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Trinity College Dublin
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Delineating the Impact of Executive Dysfunction on Social Cognition for Patients and Caregivers in Amyotrophic Lateral Sclerosis

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A dissertation submitted to Trinity College Dublin in fulfilment for the award of Doctor of Philosophy (PhD)

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September 2016

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Abstract

Amyotrophic Lateral Sclerosis (ALS) is a rapidly progressive neurodegenerative disease that implicates both motor and cognitive function, and is the most prevalent Motor Neuron Disease (MND). ALS is a clinically heterogeneous disease, one that requires detailed neuropsychological assessment to clarify the presenting cognitive phenotype of the disease. The main aim of this thesis was to investigate the impact of ALS on social cognitive processes, while considering other cognitive functions known to decline in some patients i.e., executive function.

This thesis employed a cross-sectional population-based case-controlled design, complemented by aspects of longitudinal follow-up. This thesis was further complemented by the Irish ALS register, for both ancillary data and for recruitment purposes. Data for this thesis relied on home-based cognitive assessments, as well as clinic-based recruitment and screening. Patient performance was compared to age-, gender-, IQ-, and education-matched healthy controls.

Overall, the findings from this thesis suggest that social cognitive deficits do occur in ALS patients, and appear to be associated with the negative trajectory of executive dysfunction, within this cohort. This research shows the reliability and validity of the measure used, provides normative data, and details the difficulty and discrimination coefficients of the test. This thesis highlights the need for within group analyses by demonstrating greater social cognitive impairment in bulbar-onset ALS patients. This thesis also reports the burden experienced by caregivers, and identifies predictors, which may be informative for clinical intervention. These findings have many practical clinical implications, which may inform future ALS research.

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2014	Federation European Societies of Neuropsychology Bursary	**€500**
2013	British Neuropsychological Society Bursary	**€500**

Glossary Of Terms

AC.....Anterior Clingulate

ALS.....Amyotrophic Lateral sclerosis

ALSFRS-R.....Revised Amyotrophic Lateral Sclerosis Functional Scale

AR.....Articulatory Rehearsal

bvFTD.....Frontotemporal degeneration- Behavioural variant

BKDS.....Backward Digit Span

BNT.....Boston Naming Test

BSAT.....Brixton Spatial Anticipation task

CAG.....Cytosine Adenine, Guanine

CatVFI.....Categorical verbal fluency index

CE.....Central Executive

CI .....Confidence Intervals

CO2.....Carbon Dioxide

DAT.....Dementia of the Alzheimer's Type

D-KEFS.....Delis-Kaplan Executive Function System

DTI.....Diffusion Tensor Imaging

DSM-IV.....Diagnostic and Statistical Manual of Mental Disorders

ECAS.....Edinburgh Cognitive and Behavioural Assessment

FALS.....Familial Amyotrophic Lateral Sclerosis

FAB.....Frontal Assessment Battery

FrSBe.....Frontal System Behavioural Scale

FTLD.....Fronto-temporal lobar degeneration

FSIQ.....Full Scale Intelligent Quotient

FVC.....Forced Vital capacity

FUS.....Fused In Sarcoma

HADS.....Hospital Anxiety and Depression Scale

HC.....Healthy Controls

HD.....Huntington's disease

HR.....Hazard Ratio

IQR.....Inter-Quartile Range

IS.....Inner Scribe

LM-I..... Logical Memory Task-Immediate Recall

LM-II.....Logical Memory Task-Delayed Recall Trial

LM-Ret.....Logical Memory Task-Retention Trial

MMSE .....Mini Mental State Examination

MND.....Motor Neurone Disease

MoCA.....Montreal Cognitive Assessment

MRI.....Magnetic Resonance Imaging

MRS.....Magnetic Resonance Spectroscopy

NIV.....Non-Invasive Ventilation

O2.....Oxygen

PET.....Positron Emission Tomography (PET)

