut-off, while most of the patients in the mild and moderate groups scored below the abnormality cut-off (see figures 43 and 44). In the Memory domain all patients of the healthy group scored above the abnormality cut-off, and the questionable group scored mostly

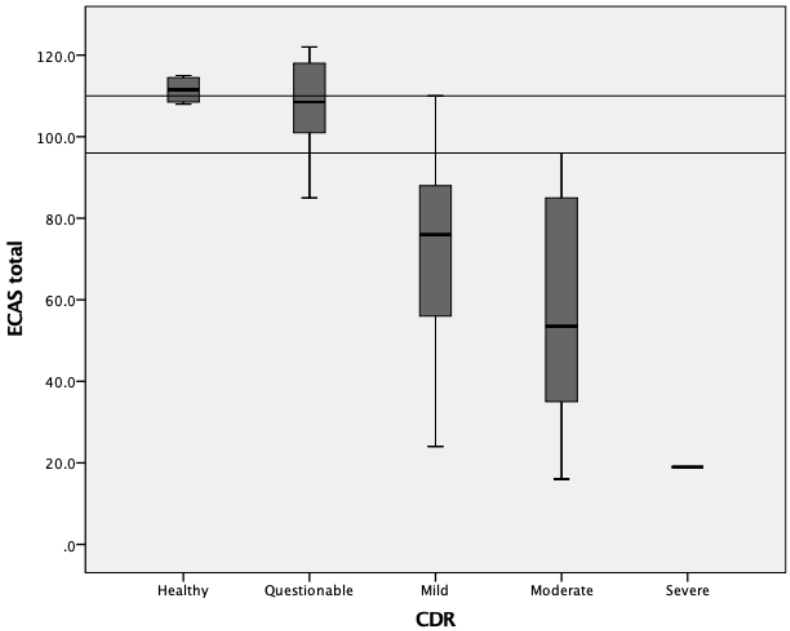
above the abnormality cut-off; however, most of the patients in the mild and moderate groups scored very few points resulting in a floor effect (see figure 46). In contrast, there is a ceiling effect on the visuospatial domain, where all the healthy and questionable patients scored above the abnormality cut-off, and about half the mild patients scored above the abnormality cut-off; patients from all groups scored the maximum points (see figure 47).

Figure 39: ECAS total scores by severity CDR-FTLD and diagnosis



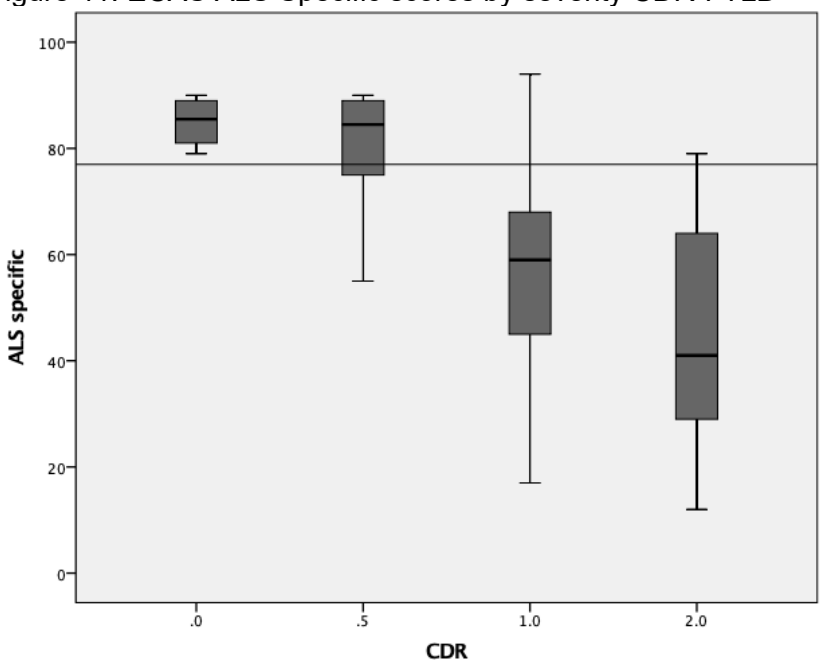
Lines presented for borderline range: 110=original upper cut-off for abnormality borderline range, 96=proposed bottom cut-off of impairment borderline range

Figure 40: ECAS total scores by severity CDR-FTLD



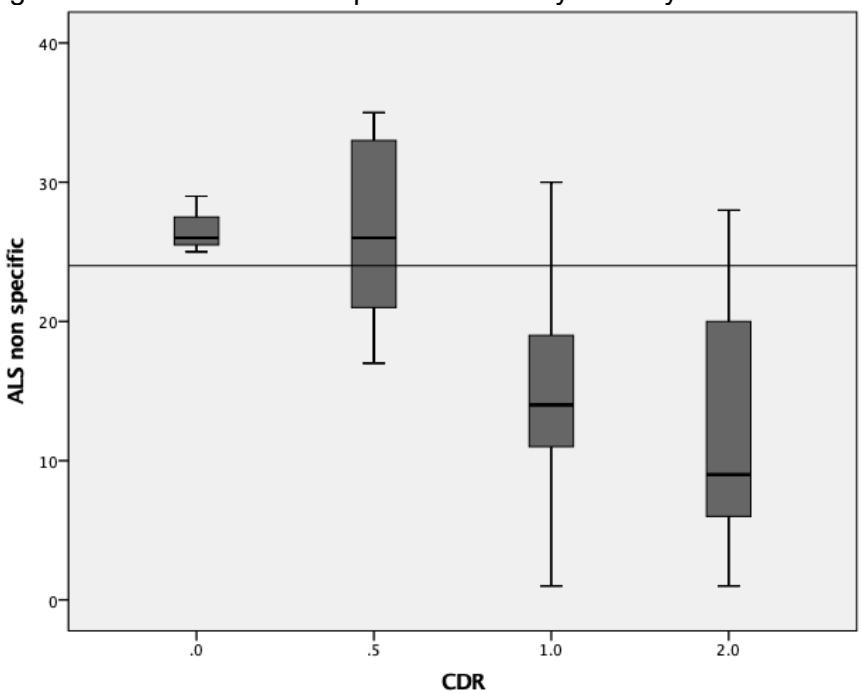
Lines presented for borderline range: 110=original upper cut-off for abnormality borderline range, 96=proposed bottom cut-off of impairment borderline range

Figure 41: ECAS ALS Specific scores by severity CDR-FTLD



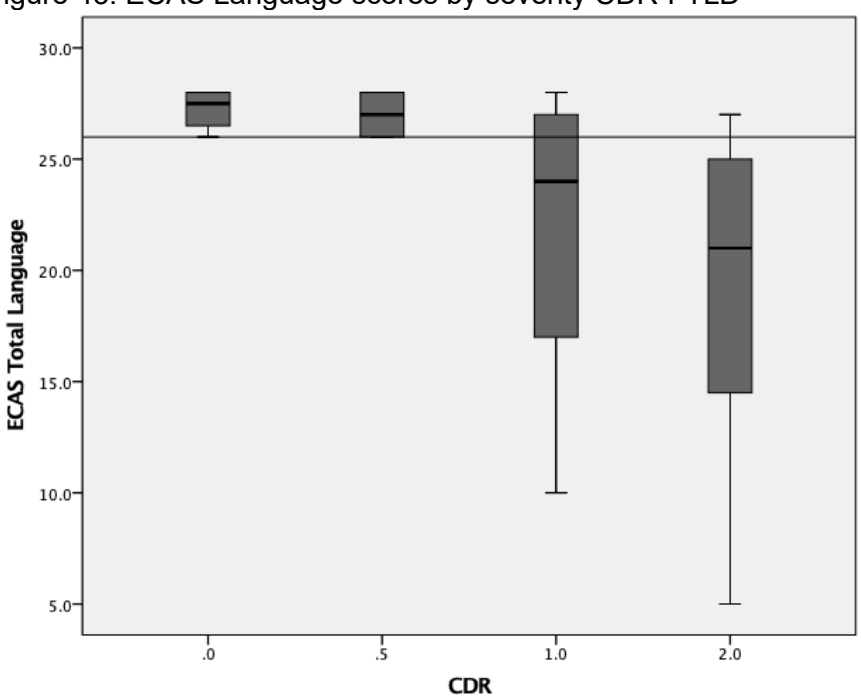
Line presented for abnormality cut-off: 77

Figure 42: ECAS ALS non Specific scores by severity CDR-FTLD



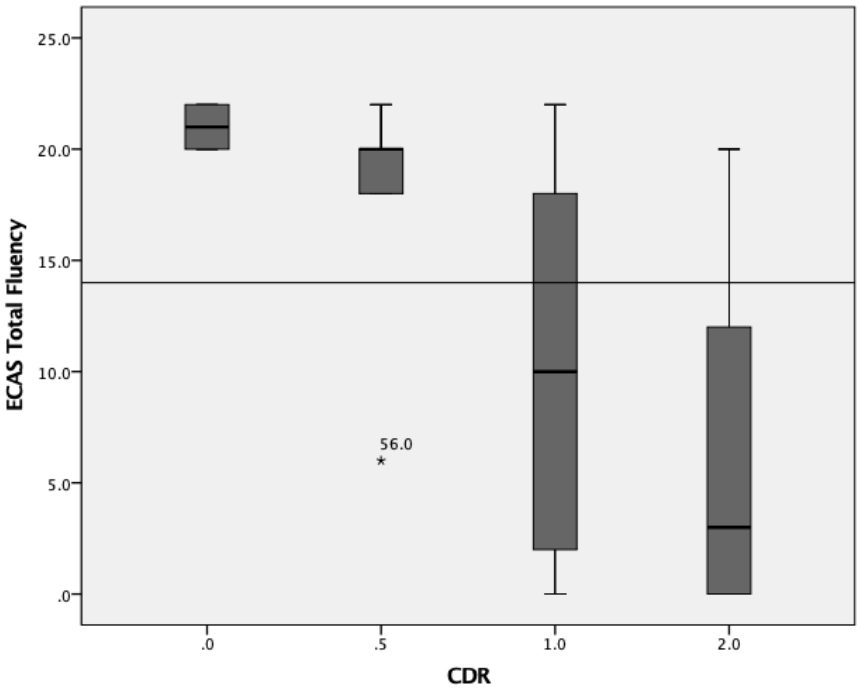
Line presented for abnormality cut-off: 24

Figure 43: ECAS Language scores by severity CDR-FTLD



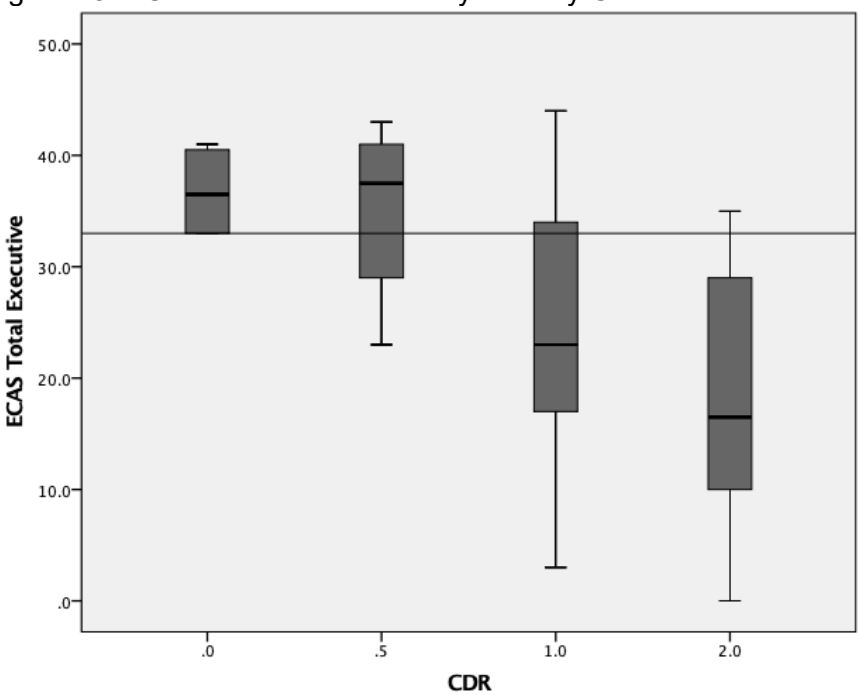
Line presented for abnormality cut-off: 26

Figure 44: ECAS Fluency scores by severity CDR-FTLD



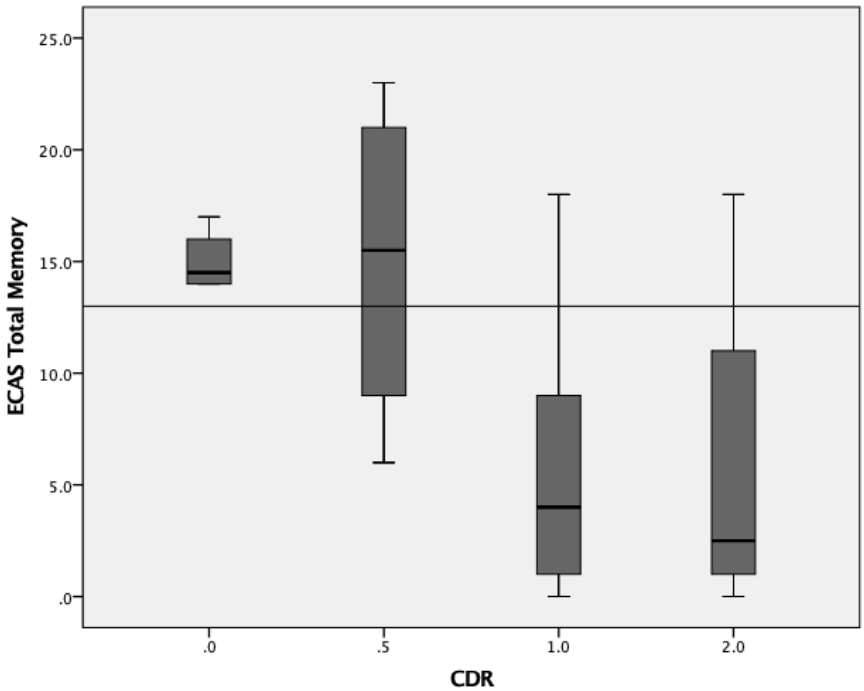
Line presented for abnormality cut-off: 14

Figure 45: ECAS Executive scores by severity CDR-FTLD



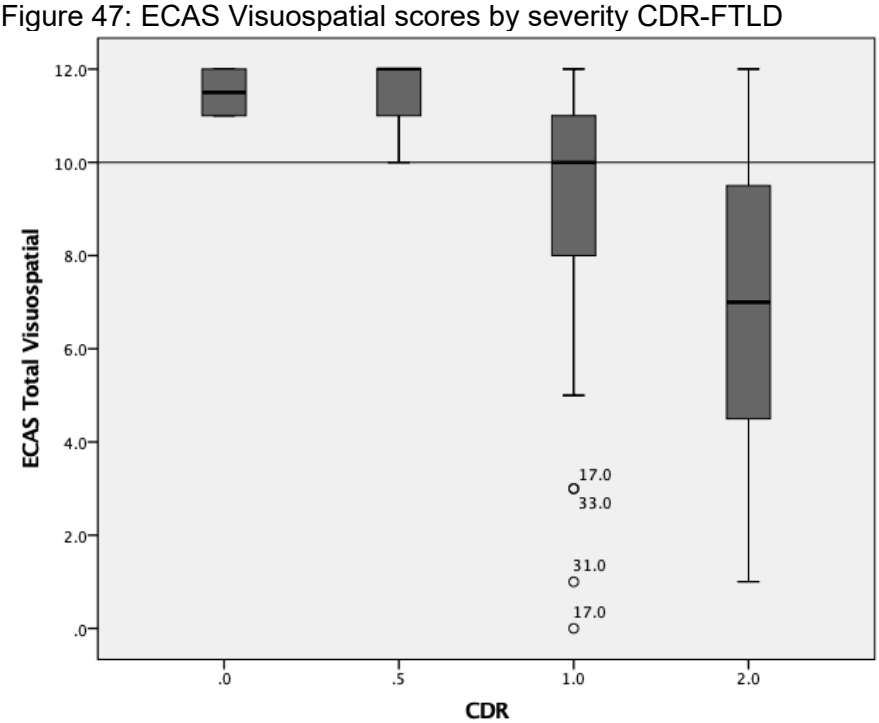
Line presented for abnormality cut-off: 33

Figure 46: ECAS Memory scores by severity CDR-FTLD



Line presented for abnormality cut-off: 13

Figure 47: ECAS Visuospatial scores by severity CDR-FTLD



Line presented for abnormality cut-off: 10

4.1.3.3 Longitudinal assessment using the ECAS

Ten patients completed the 3 assessments (2 AD, 1 bvFTD, 3 PPA, 1 MCI, and 3 "other"). The change in scores for most of those patients (60%) was not greater than the reliable change index (9 points) (Crockford et al., 2018b) in between the first assessment and the third assessment on the ECAS total score (see figure 48). The change in three patients' ECAS total scores exceeded the reliable change index with a decline ranging from 15 to 40 points. One patient (behavioural variant AD) had an increase of 12 points on the ECAS total score, while also showing behavioural decline by increasing the amount of behavioural changes on the ECAS interview (from 3 to 5), and increasing scores on the FBI, FRS and CDR-FTLD. The increase on the ECAS domain scores for this patient was fluency (from 16 to 18), executive (from 17 to 35, with an increase in every subtask), and declining in memory (from 10 to 2). One-way between groups analysis of variance (ANOVA) were undertaken to assess the difference between the three assessments, but no significant differences were found in any of the measurements (see table 27).

Table 27: Performance across 3 Assessments.

(n=10)	1	2	3
ECAS total	80.80 (±33.00) 31-122	75.70 (±36.69) 28-118	73.50 (±43.11) 16-121
ECAS ALS Specific	64.00 (±25.64) 22-90	57.40 (±29.44) 19-93	58.10 (±34.41) 12-94
ECAS ALS non Specific	17.90 (±7.69) 9-33	17.70 (±10.53) 1-35	15.40 (±10.17) 3-34
ECAS behavioural	1.90 (±2.72) 0-9	2.77 (±2.48) 0-8	2.87 (±2.64) 0-8
FBI	17.55 (±16.14) 1-53	14.33 (±11.33) 1-36	21.12 (±13.87) 0-48
FRS	10.70 (±7.33) 0-21	13.55 (±11.52) 0-34	19.87 (±12.46) 1-36
CDR-FTLD	.85 (±0.45) .18-1.43	1.16 (±0.57) .12-1.87	1.26 (±0.79) .06-2.37

Results are presented Mean (SD) Range

Figure 48: ECAS total scores across 3 longitudinal points

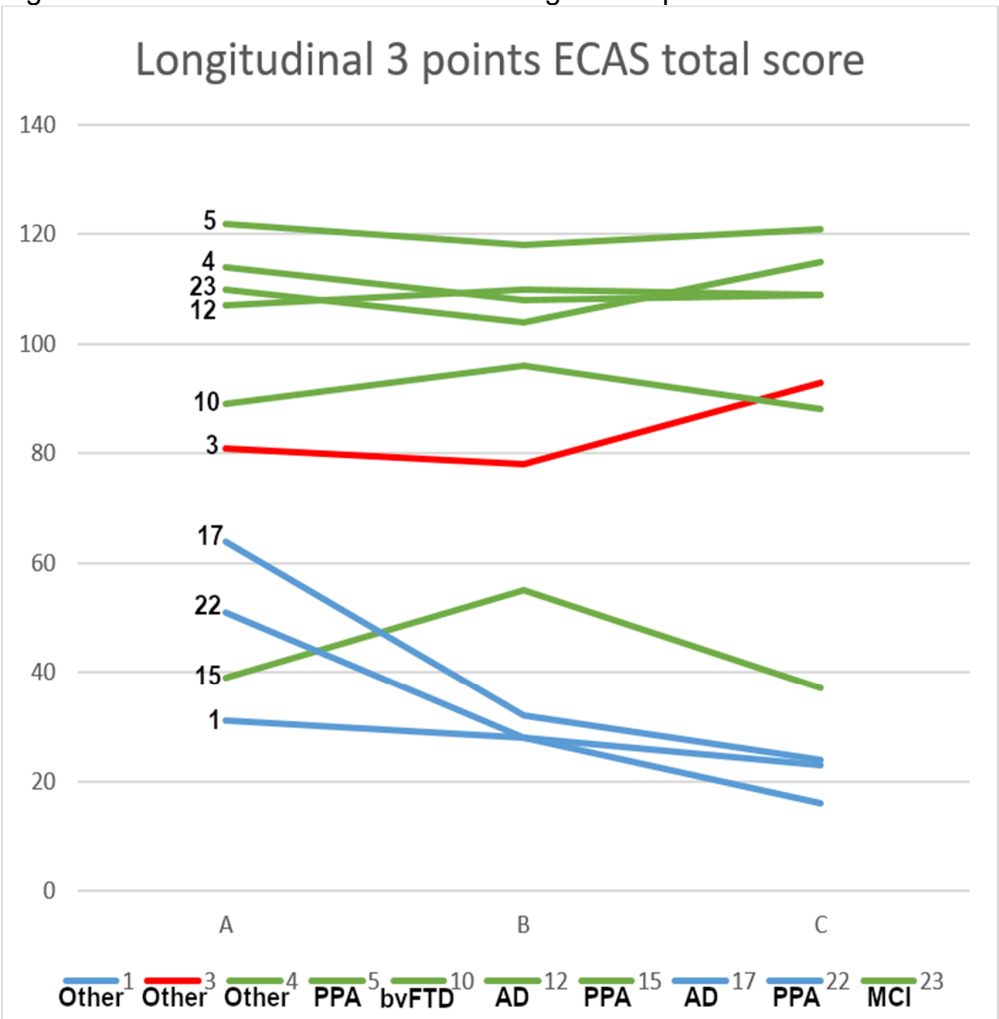


Chart coloured by reliable change index (Crockford et al., 2018b) from A to C: No change (≤8 points difference) (green n=6, 60%), Decrease in score 9 points or more (blue n=3, 30%), Increase in score 9 points or more (red n=1, 10%)

Twenty-five patients completed 2 assessments. Most of those patients again (52%) did not have a significant change (Crockford et al., 2018b) in between the first assessment and second assessment on the ECAS total score (see figure 49). However, ten patients (40%) (5 AD, 1 bvFTD, 1 PPA, and 3 “other”) had a significant decline on the ECAS total score, ranging from 9-32 points in difference. Two patients had an increase of 16 (patient 15 with a diagnosis of PPA) and 35 (patient 18 with a diagnosis of AD) points on the ECAS total

score. Patient 15 increased 12 points in the memory domain between assessments 1 and 2; but as seen in figure 20, when he returned for a third assessment his scores decreased to a similar level as the first assessment. On the other hand, I only have two assessments for patient 18. She improved in language (2 points), fluency (8 points), executive (21 points) and memory (5 points), and decreased 1 point in visuospatial functions. She scored only one behavioural change on the ECAS interview in both assessments, scored the same on the FBI, scored only a couple of points lower on the FRS and scored mild dementia on the CDR-FTLD for both assessments. One-way between groups analysis of variance (ANOVA) were undertaken to assess the difference between assessments one and two, the only variable that was significantly different (*p*=.05) between assessments was the CDR-FTLD (see table 28).

Table 28: Performance across 2 Assessments.

(n=25)	1	2
ECAS total	74.64 (±27.30) 24-122	68.60 (±32.22) 16-118
ECAS ALS Specific	57.76 (±21.07) 19-90	53.72 (±25.59) 14-93
ECAS ALS non Specific	16.48 (±7.05) 5-33	14.64 (±8.98) 1-35
ECAS behavioural	2.79 (±2.71) 0-10	3.21 (±1.92) 0-8
FBI	20.81 (±15.07) 1-56	21.09 (±10.98) 1-42
FRS	16.29 (±13.74) 0-35	20.59 (±13.74) 0-42
CDR-FTLD	1.12 (±0.53) .18-2.37	1.45 (±0.62) .12-2.62

Results are presented Mean (SD) Range

Figure 49: ECAS total scores across 2 points

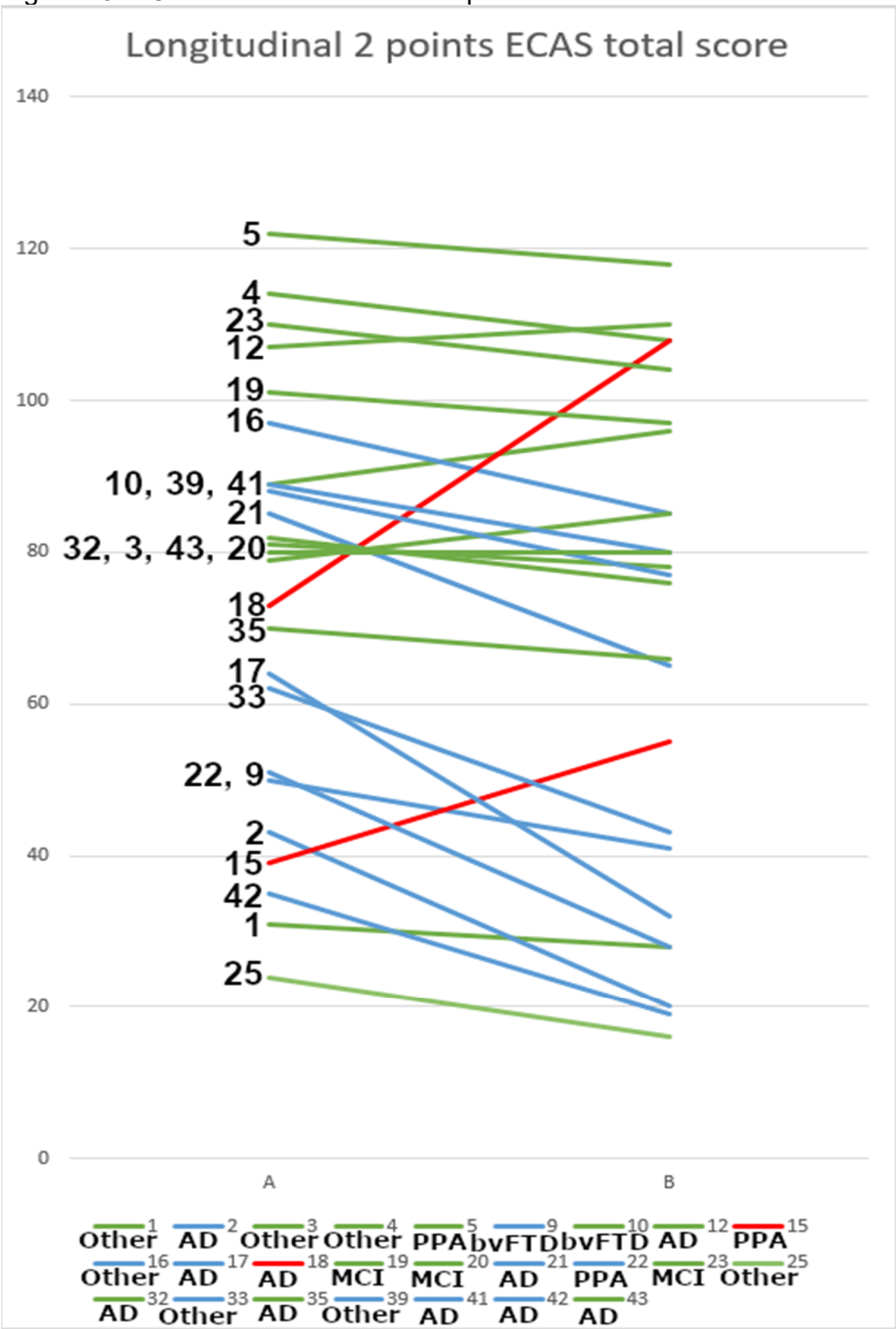
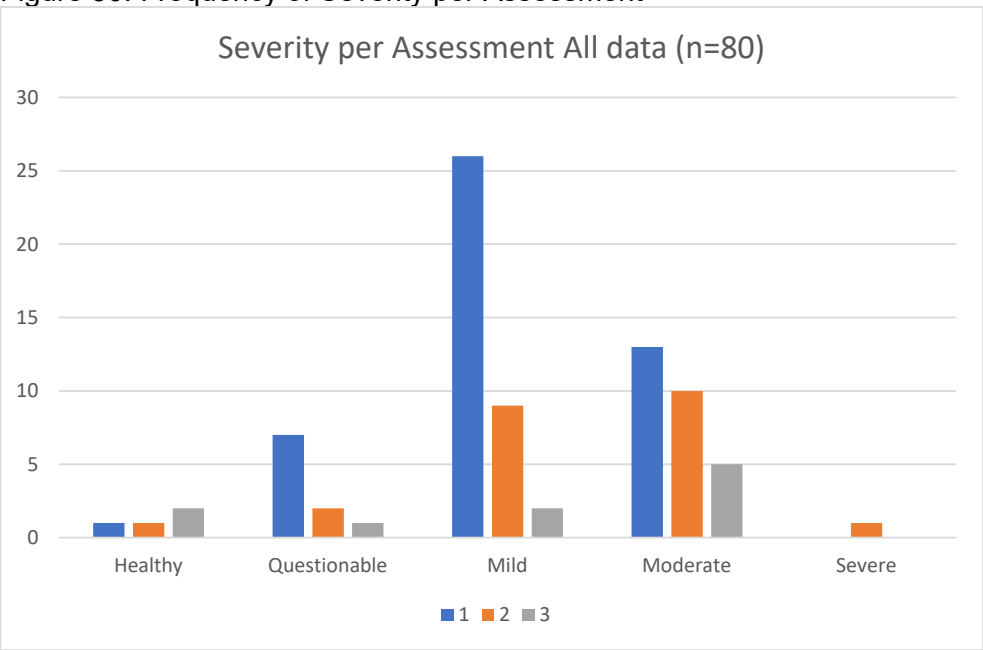


Chart coloured by reliable change index (9 points) (Crockford et al., 2018b) from A to B: No change (≤8 points difference) (green n=13, 52%), Decrease in score 9 points or more (blue n=10, 40%), Increase in score 9 points or more (red n=2, 8%). Comma delimited values correspond to the line order from top to bottom.

The frequency of each CDR-FTLD severity group across assessments can be observed in figures 50 to 52. From the data collected most patients presented with a mild dementia on the first assessment, while most patients from the second and third assessments presented moderate dementia. In figure 51 it can be observed that there is a trend of functional decline between the first two assessments, as there are less patients with questionable and mild dementia in the second assessment, with an increase of moderate and severe cases. In figure 52 it can be observed the continuing trend of decline as more patients from the mild category develop into a moderate dementia in the third assessment. Since the assumption of minimum expected cell frequency was violated, a chi square analysis to measure impairment was not applicable.

Figure 50: Frequency of Severity per Assessment



N= 47 for the first assessment, n= 23 for the second assessment and n=10 for the third assessment

Figure 51: Frequency of Severity for 2 Assessments

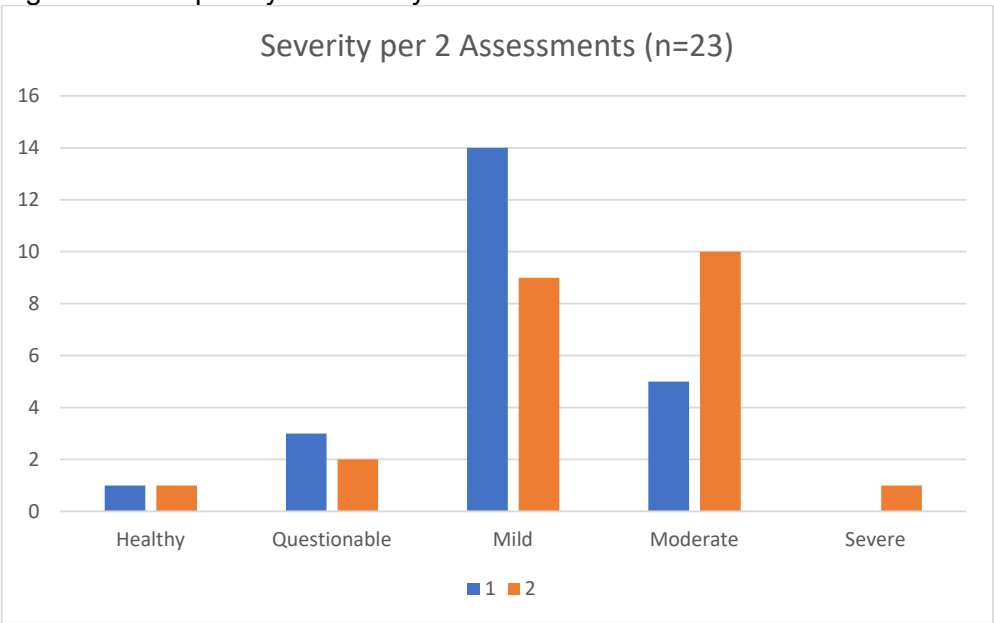
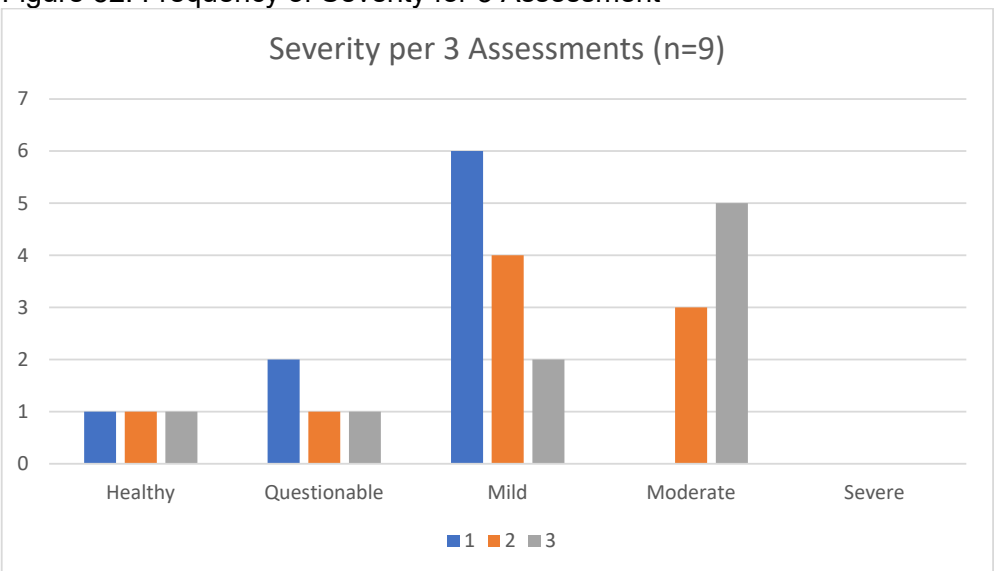


Figure 52: Frequency of Severity for 3 Assessment



An ANOVA stepwise linear regression model for the ECAS Total score was undertaken including the variables of FIQ, age, gender, CDR-FTLD, FBI, FRS, and ECAS behavioural score. The most significant model predicted 71.3% of the variance of the ECAS Total Score ($F(4,62)=38.54$, $p< .001$). This model

included the variables of CDR-FTLD (β=-.989, *t*=-8.07, *p*<.001), FIQ (β=.537, *t*=7.06, *p*<.001), FBI (β=.435, *t*=4.12, *p*<.001) and FRS (β=.309, *t*=2.30, *p*=.025). CDR-FTLD alone predicted 39% of the variance of the ECAS total score (F(1,76)=49.63, *p*< .001), while FIQ alone predicted 36% of the variance of the ECAS total score (F(1,72)=39.94, *p*< .001).

An ANOVA stepwise linear regression model for the ALS Specific score was undertaken including the variables of FIQ, age, gender, CDR-FTLD, FBI, FRS, and ECAS behavioural score. The most significant model predicted 65.3% of the variance of the ECAS ALS Specific (F(3,63)=39.45, *p*< .001). This model included the variables of CDR-FTLD (β=-.778, *t*=-7.41, *p*<.001), FIQ (β=.506, *t*=6.21, *p*<.001), and FBI (β=.519, *t*=4.90, *p*<.001). CDR-FTLD alone predicted 36.1% of the variance of the ECAS ALS Specific (F(1,76)=42.95, *p*< .001), while FIQ alone predicted 34.9% of the variance of the ECAS ALS Specific (F(1,72)=38.64, *p*< .001).

An ANOVA stepwise linear regression model for the ALS non-specific score was undertaken including the variables of FIQ, age, gender, CDR-FTLD, FBI, FRS, and ECAS behavioural score. The most significant model predicted 50.4% of the variance of the ECAS ALS non-specific (F(3,63)=21.35, *p*< .001). This model included the variables of CDR-FTLD (β=-.730, *t*=-5.82, *p*<.001), FIQ (β=.396, *t*=4.06, *p*<.001), and FBI (β=.458, *t*=3.62, *p*=.001). CDR-FTLD alone predicted 30.8% of the variance of the ECAS ALS non-specific (F(1,76)=33.87, *p*< .001), while FIQ alone predicted 23.7% of the variance of the ECAS ALS non-specific (F(1,72)=22.33, *p*< .001).