PD.....Parkinson's Disease

PLS.....Primary Lateral Sclerosis

PMA.....Progressive Muscular Atrophy

PNFA.....Progressive Non-Fluent Aphasia

PS..... .....Phonological Store

OR.....Odds ratio

RBANS.....Repeatable Battery for the Assessment of Neuropsychological Status

RCI.....Reliable Change Index

RCPM .....Raven's Coloured Progressive Matrices

RMET.....Reading the Mind In the Eyes Task

ROCF.....Rey-Osterrieth Complex Figure Test

SEF.....Stroop Executive Factor

SD.....Standard Deviation

SemD.....Semantic Dementia

SNIP.....Sniff Nasal Inspiratory Pressure

SPECT.....Single Photon Emission Computed Tomography

SOD1..... .....SuperOxide Dismutase 1

Stroop CWIT.....Stroop Colour Word Interference Task

TARDBP.....TAR-DNA-Binding Protein gene

TDP-43.....Tar DNA-binding protein 43

ToM.....Theory of Mind

TOPF^{UK}.....Test of Premorbid Function – UK Edition

UBQLN2.....Ubiqulin 2

UHDRS.....,Unified Huntington's Disease Rating Scale

VBM.....Voxel-based Morphometry

VC.....Visual Cache

VFI .....Verbal Fluency Index

WMS.....Wechsler Memory Scale

WTAR.....Wechsler Test of Adult Reading

1.0 A Clinical Introduction to ALS

1.1 A Clinical Introduction to Amyotrophic Lateral Sclerosis

1.2 Homogeneity and Heterogeneity of ALS

1.3 Classifying Cognitive Impairment in ALS

1.4 Behaviour Change in ALS

1.5 Epidemiology and Aetiology of ALS in Ireland

1.6 Diagnostic Criteria

1.7 Staging in ALS

1.8 Clinical Management and Treatment for ALS

1.9 Caregiver Burden in ALS

1.10 Caveats of Repeat Neuropsychological Assessment in ALS

1.11 Rationale for the Present Study

1.12 Ontological and Epistemological Approach

1.13 Summary

1.1 Amyotrophic Lateral Sclerosis

Motor Neuron Disease (MND) is a clinical classification, which refers to a class of progressive neurodegenerative disorders, characterised by selective atrophy of upper and/or lower motor neurons in the central nervous system (Burrell, et al., 2016). Amyotrophic Lateral Sclerosis (ALS) is the most prevalent form of MND and is commonly used interchangeably with the 'MND' term in the literature. Throughout this thesis 'ALS' will refer exclusively to the most prevalent subtype while 'MND' will refer to all disease subtypes, including ALS. Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects nerve cells in the brain (upper motor neurons) and the spinal cord (lower motor neurons). Motor neurons reach from the brain to the spinal cord and from the spinal cord to the muscles throughout the body. The progressive degeneration of the motor neurons in ALS eventually leads to their death. A-myo-trophic comes from the Greek language. "A" means no. "Myo" refers to muscle, and "Trophic" means nourishment – "No muscle nourishment." When a muscle has no nourishment, it "atrophies" or wastes away. "Lateral" identifies the areas in a person's spinal cord where portions of the nerve cells that signal and control the muscles are located. As this area degenerates it leads to scarring or hardening ("sclerosis") in the region. When the motor neurons die, the ability of the brain to initiate and control muscle movement is lost. With voluntary muscle action progressively affected, patients in the later stages of the disease may become totally paralyzed. A compromised respiratory function is the leading cause of death in late stage ALS.

ALS is a fatal neurodegenerative diseases encompassing motor involvement, cognitive decline, and has associated psychiatric features (Abrahams, 2000). It is a rapidly progressive condition involving the degeneration of both upper and lower motor neurons, characterized by weakness, spasticity and wasting evidenced in the limbs (Abrahams et al., 2000). There is no known cause, cure or definitive pre-symptomatic test for ALS. Other types of Motor Neuron Diseases (MND) have differing phenotypes and clinical presentations depending on the degree of upper/lower motor neuron involvement (See Figure 1), such as Progressive Muscular Atrophy (PMA) and Primary Lateral Sclerosis (PLS). ALS is the most common type of MND in Ireland (O'Toole et al., 2008) and, indeed, the world (Watermeyer et al., 2015).