An ANOVA stepwise linear regression model for the ECAS behavioural score was undertaken including the variables of FIQ, age, gender, CDR-FTLD, FBI, FRS, ECAS total, ECAS ALS Specific, and ALS non-specific. The most significant model predicted 74.7% of the variance of the ECAS behavioural score (F(3,63)=62.03, *p*< .001). This model included the variables of FBI (β=.853, *t*=11.85, *p*<.001), FIQ (β=.181, *t*=2.57, *p*=.012), and age (β=-.152, *t*=-2.16, *p*=.034). FBI alone predicted 70.5% of the variance of the ECAS

behavioural score (F(1,69)=168.34, p< .001), while age alone predicted 17.9% of the variance of the ECAS behavioural score (F(1,73)=15.94, *p*< .001).

An ANOVA stepwise linear regression model for attrition was undertaken including the variables of FIQ, age, gender, CDR-FTLD, FBI, FRS, ECAS total, and ECAS behavioural score. The most significant model predicted 20.4% of the variance of attrition (F(1,47)=12.04, *p*< .001) and included the single variable of FRS.

4.1.4 Discussion

The ECAS total score had good convergent validity with the CDR-FTLD severity classification, while the ECAS behavioural screen had convergent validity with the FBI, FRS and CDR-FTLD. This indicates that lower cognitive scores on the ECAS are associated with greater functional impairment. Similarly, the more behavioural changes are reported on the ECAS behavioural screen, the more behavioural and functional impairments are on the FBI, FRS and CDR-FTLD. Although there was a correlation between the ECAS total score and the CDR-FTLD, and there was a significant difference between CDR-FTLD groups, I was only able to create an impairment cut-off score of 96 (sensitivity 84%, specificity 90%) to differentiate the groups of questionable versus mild dementia. Unfortunately, the scores on the ECAS total were not significantly different between the mild and moderate groups, as there was too much overlap in scores. I also did not have enough patients within the severe group to create further cut-off scores to differentiate severity between these groups.

The domain of memory on the ECAS suffered from floor effects unlike the rest of the domains. Nevertheless, the findings in Chapter 2 with a healthy population showed a normal curve for this domain, without ceiling nor floor effects. The findings here might be explained by the sample, as the diagnosis

group with the highest number of patients was Alzheimer's disease. Therefore, these results are congruent with the type of impairment one would expect to find when a large proportion of our sample has AD (McKhann et al. 2011).

The CDR-FTLD, FIQ, FBI, and FRS predicted 71.3% of the variance of the ECAS Total Score. This finding demonstrates that the ECAS is truly a valid assessment for dementia, as its total score is associated with how functionally affected the patient is and how severe the dementia diagnosis. Furthermore, the ECAS provides a cognitive profile useful for diagnosis and clinical intervention. The CDR-FTLD, FIQ, and FBI predicted the scores of the ALS Specific (65.3%) and ALS Non-specific (50.4%) composite scores. Both the CDR-FTLD and FIQ predicted more the scores of the ALS Specific (36.1%, 34.9% respectively) than the ALS Non-specific (30.8%, 23.7%) composite scores.

An interesting difference between this study and the study in Chapter 2, was that for the dementia population IQ predicted 36% of the variance of the ECAS total score, while on the healthy controls IQ predicted 24% of the variance (De Icaza Valenzuela et al., 2018); however, the healthy controls were assessed with the Wechsler Abbreviated Scale of Intelligence (WASI-II) using 2 subtests (Wechsler, 2011a) and the patients IQ was assessed here with an estimation of their premorbid IQ, using the Test of Premorbid Functioning (TOPF) (Wechsler, 2011b). As mentioned previously, the TOPF is an estimation of premorbid IQ, while the WASI-II is a measure of current IQ; therefore, some discrepancies were expected. Discrepancy between the TOPF and the Wechsler Adult Intelligence Scale- Fourth Edition (WAIS-IV) (Wechsler, 2008) has been found to vary between 10% to 17% by one Standard Deviation or more (Shura et al., 2020). Furthermore, another study found that the TOPF predicted 71% of the variance of the WASI-II using 2 subtests (Holdnack et al., 2013).

The ECAS behavioural screen had the strongest correlation with the FBI, which was expected as there is overlap between the two measures on the types of behaviour assessed; such as apathy, perseverations, and inappropriateness (Kertesz et al., 1997; Kertesz et al., 2000). An advantage of the ECAS behavioural screen over the FBI might be the time of administration; as the ECAS behavioural screen contains 13 questions versus 24 questions on the FBI. The ECAS and its behavioural interview serve as a brief assessment and can be used to screen patients, and therefore they would be more appropriate as a first line of assessment to determine the possibility of an impairment before doing a full neuropsychological assessment of cognition and behaviour (Niven et al., 2015). The ECAS behavioural screen could also be more appropriate than the FBI to assess behavioural changes in AD, as this patient group presents typically with few behavioural changes, and therefore do not always require a more in-depth behavioural assessment. However, the AD patients in this sample scored higher than what has been previously reported on the FBI, while the bvFTD patients scored similar to what has been previously found (Milan et al., 2007; Milan et al., 2008). This discrepancy could be explained by the type of patients referred to the clinic where our research took place, as I mentioned in the previous chapter, the AD patients usually referred to this clinic tend to have complex or atypical presentation.

The ECAS behavioural screen had a moderate correlation with the FRS. This was an expected finding as the FRS includes a behavioural section (apathy, affection, orientation, and impulsivity) and some of the questions in the functional section of the test could also relate to apathy (for example: lacks motivation to perform household chores), impulsivity and food preferences which are also included in the ECAS (Mioshi et al., 2010). Nevertheless, the CDR-FTLD correlated the most with the FRS because of the functional assessment included there, more so than the behavioural aspects assessed on the ECAS behavioural screen and the FBI. A strong correlation between both versions of the CDR (with and without the domains of language and

behaviour) and the FRS have been previously reported in the literature with frontotemporal dementia patients (Mioshi et al., 2010; Turró-Garriga et al., 2017), and a mixed group of dementia patients (Lima-Silva et al., 2018).

The variance of the ECAS behavioural score was predicted 74.7% by the FBI, FIQ and age. The effect of the FBI to the ECAS behavioural score was in line with our correlation results. Although FIQ has been found to be involved in the prediction of other behavioural screens for dementia (Cerejeira, Lagarto and Mukaetova-Ladinska, 2012; Starr and Lonie, 2007); the effect in our sample was in the opposite direction, as higher FIQ was associated with more behavioural changes. However, the bvFTD patients in our sample had a slightly higher FIQ than the AD, PPA and MCI patients which could have had an impact on the result. The negative association between age and the ECAS behavioural score was due to the fact that the youngest bvFTD patients were the ones with the highest behavioural scores; the negative association between age and behavioural symptoms in FTD has been previously reported (Diehl and Kurz, 2002).

The FRS was the single variable to predict attrition by 20.4%. The FRS includes questions that could be directly related to the functional ability of patients to attend the clinic for an assessment; such as the ability to use transportation, the ability to organize correspondence and intrinsic motivation. Attrition has been associated with low cognitive ability and poor health in longitudinal dementia studies (Sliwinski et al, 2003; Rabbitt et al., 1994; Cooney, Schaie, and Willis, 1988). Some of the patients I invited for the second and third assessment, but were unable to attend, had gone to live permanently in care homes. Another common issue I experienced was that patients would not attend the second and third scheduled assessments because they had forgotten the day or the time of the appointment, and sometimes they did not attend because they did not feel well on that particular day. All of these scenarios could point to a possible health or cognitive decline in some our

patients that prevented them to attend the clinic for a second or third time; therefore, having an effect on attrition.

In our study there was no significant difference of ECAS scores between assessments. However, 40% of patients in the 2 assessments had a significant decline between assessments. Perhaps a less diverse dementia group without the inclusion of MCI patients would have a significant decline in scores across time. As mentioned earlier, perhaps the patients that experienced a health or cognitive decline did not attend the follow up assessments, which could have impacted our results. Some of the limitations for this study were the sample size that completed the follow up assessment, and the time in between the assessments. The means between the sample with the three assessments, and the means between the sample with the two assessments presented a small decline over time, albeit this difference did not reach significance in both cases. Nevertheless, there was a significant difference of CDR-FTLD scores between the two assessments. An opposite result was found with the Italian ALS sample, as the ALS patients that attended three assessments improved significantly (Poletti et al., 2018). The factors that influence attrition, the differences in diagnoses, and the lack of alternative forms of the ECAS in their study could explain some of the discrepancy between our findings.

As the CDR-FTLD predicted 39% of the variance of the ECAS Total Score in our study, a bigger sample with longer time in between assessments could evaluate if there is a change in ECAS scores overtime within a dementia population. Another future study could explore the relationship between the ECAS and the CDR in AD patients, and the ECAS and the CDR-FTLD in bvFTD patients. This study would have to aim to recruit patients that have had a dementia diagnosis for a longer time, and/or which have previously been classified as moderate or severe in the CDR if they intended to create moderate and severe abnormality cut-off scores.

4.1.5 Conclusions

The ECAS showed good convergent validity with the CDR-FTLD severity classification indicating that lower cognitive scores on the ECAS are associated with greater functional impairment. The ECAS behavioural screen showed good convergent validity to the FBI, FRS and CDR-FTLD. ECAS scores were able to differentiate between questionable and mild dementia (CDR-FTLD) but did not show a good differentiation between the other more severe classifications. Functional and behavioural assessments, alongside IQ predicted the ECAS Total Score; while the FBI behavioural inventory, age and IQ predicted the ECAS behavioural score. FRS was the single variable to predict attrition. There was no significant difference of ECAS scores between assessments; although some individual cases did decline overtime. However, a bigger sample with longer time in between assessments could evaluate if there is a true change in ECAS scores overtime.

Chapter 5

Discussion

In this thesis I explored whether the Edinburgh Cognitive Examination ALS Screen (ECAS) (Abrahams et al., 2014) is a sensitive brief assessment for the types of cognitive impairment and behavioural changes in people with early onset dementia without Amyotrophic Lateral Sclerosis (ALS). The novelty of this thesis was the validation of the ECAS for different types of dementia without ALS against a comprehensive neuropsychological assessment, the comparison of the ECAS with the ACE-III, the comparison with functional and behavioural questionnaires, and the analysis of behaviours that differentiate between bvFTD and AD.

5.1 Relationship between the ECAS and the ACE-III in a healthy sample

When assessed with healthy controls, the ECAS had good convergent validity with the ACE-III. All the domains of the ECAS correlated with their counterparts in the ACE-III with the exception of visuospatial functions. This difference was somewhat expected, as although both tests assess visuoperceptual and constructional abilities, the ACE-III includes drawing tasks and therefore also relies on hand eye coordination. The ECAS had less ceiling effects than the ACE-III on the total scores and the domains of memory and fluency. The ECAS was also less influenced by intelligence, as IQ predicted 46% of the variance of the ACE-III versus 24% of the variance of the ECAS. Therefore, the ECAS could be a better screening tool than the ACE-III in patients with a higher IQ as ceiling effects would be avoided.

5.2 The effect of age, education gender and IQ on the ECAS

Age, gender and IQ were significant predictors of the ECAS total score. Education was not a significant predictor of the ECAS total score when IQ was included in the model as they correlated strongly. The relationship between the ECAS and IQ has not been explored elsewhere in the literature. The

correlation of age and the ECAS was congruent with what was previously found (Lulé et al., 2015; Loose et al., 2016; Poletti et al., 2016; Pinto-Grau et al., 2017); in contrast, gender was not significant as in previous studies (Poletti et al., 2016; Ye et al., 2016). IQ was the most important predictor for the domains of the ECAS, with Language being the most dependent on IQ. IQ also had a significant effect on fluency, while Memory was the domain the most dependent on age. Both of these findings were congruent with what has been found in the literature with other tests assessing the same functions (von Stumm and Deary, 2013; Fritsch et al., 2007; van Geldorp et al. 2015).

Age and education abnormality cut-offs of the ECAS total score were created and published in De Icaza Valenzuela et al. (2018). I decided to create age and education abnormality cut-offs, instead of using age and IQ, as education information is readily available for clinicians and does not require a separate test. As education had a strong correlation with IQ, I decided to choose education over IQ to make the abnormality cut-offs of the ECAS more accessible. This way, the abnormality cut-offs can be incorporated into the ECAS when it is used as the first screen of cognition by health professionals who perhaps do not assess IQ. These abnormality cut-off scores ranged between 98 and 110. There was a 10-point difference between the abnormality cut-offs of those with a university degree and those without, which was consistent with IQ and education being the stronger predictors. On the contrary, there was only a 2-point difference between the abnormality cut-offs of those age groups. The abnormality cut-off scores I created were similar to the original cut-off score of 105 (Abrahams et al., 2014), and to the borderline range (105-110) (Niven et al., 2015), although both abnormality cut-offs for those without a university degree were slightly lower. The abnormality cut-off scores I created were slightly higher than those of the Irish sample for the younger group (96 no university degree, 100 with university degree), however there was more discrepancy between our results with their older group (76 no university degree, 95 with university degree) (Pinto-Grau et al., 2017).

Even though these age and education abnormality cut-offs could be very useful for the clinical practice, they were not used in the final analyses of our other experiments (Chapters 3 and 4). I decided to use the more well-established original abnormality cut-offs as I found no difference when using these or the newer age and education abnormality cut-offs in the dementia groups (Chapter 3). With regard to the group of 12 people with MCI, using the new age and education abnormality cut-offs, 3 people were no longer classified as impaired on the ECAS Total Score. However, there was missing data for years of education of 2 additional patients who scored in between the two cut-offs. Because of the missing data, and for consistency, I decided not to use the new age and education abnormality cut-offs for the analysis in Chapter 3. However, the small difference found in our MCI group points out the possible benefit of using the age and education adjusted abnormality cut-offs when scoring the ECAS in this clinical population.

5.3 The ECAS vs the ACE-III in a population with dementia

The ECAS Total Score (sensitivity 94% and specificity 96%) was more sensitive than the ACE-III (sensitivity 79%, specificity 98%) at detecting bvFTD. On the ECAS the executive functions domain was the most sensitive domain at detecting bvFTD. In contrast, the ACE-III lacks a separate domain of executive functions. Furthermore, the ACE-III sensitivity to detect bvFTD has been inconsistent (Elamin et al. 2015; Bruno et al., 2020). The ECAS could therefore be used as a first line of assessment for the cases in which bvFTD is suspected, as it was more sensitive than the ACE-III in our study, and it includes a behavioural interview based on the diagnosis criteria for bvFTD. The ECAS Total Score (sensitivity 94% and specificity 96%) was also more sensitive than the ACE-III (sensitivity 85%, specificity 98%) at detecting AD. The ECAS Total Score (sensitivity 91%, specificity 96%) was more sensitive to detect MCI than the ACE-III, which sensitivity was vastly different between both of the published impairment cut-off scores; as the cut-off of 82 had a sensitivity of 18% (specificity 98%), and the cut-off of 88 had a sensitivity of 73% (specificity 86%). Furthermore, the

ECAS Total score (sensitivity 88%, specificity 96%), and both composite scores were more sensitive to PPA than the ACE-III (75%, 98%). Finally, the ECAS and the ACE-III had equal sensitivity of 100% for the diagnosis of PCA. The ECAS could be more suitable for the assessment of cognitive impairment in these diagnoses (bvFTD, AD, MCI, PPA, and PCA) than other short screening tests, such as the ACE-III, because of its higher sensitivity, its lack of ceiling effects, and the inclusion of other cognitive functions and a behavioural assessment that provided a broader panorama of what the patient might be impaired on. As the ECAS also provides separate composite scores of anterior and posterior impairments, it serves its purpose as a brief assessment to screen for typical profiles of impairment in dementia. While the individual domains can give the clinician an accurate overview of the cognitive functions the patient is impaired on. This information could be of relevance for the treatment and management of patients (Snowden et al., 2011), without the need to do a comprehensive neuropsychological assessment.

5.4 The ECAS as a brief assessment for bvFTD

The ECAS was developed to screen for cognitive and behavioural changes that occur in amyotrophic lateral sclerosis (ALS) (Abrahams et al. 2014). As these changes are in line with the bvFTD diagnosis, it was not surprising that I found the ECAS to be sensitive at detecting cognitive impairment in bvFTD without ALS, when compared to healthy controls. The ECAS ALS Specific Composite score (Anterior), which comprises the domains of Fluency, Executive Functions and Language, (sensitivity of 94% and a specificity of 92%) and the ECAS Total Score (sensitivity 94% and specificity 96%) were highly effective at detecting bvFTD when compared to healthy controls. These results were similar to another study which found 87% of bvFTD patients to be impaired on the ALS Specific Composite score, and 91% to be impaired on the ECAS Total Score (Saxon et al., 2020). Furthermore, there was a perfect concordance of the ECAS total score and ECAS ALS Specific Composite score to impairment on the anterior functions' tests of

the neuropsychological battery for this group; with 100% sensitivity, and 100% specificity. The only bvFTD patient who was not impaired on the ECAS total score, nor on the ECAS ALS Specific Composite score was also not impaired in the anterior functions tests of the neuropsychological battery. This patient however presented changes in the 5 behavioural domains of the ECAS. This dissociation between cognition and behaviour in FTD has been well documented (Koriath et al., 2017). Therefore, the ECAS was able to detect the cognitive profile of a group of bvFTD as well as a full neuropsychological assessment.

5.5 The ECAS as a brief assessment for AD

The ECAS was sensitive to detecting cognitive changes present in AD when compared to healthy controls. The ALS Non-Specific Composite score (Posterior) (Memory and Visuospatial domains) (sensitivity 97% and specificity 96%) and the ECAS Total Score (sensitivity 94% and specificity 96%) were highly effective at detecting AD when compared to healthy controls. The results in this study were incredibly similar to those of the Greek sample, as they found the ALS Non-Specific Composite score (sensitivity 97.4% and specificity 97.4%) and the ECAS Total Score (94.7% and 97.4%) to be sensitive to AD (Kourtesis et al., 2020). It was not surprising that the ALS Non-Specific Composite score was more sensitive to detect AD than the ECAS total score in our sample, as most AD patients present predominately with a memory impairment (Hugo, and Ganguli, 2014). In our study, the memory domain was the most sensitive domain to detect AD on the ECAS. Furthermore, there was also good concordance between the deficits detected on the ECAS Total score (93%) and the ALS Non-Specific Composite score (97%) and impairments in posterior functions tests in the neuropsychological assessment for the AD group. Therefore, the ECAS was an accurate brief assessment for AD, as it was able to detect the cognitive and behavioural changes occurring in this patient group.

5.6 The ability of the ECAS at differentiating between bvFTD and AD

There were no significant group differences between the two types of dementia in the ECAS composite scores. While most AD patients scored as more impaired on the ALS Non-Specific Composite score than on the ALS Specific Composite score, the difference was small and not significant. In our sample, bvFTD patients scored similarly in both composite scores. Our results were different from what was found previously by Kourtesis et al., (2019); which found the ECAS ALS Non-Specific Composite score was successful at discerning between ALS and AD with a sensitivity of 96% and a specificity of 91%. Nevertheless, it is important to notice the different patient groups between our samples; as our sample had bvFTD patients without ALS, and Kourtesis et al. (2019) had ALS patients without FTD. The lack of dementia cases in their ALS sample could explain the high sensitivity of the ECAS to differentiate these diagnoses. I did however find that a cut-off of 4 or more behavioural domains affected had a 79% sensitivity and 87% specificity to differentiate between the diagnoses of bvFTD and AD. Our results affirm the importance of assessing AD patients with a behavioural inventory. As it can be used to differentiate between other diagnoses, and also to inform the clinician about other behavioural symptoms that the patient or their carer might not have reported. I reiterate that as most AD patients will develop some behavioural changes, particularly apathy, clinicians should be aware of these behavioural changes as early as possible, to therefore provide treatment and management when appropriate and reduce carer burden (Mandell and Green, 2011; Hugo, and Ganguli, 2014).

5.7 The ECAS behavioural interview in bvFTD and AD

Most bvFTD patients had behavioural changes in the five domains of the ECAS behavioural interview, whereas most AD patients had behavioural changes in two domains. The most prevalent behaviour in both patient groups was apathy, which was consistent with the literature (Radakovic et al., 2020; Radakovic et al., 2014; Landes, Sperry and Strauss, 2005); followed by

disinhibition in the bvFTD group, and perseverative behaviour in the AD group, which were also congruent with the literature (Mendez et al., 2008; Ossenkoppele et al., 2015). Loss of sympathy or empathy was the third most common behavioural change for bvFTD patients, which has been a symptom widely recognised in bvFTD (Carr and Mendez, 2018). Our results were similar to that found by Saxon et al., (2017) in which bvFTD patients' most common behavioural changes were apathy (86%), loss of decorum (83%) and reduced interpersonal warmth (74%). As the diagnosis of bvFTD is made on the basis of the 5 domains of behavioural changes included on the ECAS, the ECAS could be used to support diagnosis in its clinical application.

I found differences in the themes reported on the behavioural interview between bvFTD and AD patients. While the most common theme for bvFTD was loss of sympathy and empathy; themes surrounding impulsivity, apathy, perseverative behaviour and eating more carbohydrates were found in the majority of patients. Although these behavioural changes have been widely reported in the literature (Bathgate et al., 2011; Rascovsky et al., 2011), there has not been a previous thematic analysis comparing the behavioural changes of both diagnoses. Loss of sympathy and empathy ranged from diminished responsiveness or a lack of care, to hostility towards specific family members. Some studies have found bvFTD patients to not include others in conversation, loose tact, decrease perception and response to social cues, and lack empathy (Mendez et al., 2014; Seeley et al., 2007; Shany-Ur and Rankin, 2011; Eslinger et al., 2007). The most common theme found in AD was apathy, with over half of patients reporting this symptom. Apathy has been previously found in 72% of AD patients, with executive-initiation apathy being the most common subtype of apathy in this group (42.2% of patients) (Mega et al., 1996; Radakovic, Starr and Abrahams, 2017).

Some of the themes which were present in bvFTD but not in AD patients were the need to do things immediately and lacking patience, a lack of manners,

accidental oversights or mistakes, a drastic change in personality, and binge eating. Changes in personality are so common in bvFTD that they are often mentioned as part of the description of the clinical presentation in terms of behavioural features (Piguet et al., 2011). In our sample, a carer said about their mother “Not my mum. Used to be incredibly polite and now quite rude”. Personality changes have also been found useful to differentiate between bvFTD and the behavioural variant of AD (Mendez et al., 2013). Some of the themes found in AD only were eating less or losing weight, losing confidence, stopped reading and avoiding cooking. Binge eating in bvFTD has been associated with right orbitofrontal-insular-striatal atrophy, and changes in functional neural networks involved with neuroendocrine and rewards processes (Wolley et al., 2007; Ahmed et al., 2016 a). In contrast, weight loss occurs in ~40% of AD patients; and has been shown to be a predictor of rapid cognitive decline (Guérin et al., 2005; Soto et al., 2012). Weight loss in AD can be caused by hypermetabolic state, increased physical activity (by being restless and using more energy when completing tasks because of difficulties), and a lower energy intake that is often due to changes in appetite-regulating mechanisms (Sergi et al., 2012). Some brain areas that have a role in food intake regulation are susceptible to amyloid deposition; such as the medial temporal cortex, the olfactory epithelium and the anterior cingulate cortex (Sergi et al., 2012).

Level of insight and awareness/insight may be a factor influencing behaviour. A lack of insight is a common factor in bvFTD (Scherling et al., 2017). For example, AD patients often avoid situations out of fear of doing something wrong, such as cooking, and they lose confidence about their own abilities as they are aware of their diagnoses and cognitive impairment in the early stages of the disease (Clare, 2003). Some of the AD patients in our study avoided social situations because of the fear of saying something embarrassing, either by repeating themselves or by forgetting things previously mentioned. These reasons for social avoidance have been found previously in the literature (Clare, 2002). In contrast, bvFTD patients could have more accidental

oversights (such as making mistakes while cooking), in part because of the cognitive impairment on executive functions (e.g. attention), but also because of the lack of awareness of these types of impairments within themselves. For example, a patient in our sample would become verbally aggressive when his relatives suggested that he was unable to drive anymore as he had dementia, after he had already received his diagnosis and had previous road incidents. A study found that even though bvFTD patients recognise the mistakes they make when given immediate feedback, they do not attribute the necessary emotional significance to them, which could prevent them from adjusting their daily activities according to their level of impairment (Scherling et al., 2017). In contrast, AD patients adjusted the estimations of their performances based on feedback, similar to healthy controls. Opposite to the fear of making mistakes reported in AD, social avoidance in bvFTD was linked to egocentricism and lack of empathy in our sample. A carer said that a bvFTD patient “will not say hello to his daughter or any other person he knows” and “blatantly ignores them”; whereas another carer said that an AD patient “has lost interest in seeing her friends as X can’t cope to be around many people at once”. Therefore, even though social avoidance can be a behaviour expected in both diagnoses, the mechanisms that underpin this avoidance differ. The behavioural interview of the ECAS could be a very useful tool for clinicians to assess behavioural changes in early onset dementia patients to speed up diagnoses and manage symptoms, such as apathy.

5.8 The ECAS as a brief assessment for MCI

The impairment cut-off of 105 on the ECAS had a sensitivity of 91% and a specificity of 96% to detecting MCI. The ALS Non-Specific Composite Score was more sensitive to MCI than the ALS Specific Composite Score, while Memory was the most sensitive domain. This finding was also replicated in the neuropsychological assessment where more patients were impaired on the Posterior tests (more so in Memory) than on the Anterior tests. Therefore, the ECAS had convergent validity with the neuropsychological assessment, making the ECAS a suitable brief assessment for MCI. As I mentioned earlier,

I did find some differences when using the ECAS adjusted age and education cut-offs that were created on the previous study; however, as our sample was quite small and I had some missing data regarding the years of education, I decided against using the age and education cut-offs. Most MCI patients of our sample scored close to the cut-off scores on the ECAS and the ACE-III. Caution should be used when interpreting results in this patient group, and premorbid abilities should be carefully considered when giving a diagnosis; due to the small overlap of scores between healthy controls and MCI patients (Portet et al., 2006).

5.9 The ECAS as a brief assessment for PPA

The ECAS Total score was sensitive to PPA (sensitivity 88%, specificity 96%). Fluency followed by language were the domains of the ECAS the most sensitive to PPA. With the exception of one PPA patient who was not impaired in any of the tests of the experiment, all other PPA patients were impaired on the fluency evaluation of the neuropsychological assessment. The report of this patient mentioned that previous neuropsychology was supportive of their assessment, as well as imaging indicating a frontotemporal hypoperfusion which progressed overtime. However, the patient did not decline in ACE-III scores over a period of 5 years (ranging scores between 89 and 96). In addition, the patient developed swallowing problems later on, which questioned the possibility of this being an MND case. The results in our study support the use of the ECAS in PPA. However, as the sample was small and the case mentioned earlier was an outlier, a larger sample would be needed to validate the use of the ECAS in PPA. Our PPA patient group also included the variants of logopenic, nonfluent, and semantic. As the sample numbers for each of these variants were small, a bigger sample would also be needed to evaluate the differences on the ECAS for each variant. Perhaps different profiles involving the domains of language, fluency and memory (due to immediate story recall) could be found in the ECAS for these variants; for example, an impairment in the subtests of naming and comprehension could indicate semantic dementia (Gorno-Tempini et al., 2011).

5.10 The ECAS as a brief assessment for PCA

The ECAS had a sensitivity of 100% for the diagnosis of PCA. As mentioned earlier, the cognitive assessment of PCA patients can be difficult because of the visual impairments characteristic of this disease (Crutch et al., 2017). Although the ECAS has disability adjustments for motor impairments that often occur in ALS, it does not include adjustments for visual disabilities. Patients with PCA could be experiencing difficulties with some of the other domains of the ECAS because of the visual component; such as the identification of figures in naming or understanding the elements of the Social Cognition task in recognizing the objects and seeing the direction of the eye gaze. Although the ECAS total score was sensitive to PCA, clinicians should decide on a case by case basis if the ECAS would be suitable to assess that particular PCA patient depending on the severity and type of visual impairment. As otherwise assessing verbally all other domains could be more suitable for some of these patients (Schott and Crutch, 2019).

5.11 Relationships between the ECAS, the CDR-FTLD, FBI and FRS

The ECAS had good convergent validity with the severity scores of the functional assessment, the Clinical Dementia Rating Scale with the additional domains of language and behaviour (CDR-FTLD). The ECAS behavioural interview had convergent validity with the behavioural questionnaires and functional assessments: The Frontal Behavioral Inventory (FBI), The Frontotemporal Dementia Rating Scale (FRS) and CDR-FTLD. The more behavioural changes were reported on the ECAS, the more behavioural and functional impairment were on the FBI, FRS and CDR-FTLD. The CDR-FTLD, FBI, FRS and IQ predicted 71.3% of the variance of the ECAS Total Score in the dementia patients. These results provide evidence of the validity of the ECAS as an assessment tool to predict functional impairment in daily life. An important note, however, is that the patients were referred in most part for their

first neuropsychological assessment to the clinic in which the study took place. Consequently, most of the patients included in this study would be classified by the CDR as mild dementia, and none of the patients in the initial assessment would be classified with severe dementia.

I was able to create an abnormality cut-off score of 96 that had a sensitivity of 84% and a specificity of 90% to differentiate the groups of questionable versus mild dementia. This abnormality cut-off expands on the borderline ranges created by Niven et al. (2015) and could be useful for discriminating between those with mild cognitive impairment versus those with dementia. As an example of this using our sample of 12 MCI from Chapter 3, 2 (16%) scored above the original cut-off score, 7 (58%) scored between the new questionable versus mild dementia cut-off, and 3 (25%) scored below this cut-off. However, there was a significant overlap of scores between the mild and moderate cases. Because of this reason I was not able to create a separate abnormality cut-off score to differentiate between these severity categories. Similar issues to ours were probably experienced by the study of So et al. (2018) when they created severity cut-off scores for the ACE-III, as some of their sample sizes per diagnosis (smallest samples n=23) seem to be too small to be further divided by severity. Although they provide severity cut-off scores per diagnosis, they stated that some statistical assumptions were violated (without specifying more) in the creation of these cut-offs.

The strongest correlation of the ECAS behavioural screen was with the FBI. This result was expected due to the overlap of behaviours between the assessments. As the ECAS behavioural interview is shorter than the FBI and more focused in the diagnostic criteria for bvFTD, it could serve as the first line of behavioural assessment alongside the cognitive screen of the ECAS. The ECAS behavioural interview could also be the first line of behavioural assessment for AD, as the shorter behavioural questionnaire could suffice for the amount of behavioural changes commonly present in AD. The FBI, IQ and age predicted 74.7% of the variance of the ECAS behavioural score.

5.12 Longitudinal assessment using the ECAS

As with many longitudinal studies, I encountered difficulties with attrition. The FRS was the single variable to predict attrition by 20.4%. The FRS includes questions regarding transport, organising correspondence and intrinsic motivation. All these variables could point to the areas in which some patients might experience difficulties; and therefore, were unable to attend for the following appointments. Some of the patients unable to attend had gone to live permanently in care homes, while others forgot the time of the appointment, or felt unwell and cancelled. These situations could be related to health or cognitive decline in patients, which is congruent with the literature as causes for attrition (Sliwinski et al, 2003; Rabbitt et al., 1994; Cooney, Schaie, and Willis, 1988).

I found no significant difference on ECAS scores between assessments, although 40% of patients had a significant decline between the two assessments. This result could be due to the inclusion of MCI cases, the small sample size in our second and third assessments; or the length in between assessments, as there were only 6-11 months in between assessments which might be too early to find a significant cognitive decline. Perhaps a bigger sample with fewer diagnoses and a longer time in between assessments could find a significant difference of decline of ECAS scores overtime. However, another explanation could be that patients who deteriorate faster may not be returning to follow up assessments due to health issues.

5.13 Future studies

The ECAS accommodates for disabilities, such as the fluency index calculation. Consequently, the ECAS could be a suitable brief assessment for cognitive impairment in patients with motor and/or speech disabilities; who might have difficulties drawing, or when the speed of speech needs to be taken into account for scoring fluency tasks. The ECAS has already been validated in populations with motor dysfunction without ALS, such as Parkinson's

disease and progressive supranuclear palsy (Foley et al. 2018); therefore, it is possible that the ECAS could be used to measure cognitive impairment typically associated with dementia in other clinical groups, such as corticobasal degeneration. The ECAS could also be used in patients who develop cognitive impairment or dementia and who have motor difficulties, such as in arthritis or cerebral palsy; as these patients might struggle with other dementia assessments because of the motor demands. These accommodations make the ECAS a more inclusive mini assessment to screen for dementia when compared to other similar short cognitive assessments, such as the ACE-III.

If there was to be a future version of the ECAS, some of the behavioural themes present in AD could be included. The score of the behavioural interview could be divided by profiles as the cognitive screen is, to include for example losing weight and cooking avoidance in food preferences. Likewise, apathy could be divided in subcategories separating the lack of motivation to do household chores, vs hobbies, vs being emotionally flat. Knowing which of these instances the patient experiences could help with the management of this behavioural change; especially since apathy was the most common behavioural change in our bvFTD and AD groups.

In our study, the ECAS showed promise in its utility as a cognitive screen for MCI. A future study could be done specifically with a bigger sample of MCI to assess how effective it is to have age and education cut-off scores vs the general impairment cut-off score in this patient group. A bigger sample could also further validate the utility of the ECAS on MCI. A bigger sample of PPA divided by logopenic, nonfluent, and semantic variants could validate the ECAS for each variant of PPA. As mentioned earlier another longitudinal study with fewer diagnoses, a bigger sample and with a longer time in between assessments could be done to assess if there is a decline overtime on ECAS scores. If the study also aimed to recruit patients with moderate and severe dementia, perhaps further severity cut-off scores (for example moderate to severe) could be created.

As was done with ALS patients (Hodgins, Mulhern and Abrahams, 2019), the ECAS could be incorporated more into the clinical practice to screen for dementia in lieu of other brief assessments. If the ECAS was routinely used in dementia clinics, the time of diagnosis for early onset dementia, but more specifically for bvFTD patients, could improve dramatically. The behavioural screen could also raise awareness of these possible changes for patients, carers, and clinicians to improve management of symptoms.

5.14 Conclusions

The ECAS is a sensitive brief assessment for the types of cognitive impairment and behavioural changes in people with early onset dementia without ALS. The ECAS was a more sensitive brief assessment for bvFTD, AD, PPA and MCI than the ACE-III, with identical sensitivity for PCA. In addition, the ECAS had less ceiling effects, was less influenced by intelligence, and includes an assessment of executive functions and a behavioural interview, which sets it above the other brief assessment used in these studies. As the ECAS also provides separate composite scores of anterior and posterior impairments, it serves its purpose as a brief assessment to screen for typical profiles of impairment in dementia. The ECAS behavioural interview additionally differentiated between bvFTD and AD patients based on the number of behavioural domains changed. The ECAS is a useful tool for the screening of bvFTD and AD, as was validated by a comprehensive neuropsychological assessment. The ECAS could also be useful for the screening of other diagnoses such as PPA, MCI and PCA. The research in this thesis furthers the utility of the ECAS for the screening of dementia in patients without ALS.

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Appendix I

ECAS

EDINBURGH COGNITIVE AND BEHAVIOURAL ALS SCREEN – ECAS
English Version (2013)

Date of testing: .....
Age at leaving full-time education: .....
Occupation: .....
.....
Handedness: .....

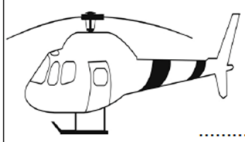
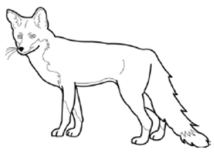
Name: .....
Date of Birth: .....
Hospital No. or Address: .....
.....
.....

LANGUAGE - Naming

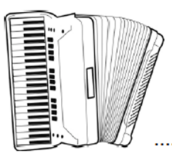
➲ Ask: Say or write down the names of these pictures:

Score 0-8 ☐







LANGUAGE - Comprehension

➲ Ask: point to the one which is:

Score 0-8 ☐

1. Something you can fly in .....
2. Something with webbed feet .....
3. An animal that climbs trees .....
4. Something used for chopping .....
5. A means of transport .....
6. Something with a sharp edge .....
7. Something with a sting .....
8. Something with a diet of nuts and seeds .....

 1

MEMORY – Immediate recall

Score 0-10 ☐

Also use this score to calculate % retention later

➲ Say: 'I am going to read you a short story. Please listen carefully. When I am finished, say or write as much as you can remember'. Score 1 point for each (either entire or part of) underlined section recalled.

Last Sunday, the annual litter collection took place in Primrose Woods. Forty two people joined in to remove old bicycles and shopping trolleys. Mr Douglas Watt from the woodland project told local reporters that he was very impressed and especially proud of the 17 children who came along.

LANGUAGE - Spelling

Score 0-12 ☐

➲ Say: 'Spell, either by writing or speaking, the following words.' If the person is using assistive technology, ask them to turn off any predictive text facility.

1. Envelope	2. Skateboard .....
3. Constructing	4. Partner .....
5. Biscuit	6. Lawnmower .....
7. Deliver	8. Recorded .....
9. Coathanger	10. Orchestra .....
11. Screwdriver	12. Brought .....