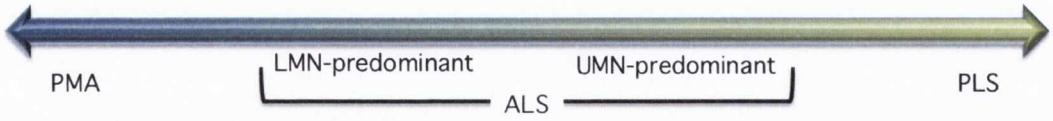

Figure 1.1. Clinical phenotypes of MND, depending on the degree of upper/lower motor neuron involvement.

ALS is a condition with high clinical diagnostic accuracy during life due to its clinical presentation, where motor decline is a major component, and constitutes a predominantly progressive impairment of cognitive processes, specifically executive function. Based on clinical, genetic, and recent pathological insights (Devenney, Vucic, Hodges, & Kiernan, 2015), ALS is now considered to exist on a cognitive-behavioural continuum with Fronto-temporal Dementia (FTD; See Figure 2).

Approximately 15% of ALS patients are diagnosed with a behavioural variant of FTD (bvFTD; Byrne et al., 2012).

Figure 1.2. Cognitive-behavioural continuum between ALS, ALS-FTD, and FTD.

This chapter will introduce the core clinical, cognitive, pathological characteristics of ALS. Furthermore, this chapter will also introduce core concepts discussed within the ALS literature, which are pertinent to subsequent chapters.

1.2 Homogeneity and Heterogeneity of ALS

Until recent years, the prevailing view was that ALS was a disease affecting the motor system exclusively, however considerable evidence now exists to the contrary (Giradi, MacPherson, & Abrahams, 2011; Kiernan et al., 2011). In addition to an already changing clinical view of ALS (Taylor et al., 2013), underlying pathologies (Williams et al., 2012), genetic factors (Neumann et al., 2006), neuroanatomical network disturbances (Iyer et al., 2015), and distinct neuropsychological profiles (Phukan et al., 2012) illustrate a wide clinical heterogeneity within ALS (Gordon et al 2011).

Cognitive decline in ALS is also heterogeneous in presentation, although decline is most often associated with executive function, social cognition, and language (Elamin et al., 2012;

Grossman et al., 2008; Watermeyer et al., 2015). In ALS, cognitive and behavioural impairments correlate with neuroanatomical regions localized mainly in the frontal and temporal lobes (Schreiber et al., 2005), specifically fronto-striatial and temporo-limbic regions of the cerebral cortex (Abrahams et al., 2000).

Cognitive and behavioural decline in ALS is known to occur due to the pathological nature, and natural history of the condition, and it is for this reason that posterior cognitive function is relatively preserved in non-demented ALS i.e., perceptual reasoning (Abrahams et al., 2015). Behavioural variant fronto-temporal dementia (bvFTD) is known to precede the motor presentation of ALS with frontotemporal dementia (ALS-FTD). This overlap is due to a differing pathology associated with the early stages both diseases (outlined in detail by Burrell, Halliday, Kril, Mittner, Götz, Kiernan, & Hodges, 2016), illustrated in figure 1.3, which may co-occur as the disease progresses. Frontotemporal dementia (FTD) can clinically present with prominent behavioural changes and relatively intact cognitive function. Other variants of FTD include semantic dementia (SD), and progressive non-fluent aphasia (PNFA), which initially implicate language function. The clinical diagnostic criteria of patients with FTD-SD and FTD-PNFA can be seen in appendix 5.

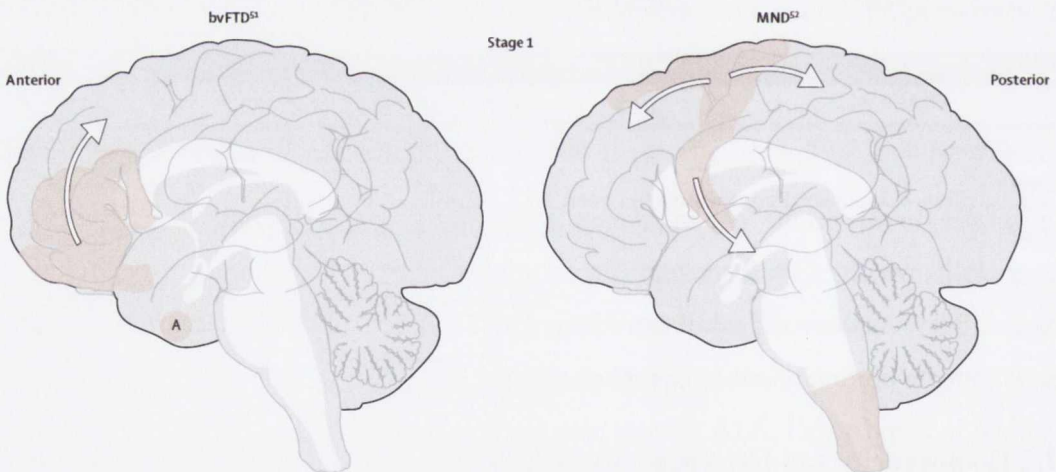

Figure 1.3. Red colouring denotes pathological implication. (A) labelled bvFTD represents pathology known to occur in the anterior frontal region, progressing toward the motor cortical regions of the frontal lobe. The right-sided MND figure displays the pathology associated 'typical' ALS, whereby the motor cortex is primarily affected, with anterior frontal regions implicated, as well as the brain stem.

1.3. Classifying Cognitive Impairment in ALS

In recent years there has been a growing interest in the cognitive profile of patients with ALS (Raaphorst, DeVisser, Linssen, DeHaan, & Schmand, 2010), fully considered in Chapter 2. Cognition is known to decline in ALS, albeit at a differing trajectory to the deterioration of motor features (Trojsi et al., 2013). Executive functions are the main cognitive processes

affected in ALS (Elamin et al., 2011), with lexical fluency and language processes also affected (Phukan et al., 2012). Recently, an Irish population-based longitudinal study demonstrated the efficacy of categorizing patients with ALS into cognitive-specific groups, based on their performance on a battery of neuropsychological tests. Survival analyses indicate that patients with executive dysfunction, or multiple cognitive impairments have the shortest mean survival time (Byrne et al., 2013; Elamin et al., 2011).

To this end, it is of fundamental importance to utilize a system modelled on internationally accepted criteria (Phukan et al., 2011; Strong et al., 2009), whereby one can accurately categorise patients based on their performance on cognitive tests (Table 1.1).

Table 1.1: Cognitive classification according to Phukan et al., (2011).

Classification	Description	Criteria
NCA	No cognitive abnormalities	No impairment on cognitive assessment.
ALS-NECI	Non-Executive Cognitive Impairment	Impairment within the domains of language and/or memory, with preserved executive function.
ALS-Ex (Single/Multiple)	Impairment in executive function (single), or in association with other cognitive domains (multi)	Impairment within the domain of executive function, or in executive function and other cognitive domains.

1.4 Behavioural Change in ALS

The co–existence of ALS symptoms and overt progressive behavioural change is recognised as ALS–bvFTD. In pure bvFTD, changes in personality, affect and social conduct are typical of the clinical picture, reflecting atrophy of the orbital and mesial frontal lobes (Neary et al., 2005). Emotional blunting or apathy as well as disinhibited, preservative and stereotyped behaviour may present, either alone or alongside executive dysfunction.

Patients may display reduced empathic response to others and lack insight into (anosognosia) or concern for (anosodiaphoria) their illness (Mendez & Shapira, 2011; Neary et al., 1998). Psychotic symptoms may also be present, complicating the diagnosis (Floris et al., 2013; Snowden et al., 2013; Woolley et al., 2007b). Altered eating habits are also common (Ikeda et al., 2002; Woolley et al., 2007a). A recent systematic review of nine studies (reporting 170 cases) described a similar profile of behavioural change in ALS–bvFTD to that of the pure bvFTD form, noting apathy, perseveration and disinhibition as the most commonly reported changes (Raaphorst et al., 2012).