FLUENCY - Letter S

No. of correct words =

Time to copy/ read aloud =

➲ Say: 'I am going to give you a letter of the alphabet and I would like you to say or write as many different words as you can beginning with that letter, but not names of people or places, or numbers.'
- If writing, say: 'You will have **two** minutes. The letter is S.'
- If speaking, say 'You will have **one** minute. The letter is S.'

➲ Next the person copies/reads these words aloud.

- If writing, say: 'copy these words as fast as possible. I will time you. Ready? Begin.'

If speaking, say: 'read aloud these words as fast as possible. Before you do this, check that you can read them. I will time you. Ready? Begin.'

Verbal Fluency Index (Vfi) calculation:

If spoken:
Vfi = $\frac{60\text{seconds} - \text{no. of seconds to read aloud words}}{\text{No. of correct words generated}}$

If written:
Vfi = $\frac{120\text{seconds} - \text{no. of seconds to copy words}}{\text{No. of correct words generated}}$

VFI conversion to score table

SPOKEN VFI	WRITTEN VFI	Score
≥ 12.00	≥ 20.00	0
10.00 to <12.00	16.50 to < 20.00	2
8.00 to < 10.00	13.00 to < 16.50	4
6.00 to < 8.00	9.50 to < 13.00	6
4.00 to < 6.00	6.00 to < 9.50	8
2.00 to < 4.00	2.50 to < 6.00	10
< 2.00	< 2.50	12

Score 0-12 ☐

EXECUTIVE – Reverse Digit Span

➲ Say: 'I am going to say some numbers and I would like you to say them back to me in reverse order. For example, if I say '2 3 4', you should say '4 3 2'. Let's have a practice. If I say '7 1 9', what would you say?' Stop when person gets both trials of a line wrong. Score total number of trials correct.

Score 0-12 ☐

Trial		Check	Trial		Check
1	2 6		2	5 8	
3	9 3 5		4	4 1 6	
5	7 2 8 4		6	9 5 7 3	
7	6 9 4 2 1		8	8 3 2 5 6	
9	8 1 3 5 7 9		10	3 6 2 7 3 4	
11	1 6 9 3 5 8 6		12	2 3 6 8 4 9 2	

EXECUTIVE – Alternation

➲ Say: 'I want you to alternate between numbers and letters, starting with 1-A, then 2-B, 3-C, and so on. Please alternate between numbers and letters, in order, without skipping any until I tell you to stop. Let's begin together: 1A, 2B, 3C…'

➲

Score 0-12 ☐

Trial		Check	Trial		Check	Trial		Check	Trial		Check
1	4-D		2	5-E		3	6-F		4	7-G	
5	8-H		6	9-I		7	10-J		8	11-K	
9	12-L		10	13-M		11	14-N		12	15-O	

FLUENCY - Letter T

➲ Say: 'I am going to give you a letter of the alphabet and I would like you to say or write as many different words as you can beginning with that letter, but not names of people or places, or numbers. This time the word must only be four letters long. No more or less than four letters'

- If writing, say: 'You will have **two** minutes. The letter is T.'
- If speaking, say 'You will have **one** minute. The letter is T.'

No. of correct words =

Time to copy/ read aloud =

➲ Next the person copies/reads these words aloud.

- If writing, say: 'copy these words as fast as possible. I will time you. Ready? Begin.'

If speaking, say: 'read aloud these words as fast as possible. Before you do this, check that you can read them. I will time you. Ready? Begin.'

Verbal Fluency Index (Vfi) calculation:

If spoken:
Vfi = $\frac{60\text{seconds} - \text{no. of seconds to read aloud words}}{\text{No. of correct words generated}}$

If written:
Vfi = $\frac{120\text{seconds} - \text{no. of seconds to copy words}}{\text{No. of correct words generated}}$

VFI conversion to score table

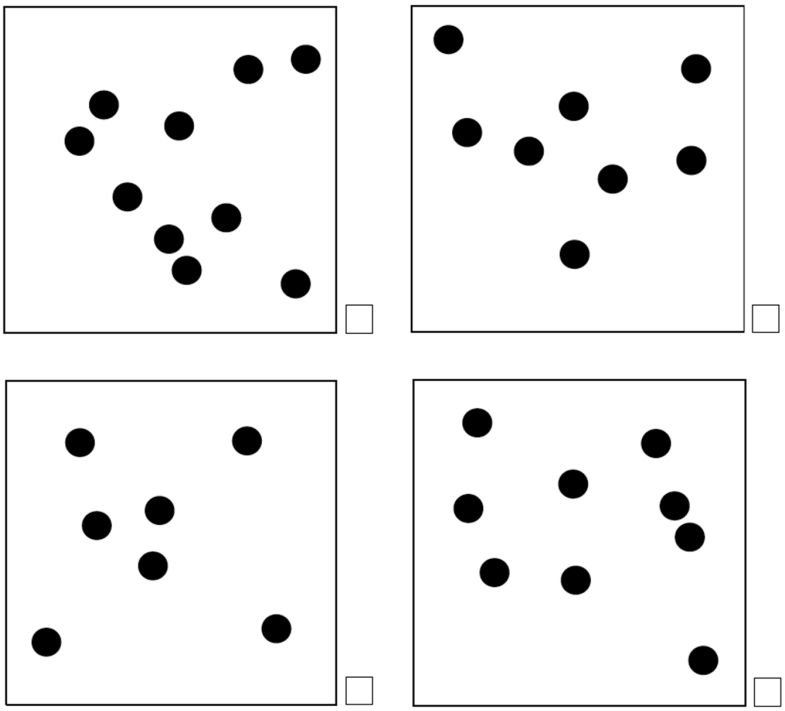
SPOKEN VFI	WRITTEN VFI	Score
≥ 20.00	≥ 27.25	0
16.75 to < 20.00	23.00 to < 27.25	2
13.50 to < 16.75	18.75 to < 23.00	4
10.25 to < 13.50	14.50 to < 18.75	6
7.00 to < 10.25	10.25 to < 14.50	8
3.75 to < 7.00	6.00 to < 10.25	10
< 3.75	< 6.00	12

Score 0-12 ☐

VISUOSPATIAL – Dot Counting

➲ Say: 'I would like you to count how many dots are in each box, but without pointing to them.'

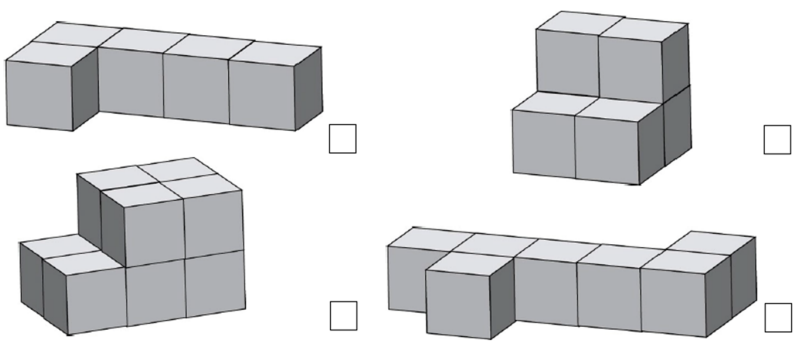
Score 0-4



VISUOSPATIAL – Cube Counting

➲ Say: 'How many cubes are in each structure, including the ones you may not be able to see?'

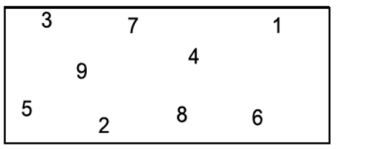
Score 0-4



VISUOSPATIAL – Number Location

➲ Say: 'Which number corresponds to the position of the dot?'

Score 0-4 ☐



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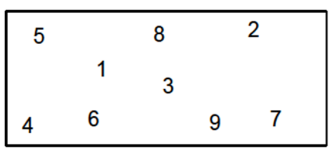

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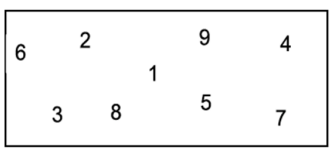


☐

EXECUTIVE – Sentence Completion

➲ Say: 'Listen carefully to these sentences and as soon as I have finished reading them, please tell me, or write, a word that finishes the sentence as quickly as possible. For example, '*She was so tired that she went straight to…bed*'. Do not score.

1. He phoned up the restaurant to reserve a .....
2. When she got up in the morning, the sun was.....

➲ Say: 'Now I'd like you to do that again, but this time the word you give should not make sense whatsoever in the context of the sentence. It must not be related to the word that actually completes the sentence. For example, '*John cut his hand with the sharp…orange*'. If the person does not respond within 20 seconds, move onto the next question.

1. The postman knocked on the .....

2. He brought his umbrella with him in case of .....

3. Sally spread her toast with butter and .....

4. John went to the barbers to get his hair .....

5. She dived into the swimming .....

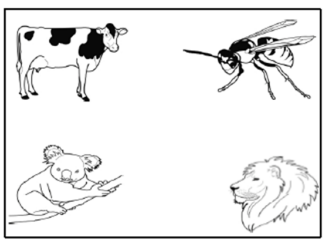
6. They all went to the local café for something to .....

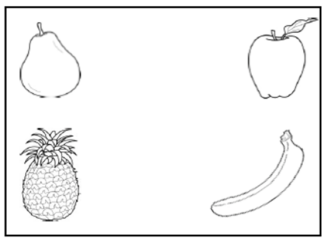
Give 2 points for different word, 1 point for related word (e.g. associated or opposite meaning) or 0 points for exact word.

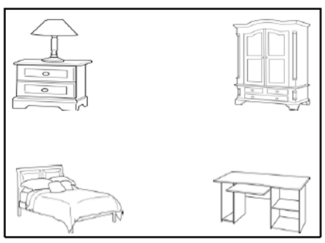
Score 0-12 ☐

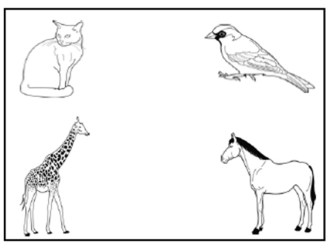
SOCIAL COGNITION – Part A

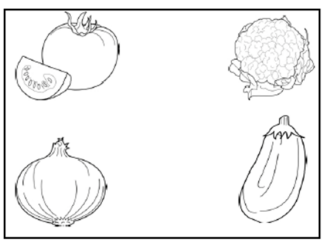
➲ Say: 'You are going to see some pictures, one in each corner of a box. You have to choose **which picture you like best.** Either point to or say which picture you like best. Please respond as quickly as possible.' Circle participant's choice.

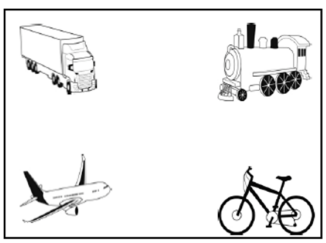








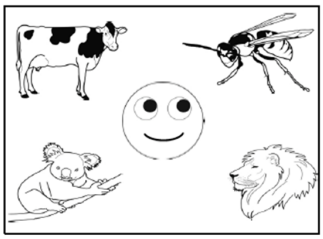


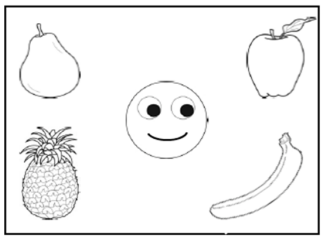


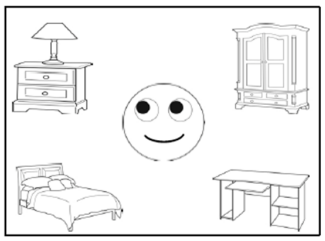
SOCIAL COGNITION – Part B

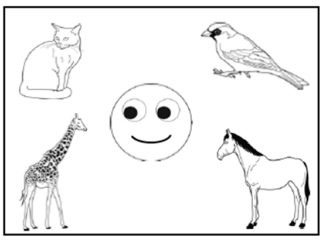
➲ Say: 'You are going to see some pictures, one in each corner of a box. You have to choose **which picture does the face like best.** Either point to or say which picture **the face likes best**. Please respond as quickly as possible.' Circle participant's choice. Correct items = 2 points, error = 1 point, egocentric error = 0 points.

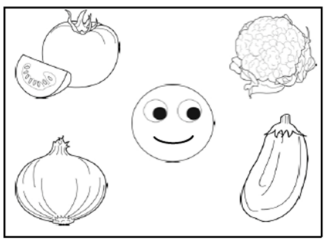
Score 0-12 ☐

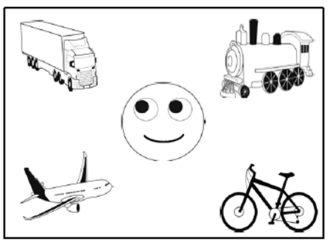












MEMORY – Delayed Recall

Scoring procedure for retention: obtain delayed recall performance (over page) and, together with immediate recall score, determine percentage retained. Convert percentage retained to Score using table below. If delayed recall = 0, score = 0.

Delayed recall to percentage retained calculation	Percentage retained to score conversion table

$$\frac{\text{(Delayed recall)}}{\text{(Immediate recall score)}} \quad x\ 100 = \%\ \textit{retained}$$

$$\frac{(\ldots\ldots\ldots\ldots\ldots\ldots)}{(\ldots\ldots\ldots\ldots\ldots\ldots)} \quad x\ 100 = \ldots\ldots\ldots\ldots\%\ \textit{retained}$$

Percentage retained	Score	Percentage retained	Score
1-10%	**1**	51-60%	**6**
11-20%	**2**	61-70%	**7**
21-30%	**3**	71-80%	**8**
31-40%	**4**	81-90%	**9**
41-50%	**5**	91-100+ %	**10**

➲ Say: 'At the beginning of this interview, I read you a short story. Tell me as much as you can remember from that story'. Mark 1 point for each (either entire or part of) underlined section recalled.

Last Sunday, the annual litter collection took place in Primrose Woods. Forty two people joined in to remove old bicycles and shopping trolleys. Mr Douglas Watt from the woodland project told local reporters that he was very impressed and especially proud of the 17 children who came along.

Delayed recall =

Score (0-10) ☐

MEMORY – Delayed Recognition

If all items recalled, skip and score 4. Otherwise ask questions below.

Say: 'Lets see if you can remember anything more about that story. I will ask you some questions, please tell me if they are true or false'.

Circle responses (true or false) and mark 1 point for each item recognised in this section. Use table below to calculate score.

Score 0-4 ☐

Was the story about an event that occurred last Saturday?	T	**F**	1
Was the event the annual litter collection?	**T**	F	1
Did this take place in Primrose Woods?	**T**	F	1
Did they remove old drink cans and sweet wrappers?	T	**F**	1
Was the man in the story called Mr Watt?	**T**	F	1
Was his first name 'Thomas'?	T	**F**	1
Was he from the local council?	T	**F**	1
Was he especially proud of the children for coming along?	**T**	F	1

Recognition to recognition score table

Number of correct answers	**Score**
0-4	**0**
5	**1**
6	**2**
7	**3**
8	**4**

SCORES

Language	Naming, Comprehension, Spelling	/28
Verbal Fluency	Fluency Letter S, Fluency Letter T	/24
Executive	Reverse Digit Span, Alternation, Sentence Completion, Social Cognition	/48
	ALS-SPECIFIC:	**/100**
Memory	*Immediate recall, Delayed recall score, Delayed recognition*	*/24*
Visuospatial	*Dot Counting, Cube Counting, Number Location*	*/12*
	ALS NON-SPECIFIC:	***/36***
	ECAS TOTAL SCORE:	**/136**

EDINBURGH COGNITIVE and BEHAVIOURAL ALS SCREEN – ECAS
English Version (2013)

BEHAVIOUR SCREEN – Carer Interview

➲ Please ask the carer about the following possible behaviours. Symptoms should have occurred repeatedly and not just on one instance, and may have occurred prior to the development of any motor signs. Tick 'Yes', 'No' or 'Don't Know'. If 'Yes', please provide a brief written description. Give one mark for every 'Yes' response (maximum = 10).

A	**Behavioural disinhibition**			
1	Socially inappropriate behaviour, e.g. *inappropriate behaviour with strangers* *criminal behaviour*	Y	N	DK
2	Loss of manners or decorum, e.g. *crude or sexually explicit remarks, jokes or opinions that may be offensive to others* *lack of response to social cues*	Y	N	DK
3	Impulsive, rash or careless actions, e.g. *new onset gambling, or buying or selling property without regard for consequences* *giving out personal information inappropriately, e.g. credit card numbers*	Y	N	DK
B	**Apathy or inertia**			
4	Loss of interest, drive or motivation, e.g. *passivity and lack of spontaneity* *needs prompting to initiate or continue routine activities*	Y	N	DK
C	**Loss of sympathy or empathy**			
5	Diminished response to other people's needs and feelings *Positive rating on this feature should be based on specific examples that reflect a lack of understanding or indifference to other people's feelings, e.g* *hurtful comments* *disregard for others' pain or distress*	Y	N	DK
6	Diminished social interest, interrelatedness, personal warmth or general closeness in social engagement, e.g. *coldness* *lack of eye contact*	Y	N	DK
D	**Perseverative, stereotyped, compulsive or ritualistic behaviour**			
7	Simple repetitive movements, e.g. *tapping, clapping* *scratching, picking skin or clothing* *repeating words*	Y	N	DK
8	Complex, compulsive or ritualistic behaviours, e.g. *counting, cleaning rituals, checking* *collecting, hoarding*	Y	N	DK

BEHAVIOUR

E	Hyperorality and altered food preferences			
9	Altered food preferences, e.g. *food fads* *carbohydrate craving (particularly sweets)*	Y	N	DK
10	Binge eating or hyperorality, e.g., *cramming or continuing to eat despite satiety* *oral exploration or consumption of inedible objects*	Y	N	DK

SCORE

TOTAL */10*

SYMPTOMS

➲ Please tick box if at least one of the symptoms was present in each of the following categories.

A. Behavioural disinhibition	
B. Apathy or inertia	
C. Loss of sympathy or empathy	
D. Perseverative, stereotyped, compulsive or ritualistic behaviour	
E. Hyperorality and altered food preferences	

ALS Psychosis Screen

➲ Please ask the carer about the following possible symptoms. Tick 'Yes', 'No' or 'Don't Know'. If 'Yes', please provide a brief written description. Give one mark for every 'Yes' response (maximum = 3).

1	Has strange and/or bizarre beliefs and behaviours	Y	N	DK
2	Hears or sees things that are not there, and/or feels the presence of someone who is not there	Y	N	DK
3	Is overly suspicious, and/or feels persecuted	Y	N	DK

SCORE

TOTAL */3*

ONSET AND DURATION OF SYMPTOMS

➲ Please tick or complete box to indicate response.

1. Do these symptoms represent a CHANGE from the patient's previous behaviour?	Y	N
If yes, did the changes occur:		
a. BEFORE the onset of the disease?	Y	N
b. at the same time as other symptoms?	Y	N
c. AFTER the onset of the disease?	Y	N
2. Do they still persist?	Y	N
3. If not, how long did they last?		