1.5 Epidemiology and Aetiology of ALS in Ireland

In Ireland approximately 5.1% (95% CI: 4.1-6.1%) variation in ALS is thought to be familial (Byrne et al., 2012) i.e., a known genetic cause is identified. The incidence rate of ALS in

Ireland is reported to be 6.0 per 100, 000 (95% CI: 5.1-6.9) for the population aged 45-75 years (O'Toole et al., 2008). Epidemiological studies of ALS in Europe have shown the incidence rate to be much lower at 2.16/100,000. Consistent with the European norm, there is a rapid decrease in incidence rates after 80 years of age (Kiernan et al., 2011). No consensus criteria exist to distinguish between familial ALS, sporadic ALS and other genetic factors influencing the cause of ALS. This can be problematic within population-based studies (Byrne et al., 2010).

In ALS there are known genetic manifestations greatly affecting the disease presentation, prognosis, and ultimately patient survival (Lattante, Ciural, rouleau, & Kabashi, 2015). Due to the severe and multisystem impact caused by the presence of expanded nucleotides i.e., extensive cortical and subcortical fronto-temporal atrophy many ALS cohorts are stratified depending on the presence of genetic expansions for research purposes (Bede et al., 2013).

One major discovery pertinent to ALS, and the presence of FTLD symptoms in particular, was the discovery of an expanded hexanucleotide expansion located at chromosome 9p21.2 termed *C9orf72* repeat expansion (Khan et al., 2012).

The C9orf72 mutation was a significant scientific discovery, as it was the first pathogen identified as a genetic link between familial FTD and ALS (Boeve & Graff-Radford, 2012). An individual with ALS, and genetically confirmed abnormal C9orf72 expansion, has a reduced lifespan by approximately 6 months from the time of disease onset (Byrne et al., 2013). The C9orf72 mutation is the most commonly identified pathogen associated with ALS, where penetrance is known to occur within approximately 10% of ALS cases (Lattante et al., 2015).

Mutations in the superoxide dismutase–1 (SOD1) genes, the Transactive response DNA Binding Protein 20 (TARDBP) genes and the fused in sarcoma/translated in lipsarcoma (FUS/TLS) gene expansions have been reported in ALS patients, which clinically correlate with the presence of FTD like features (Andersen, 2006; Daoud et al., 2009).

1.6 Diagnostic Criteria

Unlike some other neurodegenerative diseases i.e., Huntington's disease, there is currently no single diagnostic test or clinically suitable biomarker that can be used to diagnose ALS. A clinical diagnosis of ALS is made following clinical investigation. Criteria centre on the progressive nature of the illness, simultaneous upper and lower motor neuron involvement (as seen in Figure 1.1), the absence of sensory signs, and the exclusion of an alternative aetiology

for the patient's symptoms (O'Brien, Whitehead, Jack, & Douglas-Mitchell, 2011).

Traditionally developed to assist recruitment to clinical trials, the 'El Escorial Criteria', outlined in Table 1.2 (Brooks et al, 2000) is clinically employed to categorise a patient's ALS into groups ranging from "Suspected", "Possible", "Probable" or "Definite" (See Appendix 3). In order to increase the sensitivity and specificity of the diagnostic criteria, electromyography (EMG) is incorporated to assess muscle weakness and wasting over time.

Table 1.2. El Escorial Criteria adapted from Brooks et al., (2000); See appendix 3.

The diagnosis of ALS requires the presence of:	
A1	Evidence of LMN degeneration by clinical, electrophysiological or neuropathological examination
A2	Evidence of UMN degeneration by clinical examination
A3	Progressive spread of symptoms or signs within a region or to other regions
with the absence of:	
B1	Electrophysiological and pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration
B2	Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs

1.7 Staging in ALS

To map progression and support classification, staging systems have been suggested to provide a universal and objective measure of disease progression with benefits for patient care, resource allocation, and research classifications (Roche et al., 2011). Criteria to assist clinical neurologists in detailing the progression of ALS, and documenting the rate of progression traditionally consider the motor features of the disease, and quantify change over time. Two main staging systems are used within ALS, the Kings Criteria, and MITOS Staging (Chio et al., 2015; See Appendix 4). Cognitive assessment alongside staging could provide greater information needed for prognosis and clinical trial recruitment.

1.8 Clinical Management and Treatment for ALS

Although ALS remains incurable, many of the symptoms of the disease are treatable. Disease management is therefore focused on symptom control, in order to provide the best level of patient functioning and Quality of Life (QoL). The variety of symptoms and treatment options available necessitates the involvement of clinicians from diverse but related fields. A multidisciplinary approach appears to prolong survival, decrease hospital admissions, and enhance quality of life for patients attending tertiary clinics with such care models (Chio et al., 2006; Van den Berg et al., 2005).

Sialorrhea or abnormal saliva production, which affects 50% – 70% of ALS individuals (Miller et al., 2009), may be moderated through the introduction of medications such as glycopyrrolate, hyoscyamine or amytriptyline, a tricyclic antidepressants. In addition, botulinum toxin injections into the parotid and submandibular glands are effective for pronounced secretions (Jackson et al., 2009).

Maintenance of body weight and healthy nutritional intake forms an important care priority, as nutritional status represents a prognostic risk factor in ALS (Desport et al., 1999; Stambler et al., 1998). Recently, a retrospective study reported that patients with a weight loss exceeding 10% of that at time of diagnosis was associated with shorter disease duration (Limousin et al., 2010). Percutaneous endoscopic gastrostomy (PEG) is a procedure in which a tube is inserted directly into the stomach. Medication and crushed food can then be provided through the tube. A median survival benefit of 5 months has been demonstrated in ALS patients accepting this procedure (Spataro et al., 2011).

Respiratory dysfunction is a common feature in the majority of ALS cases at some stage of the disease duration. Incipient weakness of the respiratory muscles may be subtle but progress to more severe signs. These symptoms include dyspnoea (shortness of breath) on exertion or at rest; orthopnoea (shortness of breath when in the supine position) and nocturnal hypoventilation (associated with sleep disturbance; morning headaches; daytime sleepiness and poor concentration).

Defective swallow, weakened cough manoeuvre and bulbar symptoms may also be present, leading to excessive throat secretions and the blockage of the air passage, which in turn may lead to increased risk of pulmonary infection and aspiration. The management of respiratory symptoms comprises of invasive and non–evasive approaches. Forced Vital Capacity (FVC) is a standard physiological marker of respiratory function, however, this measure may be distorted for patients with bulbar weakness, as its assessment requires sufficient lip seal. For this reason, sniff nasal inspiratory pressure (SNIP), may be the preferred method for monitoring respiratory sufficiency in patients with moderate bulbar symptoms.

An excess of the excitatory neurotransmitter glutamate is associated with several neurodegenerative disorders, including ALS (Lau & Tymianski, 2010; Shaw & Ince, 1997). Riluzole, originally developed as an anti–epileptic drug, inhibits glutamate transmission and is the only approved disease-modifying treatment for the disorder.

1.9 Caregiver Burden in ALS

The term caregiver burden is used to describe changes associated with Quality of Life, but rarely is deconstructed in ALS (Chio et al., 2014; Rabkin, Wagner, & Del Bene, 2000). Caregiver burden encompasses both *objective* burden (Bruletti et al., 2014) i.e., events and activities associated with a negative caring experience and practical consequences of physical and behavioural changes of the patient, and *subjective* burden (Gauthier et al., 2007) i.e., feelings and emotional reactions of the caregiver to the experience and change of role.

Caregiver burden has been reported to be a consequence of physical impairment in ALS, worsening congruently with disease trajectory (Chio et al., 2004). Although motor disability may be an intuitive factor contributing to caregiver burden, it has not been fully elucidated within the context of other multisystem features of ALS i.e., cognitive, and behavioural impairment (Mioshi et al., 2013). Neuropsychiatric features associated with bvFTD have been shown to enhance caregiver burden also, with reports of caregiver burden affecting the psychological and physical outcomes of patients (Mioshi et al., 2014; Thommessen et al., 2002). The impact of cognitive and behavioural change on caregivers is discussed in greater detail in section 2.3.13.