Appendix II

The Edinburgh Cognitive and Behavioral ALS screen: relationship to age, education, IQ and the Addenbrooke's Cognitive Examination-III

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RESEARCH ARTICLE

The Edinburgh Cognitive and Behavioral ALS screen: relationship to age, education, IQ and the Addenbrooke's Cognitive Examination-III

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Abstract

The Edinburgh Cognitive and Behavioral ALS Screen (ECAS) was developed to assess cognitive and behavioral changes common in Amyotrophic Lateral Sclerosis and other diseases affecting motor functions. It focuses on domains typically affected by the frontotemporal syndrome (executive and language functions, fluency and behavior), but assesses also memory and visuospatial functions. *Objectives:* (A) To investigate the relationship between the ECAS and the Addenbrooke's Cognitive Examination (ACE-III). (B) To investigate the effects of age, education, and IQ on the ECAS and create appropriate cutoff scores to determine abnormality. *Methods*: (A) 57 healthy participants (aged 35–80) were assessed with the ECAS, the Wechsler Abbreviated Scale of Intelligence (WASI-II), and the ACE-III. (B) 80 healthy participants (aged 51–80) were divided into four groups according to age and education; and were tested with the ECAS and the WASI-II. *Results:* The ECAS and the ACE-III have a good convergent validity with a significant correlation. Regression analysis revealed that IQ, followed by age, were the strongest predictors of the total ECAS score. IQ predicted 24% of the ECAS and 46% of the ACE-III variance. Education was not a significant predictor over and above IQ for both the ECAS and the ACE-III. Abnormality cutoff scores adjusted for age and education are presented. *Conclusions:* The ECAS shows good convergent validity with the ACE-III, but is less influenced by intelligence and presents less ceiling effects. The inclusion of an executive function assessment and behavioral interview in the ECAS makes it particularly useful for the assessment of frontal lobe disorders.

Keywords: *ECAS, education, age, IQ, frontotemporal dementia, screen, cognition, behavior*

Introduction

The Edinburgh Cognitive and Behavioral ALS Screen (ECAS) was developed to assess the cognitive and behavioral changes associated with amyotrophic lateral sclerosis) (ALS) (1) since a significant percentage of these patients develop a fronto-temporal degenerative syndrome (2,3). The neuropsychological profile of ALS is somewhat heterogeneous and previous existent cognitive screening tests did not assess the full range of cognitive and behavior change present in ALS, and most were not suitable for patients with physical disability. The ECAS has proven to be sensitive to detect the changes in executive functions, fluency, and language in patients with ALS; in addition, it was designed to differentiate these changes from those found in other pathologies, including Alzheimer's disease (1). It has also been validated against extensive neuropsychology showing high sensitivity and specificity (4,5) and against other screening tests including the Frontal Assessment Battery, Montreal Cognitive Assessment (MoCA) and Consortium to Establish a Registry for Alzheimer's Disease plus Scale (6,7).

The Addenbrooke's Cognitive Examination (ACE-III) is a widely used dementia screening test in the UK (8). It is proven to have very good diagnostic accuracy for patients with memory complaints (9); with greater accuracy than the MoCA, the Mini-Mental State Examination and the Memory Impairment Screen (10). We chose the

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ACE-III to compare against the ECAS over other screening tests, because it is one of the most commonly used cognitive tests in the UK and beyond to diagnose dementia. It has been validated in a number of patient groups (11–13). Furthermore, both the ACE-III and ECAS are multidomain and have similar assessment times (14–16). Although designed for the detection of different types of dementia, its sensitivity to detecting frontotemporal dementia and in particular the behavioral variant (bvFTD) is inconsistent (17–19). Hsieh et al. (20) showed that patients with bvFTD displayed a cognitive profile consisting of deficits in verbal memory, attention, fluency, and language using the ACE-III. However, apart from verbal fluency, the ACE-III does not include an assessment of executive functions, the most prominent cognitive deficit in this type of dementia. Furthermore, the sensitivity and specificity of the given cutoff scores are for a general diagnosis of dementia that comprises Alzheimer's disease, bvFTD, and Primary Progressive Aphasia. They propose that fronto-temporal dementia should be confirmed with specific functional and behavioral inventories such as the Cambridge Behavioral Inventory, the Neuropsychiatric Inventory or the FTD Rating Scale FRS. Given the inclusion of tests of executive functions and an informant interview to detect abnormal behaviors, based on the most recent diagnostic criteria for bvFTD (21), the ECAS may be a more suitable test to assess this type of dementia.

The effect of demographic factors including age and education has been explored using local and/or translated versions in German, Italian, Chinese, and Irish (5–7,22,23) but not in a British population. Age has been found to significantly correlate with total ECAS scores in most studies (5–7,22), with the exception of one (23). Although education was shown to correlate with ECAS scores across studies, the relation to measures of IQ has not been explored. Given the correlation between age and education found in the German, Italian, and Irish studies, age and education adjusted local normative data have been produced.

This study had two primary aims:

Objective 1: Investigate the relationship between the ECAS and ACE-III.

Objective 2: Investigate the effect of age, education, and IQ on the ECAS in a healthy population to create appropriate adjusted cutoff scores to detect abnormality.

Methods

Relationship between the ECAS and the ACE-III

Participants

Healthy individuals ($n = 57$) between the ages of 35–80 years old were recruited from the local population and the Psychology Volunteer Panel of the University of Edinburgh. Participants did not have any neurological illness in their medical history, or current psychiatric illness, or any learning disabilities. All were native English speakers.

A minimum of 55 participants was decided for this study, in order to predict a medium effect size ($f^2 = 0.15$) (24), with an alpha of 0.05 and a power of 0.80 in a linear regression of one predictor (25). A sample size of 55 is also adequate for predicting a large effect size ($p = 0.5$), with an alpha of 0.05 and a power of 0.80 in a correlation (minimum sample size would have been of 21). Both calculations were done using G*Power (26).

Materials

ECAS. The ECAS is a short screening test (15–20 min) created to assess symptoms associated with cognitive and or behavioral impairment present in ALS. The ECAS is multidomain, providing subscores for language, fluency, executive, memory, and visuospatial abilities. Language is evaluated by naming, comprehension, and spelling. Fluency is measured by a free production of words beginning with the letter "s" and a restrained production of words beginning with the letter "t" but with only four letters. Executive functions are measured by a reverse digit span, alternation of letters and numbers, inhibitory sentence completion, and social cognition. Memory includes measurements of immediate recall, delayed percentage retention and delayed recognition. Visuospatial abilities are measured with dot and cube counting, and number location. The ECAS also includes a behavior interview based on diagnostic criteria for bvFTD that is undertaken with an informant/carer (1, see http://ecas.psy.ed.ac.uk).

ACE-III. The ACE-III is a commonly used screening test for dementia. It assesses the abilities of attention, memory, fluency, language and visuospatial functions (27).

Wechsler Abbreviated Scale of Intelligence (WASI-II). The WASI-II is the brief version of the Wechsler Adult Intelligence Scale. We used the 15 min version with two subtests to obtain a measure of intelligence (Vocabulary and Matrix Reasoning) (28).

The effect of age and IQ on the ECAS

Participants

A total of 80 participants undertook this study. A total of 33 participants from the first study were included; and an additional 47 healthy individuals between the ages of 51–80, recruited from the local population and the Psychology Volunteer Panel of the University of Edinburgh. Participants did not have any neurological illness in their medical history, or current psychiatric illness, or learning disabilities.

All were native English speakers. Social economical status was obtained based on the occupation of the participants. The classification was done according to the Standard Occupational Classification proposed by the Office for National Statistics (29).

Participants were divided into four groups according to their age and education. Age: 51- to 65- and 66- to 80-years old, these age ranges were chosen to parallel typically used division for early versus late onset dementia. Education: secondary school or a technical degree vs university degree, or postgraduate degree. A minimum of 19 participants per group was decided in order to predict a large effect size ($f = 0.40$) (24), this number of participants was obtained using an alpha of 0.05 and a power of 0.80 (25) for a one-way ANOVA using G*Power (26), we included in some of the groups 1 or 2 more participants in case we needed to exclude some outliers.

Ethical Approval

This study was approved by The Psychology Research Ethics Committee of the University of Edinburgh.

Statistical Analysis

The data were analyzed using SPSS statistics version 22. Pearson's correlations were used to assess the relationship between variables. ANOVA and t tests were undertaken on parametric data to assess the difference between groups. ANOVA stepwise linear regression was used to find the variables that predicted the final score of the ECAS. ANOVA linear regressions were done to find the effect of IQ on the ECAS and the ACE-III.

Results

Relationship between ECAS and ACE-III

The sample had 34 males and 23 females with a mean age of 56 years (±13.29, 35–80). The age of when they finished education was of 19.22 years (±3.20, 14–26), and their mean IQ was of 111.23 (±16.73, 75–156). Performance of participants on the ECAS and the ACE-III is presented in Table 1. The total scores of the ACE-III and the ECAS were significantly and moderately correlated ($r = .538$, $p < 0.001$). Memory ($r = 0.368$, $p = 0.005$), Fluency ($r = .503$, $p < 0.001$) and Language ($r = 0.411$, $p = 0.002$) correlated significantly between screens, however Visuospatial abilities ($r = 0.197$, $p < 0.141$) did not correlate between both tests.

As can be seen in Figure 1 the ACE-III suffered from more ceiling effects than the ECAS with some participants achieving full marks for the ACE-III, whereas none reached the maximum score for the ECAS. ANOVA linear regression models showed that 24% of the variance of the total score of the ECAS ($F[1,54] = 17.292$, $p < 0.001$) was predicted by IQ ($\beta = 0.492$, $t = 4.15$, $p < 0.001$), whereas 46% of the variance of the total score of the ACE-III ($F[1,54] = 46.187$, $p < .001$) was predicted by IQ ($\beta = 0.679$, $t = 6.79$, $p < 0.001$).

Table 1. Performance on the ECAS and ACE-III.

$N = 57$	(max)	Mean (SD)	Median (range)
ECAS total	136	115.87 (±11.30)	118 (88–134)
ECAS language	28	26.71 (±1.81)	27 (20–28)
ECAS fluency	24	19.40 (±3.46)	20 (10–24)
ECAS executive	48	39.71 (±4.69)	40 (22–47)
ECAS memory	24	19.22 (±3.57)	20 (7–24)
ECAS visuospatial	12	11.59 (±0.90)	12 (7–12)
ACE-III total	100	93.07 (±4.81)	94 (80–100)
ACE-III attention	18	17.01 (±1.10)	17 (13–18)
ACE-III memory	26	23.10 (±2.93)	24 (15–26)
ACE-III fluency	14	12.59 (±1.29)	13 (9–14)
ACE-III language	26	25.33 (±0.87)	26 (23–26)
ACE-III visuospatial	16	15.01 (±1.14)	15 (11–16)

SD, standard deviation; ECAS, Edinburgh Cognitive and Behavioral ALS Screen; ACE-III, Addenbrooke's Cognitive Examination; max, Maximum score.

Overall, the scores of the domains of the ACE-III were more dependent on IQ than the domains in the ECAS. The percentage of the variance explained by IQ was higher in the ACE-III for the domains of Memory (29 vs 22%) and Visuospatial (7 vs 2%). Language was the same for both tests (30%). Fluency was more dependent on IQ for the ECAS (12 vs 21%). The percentage of the variance explained by IQ was 16% for Attention on the ACE-III and 9% for the Executive domain on the ECAS.

The effect of age, education, and IQ

Demographics of the full sample are presented in Table 2. There were no significant differences regarding IQ ($F[1,78] = 0.681$, $p = 0.412$) nor in socioeconomic status ($F[1,78] = 1.084$, $p = 0.301$). Three outliers (more than 2 standard deviations from the mean) in the ECAS total score were removed from the data in the further analyses. The remaining sample presents scores from 97 to 134 on the total score of the ECAS.

An ANOVA stepwise linear regression model was undertaken including the variables of gender, age, education, and IQ. The most significant model predicted 32.5% of the variance of the ECAS Total Score ($F[3,73] = 11.736$, $p < 0.001$). This model included the variables of IQ ($\beta = 0.557$, $t = 5.54$, $p < 0.001$), age ($\beta = -2.82$, $t = -2.81$, $p = 0.006$) and gender ($\beta = 0.197$, $t = 2.04$, $p = 0.045$). Education was not significant in the model since it could be sufficiently explained by IQ ($r = 0.514$, $p < 0.001$). Women scored slightly higher on the total score of the ECAS (119.16) in comparison to men (116.21).

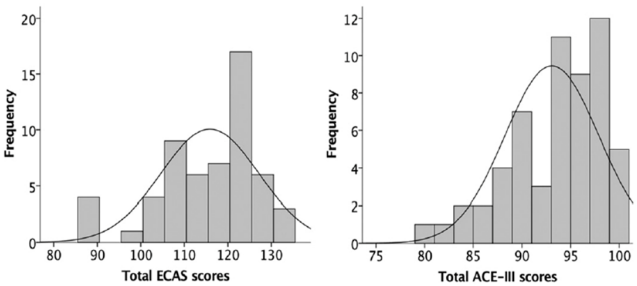

Figure 1. Distribution of scores on the (left) ECAS and (right) ACE-III. ECAS mean 115.88 (±11.303), ACE-III mean 93.07 (±4.81).

Table 2. Demographics of the effect of age, education and IQ.

Age group	Education group	Participants	Age	Age at finishing education	IQ
51–65	1	20 total (10 m)	58.3 (±4.64) 52–65	17.35 (±2.08) 15–24	108.30 (±14.56) 75–139
	2	21 total (11 m)	59.23 (±3.72) 51–65	22.52 (±1.36) 21–26	128.38 (±11.34) 103–156
66–80	1	19 total (9 m)	73.00 (±3.38) 67–78	16.94 (±1.95) 14–22	115.26 (±15.24) 87–141
	2	20 total (10 m)	72.20 (±4.00) 67–80	22.45 (±1.73) 19–26	127.25 (±10.12) 111–142

Education was divided between participants without a university degree (1) and participants with a university degree (2). m (presumably males). Results are presented mean (standard deviation) range.

Table 3. ECAS age and education adjusted cutoff scores to determine abnormality for ECAS total scores.

Age	Education	Mean (SD)	Range	Cut-off
≤65	1	119.650 (±8.628)	100–134	100
	2	123.381 (±7.221)	110–133	110
>65	1	117.000 (±8.062)	98–129	98
	2	120.895 (±6.315)	108–131	108

Education was divided between participants without a university degree (1) and participants with a university degree (2).
SD, standard deviation.

Abnormality cutoff scores

Education and age adjusted cut offs for abnormality are presented based on Education (those with and without a university degree) and age (below and above 65). Abnormality cutoffs were based on the 5 percentile (Table 3). Education was chosen over IQ to create the cutoff scores for the ease of use in association with the ECAS within the MND clinical services, since it is more easily available to than IQ.

Discussion

This study demonstrated that the ECAS has a good convergent validity with a commonly used dementia screening test, the ACE-III. A comparison of performance on the two assessments revealed that the ECAS has less ceiling effects overall in comparison with the ACE-III, since not one of the healthy participants scored full marks on the ECAS. Performance on the ECAS also seems to be less influenced by intelligence levels in comparison with the ACE-III, as IQ predicted 24% of the variance of the ECAS against 46% in the ACE-III. Visuospatial scores were more dependent on IQ in the ACE-III (7% as compared with the ECAS 2%) which is most likely related to the drawing component of the cube and the clock tasks. Fluency was more dependent on IQ in the ECAS (21%) as compared with the ACE-III (12%) which may be related to the inclusion of a constrained fluency in the ECAS and the more demanding lexical search for four letter words. Overall, IQ predicted more variance in the ACE-III over the ECAS which is most likely related to the different demands of the tests. The ACE-III includes the drawing figures such as a cube, the repetition of complex words and phrases and the inclusion of general knowledge questions. It is likely that some, if not all of these components, may be performed better in people with higher IQ.

All domains of the ECAS correlated with their counterparts in the ACE-III apart from visuospatial functions. The lack of correlation between the measurements of visuospatial abilities may be related to different methods used to assess these

functions in the two tests. The ECAS was created for people with physical disability, and therefore does not include drawing, which is required for the ACE-III. For patients with motor dysfunction impairment on the visual task in the ACE-III could be due to motor problems (weakness, dyspraxia or rigidity, interfering with the quality of drawing), while the ECAS reflects visuospatial functions independently of motor skills. A more in depth comparison of the ECAS and ACE-III in measuring the cognitive decline with patients of different dementias, in particular Alzheimer's Disease and FTD, is needed to evaluate the utility of these tests in diagnosing and assessing change of the different pathologies. The ECAS may also be applied as a useful cognitive screening tool in other neurological disorders characterized by motor as well as cognitive dysfunction, such as Progressive Supranuclear Palsy (30) or Corticobasal Degeneration (31)

The average IQ of some of our groups was higher than what you would expect in a normal population, which may be a limitation of the study. However, the literature indicates that when a sample comes from volunteers rather than randomly selected, the subjects tend to be healthier, have completed more years of education and have higher cognitive abilities (32–35). We attempted to control for this during the recruitment process, by recruiting through churches, sport centers and outside schools; and successfully controlled for years of education. It is of note that most studies which validate dementia screening tests, do not measure IQ but rely on education level as a group descriptor, and it is therefore likely that the samples used in these studies would have a higher IQ than average, similar to our study, since it is a characteristic of the volunteer sample.

IQ, age and gender were significant predictors of the total score of the ECAS. The correlation of the ECAS with age has been found previously in the German-Swiss versions of the ECAS (6,22), the Italian version (7), and the Irish version (5). Education was not a significant predictor of the ECAS when IQ was included in the model because of their strong correlation. The influence of IQ on the ECAS has not been measured previously. Somewhat surprisingly in our sample, gender was also a significant predictor of performance on the ECAS, although much weaker than age and IQ. Gender was not reported to significantly affect ECAS performance in two previous studies (7,23). In our study, women performed slightly better than men on ECAS Total Score. Within the ECAS domains, this effect was most pronounced in the Executive functions predicting 3% of the variance of the score but this difference did not reach significance.

Overall the cutoff scores for abnormality suggested from these findings were similar to those originally proposed (1), but nevertheless, may help to discern the impairment in cases where the score falls in the borderline range (4). In such situations, age and education can be taken into account; for example a score of 105 on the ECAS would not signify an impairment for someone in their 70s and without a university degree, whereas the same score would indicate a possible impairment for someone in their 50s with a university degree.

It is noted that our sample did not include people younger than 51 nor older than 80. People under 50 with a diagnosis of dementia represent 0.35% of the dementia population in Scotland (36), and it is advised in these cases that the same cutoff as 51–65 could be used. Future studies could look at creating separate cutoff scores for those over the age of 80, as they represent a larger percentage of the population with dementia (36).

Conclusions

The ECAS shows good convergent validity with the ACE-III, but is less influenced by intelligence and presents less ceiling effects in comparison to the ACE-III. Therefore, the ECAS is a suitable screening tool in particular in those: where cognitive assessment is complicated by the presence of motor symptoms; with executive dysfunction symptoms; and those highly educated high-performers with mild cognitive impairment or early dementia. The inclusion of both assessments of executive functions and behavior makes the ECAS an appropriate choice for the assessment of frontal lobes disorders.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Appendix III

Validation of The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) in behavioural variant Frontotemporal Dementia and Alzheimer's Disease

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RESEARCH ARTICLE

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Validation of The Edinburgh cognitive and behavioural ALS screen (ECAS) in behavioural variant frontotemporal dementia and Alzheimer's disease

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Abstract

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was developed to assess cognitive and behavioural changes in an anterior frontotemporal syndrome (executive functions, language, fluency and behaviour), common in Amyotrophic Lateral Sclerosis (ALS) and also assesses posterior cerebral dysfunction (memory and visuospatial abilities).

Objectives: To validate the ECAS in behavioural variant Frontotemporal Dementia (bvFTD) without ALS, as compared with Alzheimer's disease (AD), against comprehensive neuropsychological assessment. Compare its sensitivity to that of the Addenbrooke's Cognitive Examination (ACE-III) and investigate behavioural changes in both types of dementia.

Methods: Retrospective study of 16 people with bvFTD (without ALS), 32 with AD, and 48 healthy controls completed the ECAS, ACE-III and extensive neuropsychological assessment.

Results: The ECAS showed higher sensitivity (94%) and marginally lower specificity (96%) than the ACE-III for both the bvFTD and AD groups. The anterior composite subscore was sensitive for bvFTD (94%), and slightly less so for AD (84%), while the posterior composite subscore was sensitive for AD (97%), and less so for bvFTD (75%). All people with bvFTD that were impaired on the ECAS total and anterior composite scores were also impaired on the anterior function's tests of the neuropsychological assessment. A cut-off of four or more behavioural domains affected differentiated well between the bvFTD and AD groups, while a qualitative analysis of the behavioural interview found different themes between groups.

Conclusions: The ECAS is a valid and sensitive assessment for bvFTD without ALS and for AD. The carer behavioural interview makes it particularly suitable to detect behavioural abnormalities related to frontal lobe disorders

KEYWORDS
ACE-III, Alzheimer's disease, behaviour, cognition, dementia, ECAS, frontotemporal dementia, neuropsychology, qualitative, screen

Key Points

- The ECAS showed higher sensitivity (94%) and specificity (96%) for both the bvFTD and AD groups than the ACE-III.
- The ECAS performed well against standard comprehensive neuropsychological assessment with perfect concordance between ECAS Total and Anterior functions composite scores, and performance on the anterior functions' tests of the neuropsychological assessment for the bvFTD group. The ECAS total and posterior functions composite scores also showed good validity against the posterior functions' tests of the neuropsychology assessment for the AD group.
- The most recurrent abnormal behaviour for the bvFTD group was loss of sympathy/empathy (100%), while the most recurrent theme for AD was loss of interest in normal activities (56%). Important thematic differences between diagnoses were (26%) lack of awareness and (66%) lack of manners in people with bvFTD, while AD patients (33%) had a loss of self-confidence.

1 | INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is the most common form of Motor Neurone disease and has been typically characterised as a rapid neurodegenerative disease affecting movement.[1] However, between 10% and 15% of people with ALS fulfil a diagnosis of frontotemporal dementia, most commonly the behavioural variant (bvFTD), and an additional 35% have milder and more specific cognitive impairment indicating a full spectrum of frontotemporal dysfunction.[2,3] The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was developed to assess these cognitive and behaviour changes.[4] It is designed to accommodate physical disability common in ALS, allowing for both written and spoken responses. As such, it is also well suited to assess cognitive functions in other diseases affecting motor functions, including Parkinson's disease and Progressive Supranuclear Palsy.[5]

The ECAS comprises a brief assessment of cognitive domains typically affected by anterior cerebral dysfunction: executive functions (including social cognition), language and verbal fluency, characteristically impaired in ALS. It also includes assessment of the domains which are typically affected by more posterior cerebral dysfunction: memory and visuospatial abilities. These were included to differentiate between the frontotemporal syndrome in ALS, and cognitive deficits resulting from other disorders common in older adults, namely Alzheimer's disease (AD).[6] Furthermore, the ECAS includes a behavioural interview with carers which assesses five domains based on the diagnostic criteria for bvFTD.[7]

This brief assessment is sensitive in detecting mild cognitive impairment (without dementia) in ALS with impairments in executive, language and fluency.[4] It has also been validated against comprehensive neuropsychological testing in ALS, showing good sensitivity and specificity[8,9] and convergent validity against other screening tests; the Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Consortium to Establish a Registry for Alzheimer's disease plus Scale (CERAD plus) and Addenbrooke's Cognitive Examination (ACE-III).[10–12] A recent study demonstrated that both bvFTD with and without ALS were impaired on the ECAS against a healthy control group.[13] The study showed evidence of convergent validity with four standard neuropsychological tests of naming, spelling, cognitive inhibition (executive function) and social cognition. However, the study did not investigate the clinical utility of the test by validating performance against comprehensive clinical neuropsychology assessment or against more routinely used brief cognitive assessment/screening measures. The ACE-III is a commonly used cognitive screen, developed to assess different types of dementia; and was originally validated in both AD and FTD.[14] However, its sensitivity in the detection of bvFTD has been inconsistent.[15–18] Although the ACE-III includes an assessment of fluency (letters and animals), it lacks other tests of executive functions, impairment of which form part of the diagnostic criteria of bvFTD.

In the early stages of both bvFTD and AD, deterioration typically follows a region-specific pattern with frontal lobe dysfunction beginning in the orbitofrontal cortex in bvFTD[19]; and medial temporal and occipitoparietal regions in AD.[20,21] Recent studies have revealed that the ECAS composite score, compromising memory and visuospatial performance, was as sensitive to AD as the ACE-III[22] and was effective at differentiating ALS from AD in a Greek population.[6]

This study aimed to validate the ECAS and further determine its clinical utility in detecting the cognitive and behavioural impairments in bvFTD in comparison with AD. Specifically the aims were to:

- Determine whether the cognitive section of the ECAS is successful in detecting bvFTD without ALS, as compared with AD and healthy controls, and in comparison, with the ACE-III. We hypothesise that

the people with bvFTD would perform more poorly on the ECAS domains typically affected by anterior cerebral dysfunction (executive functions, fluency, language). In contrast people with AD would perform more poorly on those affected by more posterior cerebral dysfunction (memory and visuospatial).

- Determine the validity of the ECAS total score, and composite scores against a comprehensive clinical neuropsychological assessment.
- Investigate the utility of the behavioural interview and determine whether the themes reported differed between diagnostic groups.

2 | METHOD

2.1 | Participants

In this retrospective study we analysed data collected as part of routine clinical neuropsychological assessment from 16 people with bvFTD (9 males, mean age of 61 years [±9.38, 38–72] and education of 12.56 years [±3.24, 10–20]), and 32 with AD (16 males, mean age of 61.18 years [±5.87, 49–71] and education of 12.13 years [±2.17, 10–18]) from the Edinburgh Cognitive Diagnosis Audit Research and Treatment Register (DART), hosted by the Anne Rowling Regenerative Neurology Clinic and the University of Edinburgh. For the quantitative analysis of the behavioural data, we analysed data from a subgroup of 15 people with bvFTD and 24 with AD. Qualitative data was retrospectively obtained from available hand written verbatim records of interviews with the carers/relatives of 15 people with bvFTD (10 males, mean age of 64.13 years [±8.80, 39–76] and education of 12.60 years [±2.99, 10–18]), and 25 people with AD (11 males, mean age of 62.80 years [±5.23, 53–71] and education of 12.04 years [±2.24, 10–18]), (13 and 23 of which were included in the quantitative analyses of the behavioural interview).

Diagnoses were supported by magnetic resonance imaging (MRI) brain and HMPAO-SPECT imaging findings; measures of cerebrospinal (CSF) total Tau, Phosphorylated Tau, and beta amyloid (Ab1-42); and/or disease-causing mutations identified following a neurodegenerative gene panel analysis. Diagnoses were made according to consensus criteria: Rascovsky et al.[7] for bvFTD and McKhann et al.[23] for AD.

Retrospective data of healthy participants (n = 48, 29 males) was from a larger sample previously described by De Icaza Valenzuela et al.[12] Participants were selected to match the patient groups in age (60.06 years [±11.92, 38–78]) and education (13.66 years [±3.03, 9–19]). They were previously recruited from the local population and the Psychology Volunteer Panel of the University of Edinburgh. All were native English speakers without neurological illness or learning disabilities in their medical history.

3 | MATERIALS

Neuropsychological testing included the ECAS, both cognitive and behavioural sections[4] and the ACE-III.[14] Impairments were determined using published abnormality cut-offs. The ECAS evaluates the domains of: memory, visuospatial, fluency, language and executive functions. In addition to the total score, the test also provides a composite score for more anterior cerebral functions (fluency, executive, and language, originally termed ALS-specific as these were the functions typically affected in ALS) and one for more posterior cerebral functions (memory and visuospatial, originally termed ALS non-specific). The ECAS also includes a short behavioural interview that is completed with a relative/carer of the patient. This interview includes 10 questions examining: disinhibition, apathy, loss of sympathy or empathy, perseveration, hyperorality or change in food preferences, and psychotic symptoms (4, see http://ecas.psy.ed.ac.uk). The carer is asked whether each behaviour occurs, to describe, and give examples of the behaviour.

Further extensive comprehensive neuropsychological assessment included a range of tests which are routinely clinically undertaken (Supplementary Table S1). Impairment for each test was determined according to their published cut-off scores for abnormality or based on the fifth percentile of published normative data. To determine the validity of the ECAS anterior and posterior functions composite scores against more extensive testing, the neuropsychological tests were grouped according to the cognitive domains which correspond with the ECAS (executive, language, fluency, memory and visuospatial). Each domain was assessed by two or three neuropsychological tests, and an impairment in a domain was determined when performance on at least one of the tests was impaired. A deficit in anterior functions was classified when one of the following domains was impaired: fluency, language, and/or executive functions. A deficit in posterior functions was classified when either visuospatial and/or memory was impaired.

3.1 | Ethical approval

Patient data was collected from the Edinburgh Cognitive Diagnosis Audit Research and Treatment (DART) Register, South East Scotland A Research Ethics Committee approval 12/SS/0196, IRAS no 103819. The testing of healthy control participants was approved by The Psychology Research Ethics Committee of the University of Edinburgh.

3.2 | Statistical analysis

The data were analysed using SPSS statistics version 22. One-way between groups analysis of variance (ANOVA) were undertaken on parametric data to assess the difference between groups. Homogeneity of variance for all variables was unequal as determined by Levene's test, and we therefore used Welch's ANOVA with Games-Howell post hoc tests. ROC curves assessed the sensitivity and specificity of the ECAS and the ACE-III to detect diagnosis of bvFTD and probable AD against healthy controls.

Transcripts of the behavioural interviews were analysed thematically using the Framework Analysis Method,[24] by two raters

independently. The results of both analyses were subsequently discussed amongst the research group, and an agreement of the final themes was reached.

4 | RESULTS

4.1 | Sensitivity of the ECAS in detecting bvFTD and AD as compared with the ACE-III

There was a significant difference between healthy controls and the two patient groups (bvFTD and AD) in the ECAS Total, composites and all domain scores, and in the ACE-III Total score, but the two patient groups did not significantly differ in any of these scores (see Table 1). 15 of 16 (94%) of the bvFTD group were impaired on the ECAS Total and the ECAS anterior functions composite score, while 12 (75%) were impaired on the posterior functions composite score. 14 of the bvFTD group also completed the ACE-III, of whom 11 (79%) scored within the abnormal range (82 or below) while a further patient scored within the borderline range (82–88). In the assessment of the AD group, 30/32 (94%) were impaired on the ECAS Total score, and 31 (97%) were impaired in the ECAS posterior functions composite score, while 27 (84%) were impaired on the anterior functions composite score. Twenty-five of the AD group completed the ACE-III, of which 23 (92%) scored below the cut-off of 88; and 20 (80%) scored below the cut-off of 82. The frequency of impairment on the ECAS was identical when using abnormality cut-offs adjusted for age and education.[12]

The ECAS total cognitive score showed high and equal sensitivity and specificity (94%, 96% respectively) at detecting both bvFTD and AD using the established cut-off score of 105. In comparison, the ACE-III was less sensitive but had an equal specificity at detecting either diagnosis (bvFTD 79%,98%, AD 83%,98%; see Table 2). The ECAS total score was the most sensitive measure in detecting bvFTD, followed closely by the ECAS anterior functions composite score (see Figure 1A). The ECAS posterior functions composite score was the most sensitive measure in detecting AD, followed by the ECAS total score (see Figure 1A). Although, both composite scores were sensitive to both diagnoses, there was no significant difference in any of the ECAS cognitive scores between patient groups. The anterior composite score of the ECAS had a sensitivity of 52% and a specificity of 43% to differentiate between the bvFTD and AD groups with a cut-off of 62. The posterior composite score of the ECAS had a sensitivity of 96% and a specificity of 36% to differentiate between the AD and bvFTD groups with a cut-off of 23. The ECAS Total Score had a sensitivity of 76% and a specificity of 29% to differentiate between the AD and bvFTD groups with a cut-off of 91.

Power analyses were calculated in G*Power[25] for the comparison of means on the ECAS posterior functions. The current comparison of the bvFTD group with the healthy control group had a large effect size (d = 2.52) and a power of .99 when using an alpha of 0.05; however, the comparison of the bvFTD group and the AD group had a medium effect size (d = 0.55) and a much reduced power of 0.55 when using an alpha of 0.05. Therefore, power may have been an issue in detecting a difference between bvFTD and AD patients on the ECAS composite scores.

4.2 | Validation of the ECAS against comprehensive neuropsychological assessment

Thirteen of the bvFTD group also completed the comprehensive neuropsychological assessment. Twelve (92%) were impaired on at least one of the anterior cerebral function domains of the full assessment (Fluency and/or Language and/or Executive), and all of these were also impaired on the ECAS Total and ECAS anterior functions composite scores giving perfect concordance, with 100% sensitivity and specificity. The ACE-III had a good sensitivity (82%, specificity 100%) to the anterior cerebral function domains of the neuropsychological assessment. One person with bvFTD was impaired only on the posterior functions of the full neuropsychological assessment, and was not impaired on either brief assessment, although fell in the borderline range on the ECAS Total score (scored 108). Of note this person had five behavioural domain changes. The profile of impairment across the tests are summarised in Table S2.

Two AD participants did not undertake the neuropsychological assessment, but all who did were impaired in the posterior functions of the neuropsychological assessment (Memory and/or Visuospatial). However, the ACE-III did not detect five patients, the ECAS total score could not detect two patients, and the ECAS posterior composite score could not detect one patient who were impaired on the posterior functions of the full neuropsychological assessment. Therefore, the sensitivity of these brief assessments at detecting posterior cognitive dysfunction as determined by full neuropsychological assessment, was 93% ECAS Total score, 97% ECAS posterior score, and 79% ACE-III all with a specificity of 100%.

4.3 | Behavioural interview

The carers/relatives of 15 people with bvFTD and 24 people with AD completed the behavioural interview. The majority of the bvFTD group had behavioural changes in five domains, whereas the majority of the AD group had behavioural changes in two domains (see Figure 2). The most common behavioural changes were disinhibition, apathy and loss of empathy in bvFTD and apathy and perseverative behaviour in AD (see Table S3). The total number of behavioural domains impaired differentiated between bvFTD and AD with a sensitivity of 79%, specificity 87% using a cut-off of 4 or more behavioural domains affected.

4.4 | Thematic analysis of carer behavioural interview

Several themes distinguished the bvFTD from the AD patients (see Table 3). The themes below were present in bvFTD only.

TABLE 1 Comparison of ECAS and ACE-III scores between bvFTD, AD, and control groups

	Welch's F	*p* value		Mean (SD) Range	*p* value patient group versus control	*p* value bvFTD versus AD
ECAS: bvFTD (n = 16) AD (n = 32) controls (n = 48)						
ECAS total (max 136)	(2,29.47) = 89.63	<0.001	bvFTD	69.44 (±26.03) 20–108	<0.001	= 0.946
			AD	71.84 (±21.58) 31–112	<0.001	
			Controls	118.44 (±7.98) 102–134		
Language (28)	(2,28.95) = 12.39	<0.001	bvFTD	22.50 (±5.06) 8-27	= 0.008	= 0.748
			AD	23.63 (±4.99) 8–28	= 0.002	
			Controls	27.02 (±1.49) 21–28		
Fluency (24)	(2,31.41) = 40.36	<0.001	bvFTD	8.25 (±6.84) 0–20	<0.001	= 0.180
			AD	12.00 (±6.44) 0–22	<0.001	
			Controls	20.17 (±3.08) 10–24		
Executive (48)	(2,29.51) = 52.11	<0.001	bvFTD	21.81 (±11.23) 2–37	<0.001	= 0.939
			AD	22.97 (±11.12) 7–43	<0.001	
			Controls	40.15 (±3.79) 32–47		
Memory (24)	(2,33.37) = 159.72	<.001	bvFTD	6.88 (±5.88) 0–17	<0.001	= 0.287
			AD	4.28 (±4.51) 0–15	<0.001	
			Controls	19.75 (±3.03) 12–24		
Visuospatial (12)	(2,29.78) = 11.63	<0.001	bvFTD	10.00 (±2.28) 7–12	= 0.041	= 0.433
			AD	8.97 (±3.39) 1–12	<0.001	
			Controls	11.56 (±0.94) 7–12		
Composite score of anterior functions (100)	(2,29.55) = 57.90	<0.001	bvFTD	52.56 (±20.05) 10–79	<0.001	= 0.568
			AD	58.59 (±17.45) 28–90	<0.001	
			Controls	87.13 (±6.42) 72–99		
Composite score of posterior functions (36)	(2,32.20) = 149.89	<0.001	bvFTD	16.88 (±7.39) 7–29	<0.001	= 0.215
			AD	13.25 (±5.71) 3–25	<0.001	
			Controls	31.31 (±3.30) 21–36		
ACE-III: bvFTD (n = 14) AD (n = 25) controls (n = 44)						
ACE-III total (100)	(2,23.68) = 39.84	<0.001	bvFTD	69.93 (±17.63) 22–90	= 0.001	= 1.000
			AD	69.92 (±15.24) 32–98	<0.001	
			Controls	93.82 (±4.26) 82–100		

Abbreviations: ACE, Addenbrooke's Cognitive Examination; AD, Alzheimer's disease; bvFTD, behavioural variant Frontotemporal Dementia; ECAS, Edinburgh Cognitive and Behavioural ALS Screen; SD, Standard Deviation.