1.10 Caveats of Repeat Neuropsychological Assessments in ALS

Undeniably there are caveats to undertaking research with a patient cohort who by definition have a worsening trajectory declining in tandem with the serial nature of the research design (Duff, Westervelt, McCaffrey, & Haase, 2001). Many considerations must be taken into account when conducting longitudinal research with a cohort of patients with neurodegenerative diseases (Calamia, Markon, & Tranel, 2012). For one, practice effects may mask cognitive deterioration due to familiarity and must be considered (Goldberg et al., 2007).

Functional decline, as often measured using the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R; Cedarbaum et al., 1999) may contribute to increasing attrition as longitudinal research progresses over time (Strober & Deluca, 2013). A secondary influence of functional decline is that participants may choose to withdraw from research and cease their participation (Arnett, 2013). Attrition may of course be increased by end of life issues associated with a particular condition, where a patient may reach the end of life stage while enrolled in research (Bentley, Aoun, O'Connor, Breen, & Chochinov, 2012). Although some research studies have overcome the barrier of participation associated with travelling to a research site (Meoded et al., 2013), this is not always possible i.e., in the case of travelling to a site-specific MRI machine. Practice-based evidence would suggest that this could be

conceptualised as a form of 'altruistic fatigue', where research participants are willing to engage with research for a certain period, but then disengage once an assessment has been completed (Farsides, 2007).

1.11 Rationale for the Present Study

The above information begins to describe the multidimensional approaches taken to investigate ALS, specifically pertaining to cognitive decline (Raaphorst et al., 2010). ALS is a multisystem disease affecting cognition, behaviour and movement; however, the extent of cognitive deficits, and the trajectory of cognitive decline relative to other components of the disease is still relatively unclear (Consonni et al., 2015).

Although the occurrence of executive dysfunction has been well documented specifically in relation to the negative impact on patient survival (Elamin et al., 2011), the impact of executive dysfunction on the patients i.e., behavioural manifestations, implicated verbal and visual memory, and social cognitive deficits, or their caregiver i.e., increased subjective burden, increased role burden, has received much less attention (Burke et al., 2015). To this end, a greater understanding of cognitive processes implicated by executive dysfunction, and their functional correlates in ALS could help with the identification of distinct sub-phenotypes within these diseases, create more accurate markers of disease progression, relative to social cognition and socially appropriate behaviour, and also create more detailed inclusion criteria for clinical trials in ALS (Tabrizi et al., 2012).

These studies aim to investigate the cognitive profile of patients with ALS, in the early stage of their disease, to delineate the specific role of executive dysfunction in relation to auxiliary cognitive processes such as memory, language, visuospatial abilities, emotional processing, social cognition, and behavioural manifestations. Moreover, a case-matched, cross sectional population-based research design was employed to investigate whether detailed cognitive profiling could accentuate our theoretical understanding of cognitive models relating to executive function and social cognitive processes; enhance our understanding the impact of social cognitive deficits on caregiver relationships; to further build on previous research which utilized cognitive phenotypes in order to accurately inform rates of survival in ALS.

1.12 Ontological and Epistemological Approach

Due to the social and cultural aspects of some of the data being collected, there is need to clarify the epistemological approach being adopted within the present thesis. The data collected relative to social cognition is not socially constructed and subject to interpretations

by any one individual, nor is the behavioural data collected to inform behavioural status. The data being collected by the research is standardized and scored using a coded system, rather than a single or double hermeneutic approach. No qualitative interpretative analyses are being conducted, to avoid value-laden socially constructed variables to reduce personal and flexible scoring paradigms, and increase the scientific rigour of the reported data. Instead, the research will take an objective, ontological approach where there is a single, external and objective paradigm designed to assess the proposed hypotheses and research questions. This process enables for a more precise distinction between fact and value-judgement, allowing for more robust interpretations to be made about an area of cognition, which may lend itself to subjectivity between researchers i.e., social cognition.

1.13 Summary

ALS is a complex multi–system disorder, for which there remains no cure. The current chapter detailed the physical and clinical characteristics of ALS. It highlighted on–going interdisciplinary research which support the relationship of ALS and FTLD at genetic, neuropathological and neuropsychological levels. The primary focus of the current thesis concerns the profile of neuropsychological change in ALS patients, particularly in cognitive domains such as social cognition. Chapter Two provides a detailed review of the literature in the area of cognitive and behavioural change in ALS patients. As a secondary focus, the thesis will examine the effect such change has on the ALS caregiver.