TABLE 2 Sensitivity and specificity of the ACE-III and ECAS tests scores in detecting bvFTD and AD versus controls

		bvFTD		AD	
	Abnormality Cut-off	Sensitivity	Specificity	Sensitivity	Specificity
ACE-III total	82	0.786	0.977	0.833	0.977
ACE-III total	88	0.857	0.864	0.958	0.864
ECAS total	105	0.938	0.958	0.938	0.958
ECAS total	110	1.000	0.812	0.969	0.812
Language	26	0.750	0.750	0.656	0.750
Fluency	14	0.875	0.937	0.594	0.937
Executive	33	0.813	0.958	0.844	0.958
Anterior composite	77	0.938	0.917	0.844	0.917
Memory	13	0.750	0.958	0.906	0.958
Visuospatial	10	0.438	0.917	0.531	0.917
Posterior composite	24	0.750	0.958	0.969	0.958

Note: ECAS anterior composite (language, fluency, and executive) and ECAS posterior composite (memory and visuospatial), Abnormality cut-offs are both standard and borderline for both tests (Niven et al., 2015; Hsieh et al., 2013).

Abbreviations: ACE, Addenbrooke's Cognitive Examination; AD, Alzheimer's disease; bvFTD, behavioural variant Frontotemporal Dementia; ECAS, Edinburgh Cognitive and Behavioural ALS Screen

- Immediacy/Impatience (66%)—'If he wants to do something in the moment he does, regardless of the circumstances. He just cannot stop himself.'
- Manners (66%)—'Puts his feet up on the chair in restaurants. He eats off other people's plates and licks the plates in public'
- Loss of initiation of actions (33%)—Needs prompting for daily tasks.
- Egocentrism (33%)—'Only displays interest if it is related to him or when he is the centre of attention, if not he switches off completely'
- Binge eating (46%)—'Eats non-stop…loses control'
- Strange beliefs (20%)—'Won't wash the front of her head because of her diagnosis of FTD'
- Lack of awareness (26%)—Upset about restrictions in his driver's license. Becomes verbally aggressive if he feels relative is suggesting that he has dementia
- Not the same person (46%)—'Not my mum. Used to be incredibly polite and now quite rude'
- Accidental oversights or Mistakes (60%)—'Exploded flask because he put it directly on the hob'

The themes reported for AD only were:

- Eating less or lost weight (32%)—'Doesn't eat well or the full meal'
- Avoids cooking (24%)—'…scared to touch something hot'
- Stopped reading (24%)
- Misplacing items (8%)—'Teapot in the fridge'
- Difficulties solving problems (20%)—'Couldn't figure out how to plough a field he did every year'
- Lost confidence (33%)—'Apologizes a lot'

The most common themes in the people with bvFTD were: loss of sympathy/empathy (100%)—'Always used to be caring and giving, but not so much anymore,' loss of interest in normal activities/hobbies (80%), reduced social interest, even with family and close friends (80%), simple repetitive movements (80%; such as scratching and tapping), eating more carbohydrates (80%), buying impulsively (73%)—'cannot pass a shop without buying things immediately,' and compulsive behaviour (73%)—'Besotted with puzzles, does them obsessively.' The most common themes in AD were: loss of interest in normal activities/hobbies (56%), impulsive decisions (33%), offensive/inappropriate jokes or comments (33%), and lost confidence (33%)—'apologizes a lot.'

5 | DISCUSSION

The ECAS was successful in detecting the cognitive changes present in bvFTD and AD compared to healthy controls, although there were no significant group differences in scores between the two types of dementia. Using published abnormality cut-offs,[4] the ECAS anterior functions composite score (sensitivity of 94% and a specificity of 92%; which comprises the domains of Fluency, Executive Functions and Language) and the ECAS Total Score (sensitivity 94% and specificity 96%) were the most effective measures in our study at detecting bvFTD when compared to healthy controls. The percentage of impairment on the ECAS in the bvFTD group in our sample (94%) was similar to what has been previously reported (91%).[13] The posterior functions composite score (Memory and Visuospatial domains; sensitivity 97% and specificity 96%) was the most effective measure at detecting AD when compared to healthy controls. Although the abnormality

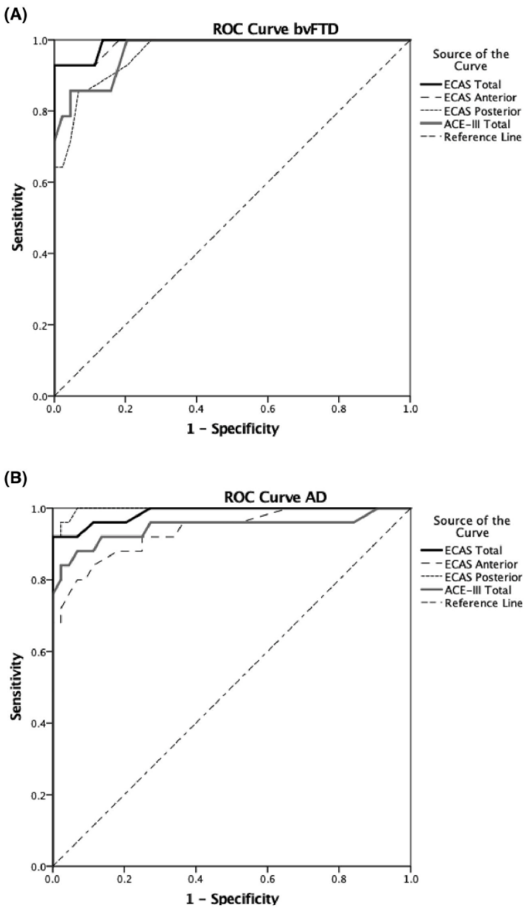

FIGURE 1 Comparison of the ECAS and the ACE-III in detecting bvFTD (A) and AD (B) against controls. ECAS Anterior composite (language, fluency, and executive), ECAS Posterior composite (memory and visuospatial). ACE, Addenbrooke's cognitive examination; ECAS, Edinburgh cognitive and behavioural ALS screen

cut-off of 88 of the ACE-III had a slightly higher sensitivity (96%) than the ECAS Total Score (sensitivity 94% and specificity 96%), it had a much lower specificity (86%) at detecting AD. In contrast the abnormality cut-off of 82 of the ACE-III had a lower sensitivity although relatively equal specificity at detecting both bvFTD (79%, 98%) and AD (85%, 98%).

The trade-off between sensitivity and specificity is important, particularly when deciding which cut-offs may be best suited for detecting a diagnosis or establishing cognitive impairments. Although both are multi-domain assessments, the ECAS and ACE-III are screening tests which should be used to indicate whether further neuropsychological investigation is warranted. In this situation, sensitivity is usually of more importance than specificity, as the screening test should capture all those cases who may have the disease/cognitive impairment. Nevertheless, it is important to balance between a small increase of sensitivity at the expense of a larger decrease in percentage of specificity.[26] The higher cut-offs of both tests (110 for the ECAS and 88 for the ACE-III) were more

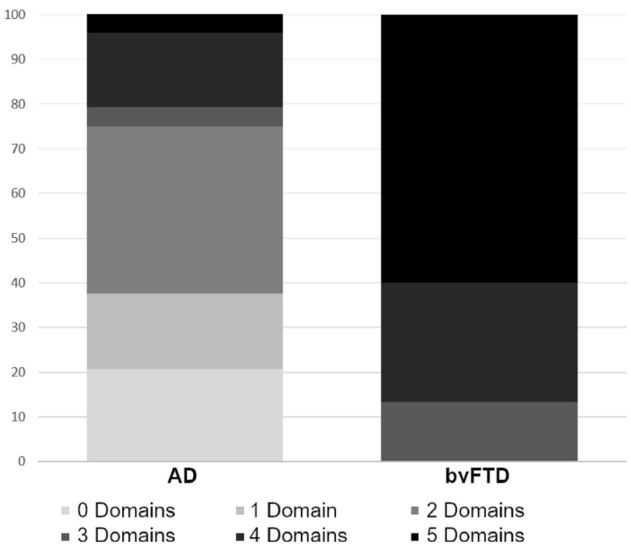

FIGURE 2 Percentage of the number of behavioural domains affected. Alzheimer's Disease (AD) n = 24, behavioural variant Frontotemporal Dementia (bvFTD) n = 15.

sensitive to both diagnoses but with much lower specificity. Therefore, the ECAS Total Score with an abnormality cut-off of 105, showed high sensitivity without a large cost of specificity.

The ECAS also showed strong validity at detecting cognitive impairments as compared with the gold standard of neuropsychological assessment. There was a perfect concordance of the ECAS scores and impairment on the anterior functions tests of the neuropsychological battery for the bvFTD group with 100% sensitivity, and 100% specificity. The only bvFTD patient that was unimpaired on the ECAS was also not impaired in the anterior functions' tests of the neuropsychological battery but showed changes in the five behavioural domains of the ECAS. The presentation of behaviour change without cognitive impairment in FTD has been previously demonstrated.[27] There was also good concordance between the deficits detected on the ECAS Total and posterior functions composite scores and impairments in posterior functions tests in the comprehensive neuropsychological assessment for the AD group. The ECAS Total score failed to detect two AD patients, while the ECAS posterior functions composite score failed to detect one patient only and the ACE-III failed to detect five patients with cognitive impairments as determined by the neuropsychological assessment. The original ECAS validation study in people with ALS also involved a comparison against extensive neuropsychological assessment, but it was a prospective study where each cognitive domain was assessed by three standardised tests.[8] Impairment in a domain of the neuropsychological assessment was defined when two out of three tests were impaired. The current study was retrospective and included data from routine clinical neuropsychological assessment, in which for some domains only two standardised tests were used. So as not to dismiss evidence of impairment and to be consistent across all our cognitive domains we defined impairment on a domain if one test was impaired only.

These findings indicate the possible utility of the ECAS in a broader clinical setting for the screening of the dementias. The ECAS has already been shown to be an effective cognitive screen for movement disorders of ALS,[4] Parkinson's disease, and Progressive Supranuclear Palsy.[5] Since the total score of the ECAS was more sensitive to bvFTD and AD than the ACE-III; and it includes a behavioural interview, the ECAS could be used as an alternative for the ACE-III for a cognitive screen in the clinical setting. The ECAS also has the additional advantage of being less prone to ceiling effects and is less influenced by IQ than the ACE-III[12]; and therefore, very useful for a young onset population in a dementia clinic.

In the quantitative analysis of the behavioural data, most bvFTD patients tended to have behavioural changes in the five domains, whereas AD patients had behavioural changes in two domains. Although only three behavioural symptoms must be present to meet current diagnostic criteria for bvFTD,[7] the cut-off of 4 or more behavioural domains affected had a higher sensitivity (79% sensitivity and 87% specificity) to differentiate between the diagnoses of

TABLE 3 Themes from the analysis of the behavioural interview bvFTD (n = 15) AD (n = 25)

bvFTD %	Themes	AD %
Impulsivity and disinhibition		
73	Buying impulsively	12
66	Immediacy/impatience	-
66	Loss of manners or decorum	-
60	Impulsive decisions	33
60	Offensive/inappropriate jokes or comments	33
46	Aggression	8
33	Hypersexual behaviour	8
Apathy		
80	Loss of interest in normal activities/hobbies	56
33	Emotional flatness	24
33	Loss of initiation actions	-
20	Neglect of self-care	12
Social interactions		
100	Loss of sympathy/empathy	32
80	Reduced social interest	32
33	Egocentrism	-
Perseverative behaviour		
80	Simple repetitive movements	24
73	Compulsive behaviour	32
40	Hoarding	20
26	Fixed routine	12
Eating and preparing food		
80	Eats more carbs	24
46	Binge eating	-
-	Eats less/lost weight	32
-	Avoids cooking	24
Psychosis		
46	Paranoia	24
20	Hallucinations	12
20	Strange beliefs	-
Other		
60	Accidental oversights/mistakes	-
46	Disorientated	20
46	Not the same person/change personality	-
26	Lack of awareness/anosognosia	-
-	Lost confidence	33
-	Stopped reading	24
-	Solving problems	20
-	Misplace items	8

Abbreviations: AD, Alzheimer's disease; bvFTD, behavioural variant Frontotemporal Dementia.

bvFTD and AD in this study. The current diagnostic criteria may therefore not be as effective at differential diagnosis, particularly as some people with AD show behavioural changes as revealed here.

Apathy was one of the most prevalent behaviours in both patient groups (bvFTD 100%, AD 58%), which is consistent with the literature.[28–30] Disinhibition was very prevalent in the bvFTD group (100%), and perseverative behaviour was the second most common behaviour in the AD group (45%, although it was also reported in 80% of bvFTD patients), which is congruent with the literature.[31,32] Identifying apathy as a behavioural change in the screening process could help orientate the carers and clinicians to manage this symptom.

The qualitative thematic analysis of the behavioural interview uncovered a number of themes which differentiated between the two patient groups. Themes present in people with bvFTD only were centred around loss of control (immediacy, loss of manners, binge eating), changes in personality (egocentrism and not being the same person), loss of initiation actions, strange beliefs, anosognosia, and accidental oversights/mistakes. The most common theme in bvFTD patients was loss of sympathy/empathy, followed by compulsions; both of which have been reported previously.[33–36] Of note both of these behaviours were also reported in ~a third of people with AD. Although changes in sympathy/empathy and compulsions may not help with differential diagnosis, they are still important for clinical management. The most common themes found in AD only were reduced eating and/or lost weight, avoids cooking, loss confidence and has stopped reading. Weight loss in Alzheimer's has been widely reported.[37,38] Avoidance of cooking observed in the AD group seem to emerge from fear of having an accident. Awareness of diagnosis in AD unlike the lack of awareness in people with bvFTD could play a role in whether people avoid certain activities and the loss in self-confidence. The types of behaviour change found in our study was in accord with the results of some previous studies; where bvFTD patients have been shown to have more compulsive behaviours, increased eating (specifically carbohydrates and binge eating), more selfishness with less social awareness, and a lack of insight regarding their own functional impairment when compared to AD patients.[39–42] However, previous studies have used more quantitative questionnaires, where a behaviour is present or not; while in the current study, although this is used for the number of domains affected, the descriptions of behaviour change were further defined by exploring the interviews qualitatively through thematic analysis. The findings demonstrate that certain behaviours may help in differential diagnosis.

The overlap in cognitive presentations with memory and executive dysfunction between these two types of dementia can make differential diagnosis very difficult. The cognitive section of the ECAS has corresponding limitations and therefore although able to detect each diagnosis, cannot reliably differentiate between the two. However, the results of the ECAS behavioural screen proved effective in differentiating bvFTD from AD. It is noteworthy that the ECAS posterior composite score was sensitive to the bvFTD group, although less than the AD group, and 75% of the bvFTD group were impaired on this score. People with bvFTD can experience memory impairments, as the processes of encoding and retrieving often

require executive functions for organising the information.[43] In parallel, the ECAS anterior composite score was also sensitive to AD, but less than the bvFTD group, and 84% were impaired on this measure. It is well recognised that people with AD may also experience executive dysfunction, and for example impairments have been repeatedly shown on tests of divided attention.[44] In addition, we have demonstrated that the between group comparison of the ECAS composite scores may have been under powered, particularly given the relatively small sample size of the bvFTD group. Nevertheless, despite this overlap in presentation, distinctive behavioural features were present which distinguished between the two groups. Of note, the ECAS behavioural screen was designed to detect behaviour changes which are typical of bvFTD, and was therefore closely based on the diagnostic criteria.[7] It was also developed to provide a standardised method for measuring and assessing these changes. Given that the bvFTD group were diagnosed on the basis of this same criteria, it is inevitable that the screen would be sensitive to the types of behaviour change in this group."

We had expected to find a difference between the bvFTD and AD samples with the composite scores, as one study previously found the ECAS posterior score to be sensitive at differentiating between AD and ALS patients.[6] However, ALS presents with a heterogenous spectrum of cognitive change, with at least 50% of patients typically cognitively intact. In line with this only 50% of their ALS patients were impaired on the ECAS Total score, whereas 94% of our bvFTD sample was impaired, indicating more severe and extensive impairment in the current patient group. Furthermore, the AD group from this previous study[6] were older than the current study (mean age of 67.19 vs. 61.18 years old respectively), and it is possible that early onset AD (<65 years of age) may have a slightly different cognitive profile from late onset.[45,46] Nevertheless, a further study which compared the Greek version of the ECAS with the ACE-III[22] found similar results to those reported here; in which both composite scores were sensitive to AD, with the posterior composite score being the most sensitive measure. Strengths of this study were its thorough investigation of the clinical validity of the ECAS with these dementia groups and the inclusion of well characterised patients (diagnoses supported by imaging, CSF, and/or genetic analysis). The validation against comprehensive neuropsychology reinforces the use of the ECAS as a useful screening tool for the cognitive assessment of patients with and without a motor disorder. Although some of the behavioural differences between bvFTD and AD have been investigated previously in other studies with quantitative questionnaires and semi structured interviews, this is the first study that analyses and compares the different themes reported on the ECAS behavioural screen in people with bvFTD and AD. The limitations of this study include the sample size, particularly for the bvFTD group, which resulted in a lack of power for the comparison between patient groups. Furthermore, the retrospective study design limited the analysis of the available neuropsychological test data.

The findings demonstrate that the ECAS could be used by clinicians to evaluate suspected frontal lobe disorders and AD. Using the ECAS as a first line screen for cognitive impairment where there is a suspicion of bvFTD could speed up the process of assessment, diagnosis and treatment for this disease. Behavioural interviews with the carers add to the utility of the cognitive screens and may bring to light possible changes which may be important for clinical management. The ECAS could also heighten awareness in carers of the possible behavioural changes the patients could experience, which may facilitate reporting to their health professional in the future.[47]

6 | CONCLUSIONS

The ECAS was successful in assessing the profile of cognitive and behavioural impairment in both bvFTD and AD. The combined score for memory and visuospatial assessment was particularly sensitive to AD, while the combined score for executive, fluency and language functions was sensitive to bvFTD. The ECAS also shows strong validity against full neuropsychological assessment and was more successful than the ACE-III at detecting impairment in both bvFTD and AD. The inclusion of a behavioural interview in the ECAS makes it particularly suitable to aid in the diagnosis of behavioural abnormalities related to frontal lobe disorders, and can aid in distinguishing between bvFTD and AD.

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CONFLICT OF INTEREST

The authors have no known conflict of interest in relation to the publication of this paper.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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