2.0: Literature Review: Cognitive and Behavioural Change in ALS

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2.3 Cognition and Behavioural Change in ALS
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  - 2.3.1.2 Attention, Inhibition and Working Memory
  - 2.3.1.3 Conception formation, problem solving, set–shifting
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2.0 Literature Review: Cognitive and Behaviour Change in ALS

2.1 Literature Search Terms

This chapter will focus on the empirical findings relative to research on cognition and behaviour in ALS. This chapter will then conclude investigating the impact of cognitive and behavioural changes on patients and their caregivers. Methods employed to conduct this review of the literature included specific search terms "Amyotrophic", "Lateral", "Sclerosis", "ALS", "MND", "Lou Gehrig's", "Cognition", "Behaviour", "Behavior", "FTD:, "Frontotemporal dementia", "Frontotemporal lobar dementia", "Pick's disease". Ebscohost, MedLine, and PubMed search engines were used, and the outcome of this review can be seen in Figure 2.1.

2.2. ALS: Historical Overview

Charcot (1870; 1874), to whom the first description of the disease is generally attributed, did not report any symptoms of cognitive or behavioural dysfunction. However, it was believed that psychiatric disturbances were relatively common in ALS (Mane, 1892); Raymond and Cestan (1905) described half of their 18 ALS patients to be "mentally feeble", with a further case described by Fragnito (1907); Westphal (1909) described schizophrenic type features in ALS patients; van Bogaert (1925) found "psychic alterations" in 13 of 31 ALS patients; irriration and aggression were notable features (Meyer, 1929). Neuropsychiatric features commonly associated with ALS today were cited i.e., Ziegler (1930) wrote about depression in ALS as an emotional phenomenon. Consistent with the current view of ALS, von Braumühl (1932) described the first suggestion that ALS and FTD might be clinically associated. Psychotic symptoms such as delusions and hallucinations were recorded (Teichmann, 1935) and emotional lability appears to be mentioned first within the literature by Brain (1962).

Manic-depression was associated with ALS (Castaigne, Lhermitte, Cambier, Escourolle, & Le Bigot, 1970), alongside a suggestion that ALS could present with a dementia-like syndrome (Yuasa, 1970). In the early 1970's, Yvonneau, Vital, Belley et al., (1971) and Finlayson, Guberman, and Martin (1979) reported familial syndromes of ALS. Soon thereafter a case of progressive cognitive and behavioural decline was presented, suggesting that cognitive and behavioural change in ALS may be a new clinic-pathological entity (Mitsuyama, 1979). Further associations were being drawn between FTD and ALS (Brion, Psimaras, Chevalier,

Plas, Masse, & Jatteau, 1980); and the interest in, and reports of cognitive decline in ALS was steadily increasing (Hudson, 1981).

Classic ALS (See chapter 1), with dementia was beginning to be reported within the literature (Wikstrom, Paetau, Palo, Sulkava, & Haltia, 1982); clinical and pathological features of ALS were compared to that of prion diseases (Salazar, Masters, Gajdusek, & Gibbons (1983) and compared to dementia, without neurofibrillary tangles, or parkinsonism (Horoupia, 1984). During the same year, Mitsuyama (1984) also present a 26 case series of dementia in motor neuron disease patients in Japan, showing their clinical presentation and pathology. A trial for amitriptyline for the treatment of pathological crying and laughing was published (Schiffer, Herndon, & Rudick, 1985) as well as a study investigating cognitive impairment in ALS (Gallassi, Montagna, Ciardulli, Lorusso, Mussuto, Stracciari, 1985).

David and Gillham (1986) report the findings of a neuropsychological study in motor neuron disease, while Poloni, Capitani, Mazzini, and Ceroni (1986) report on neuropsychological measures, and their relationship with Computerised Tomography (CT). The conclusions by Poloni et al., were quite limited due to the restricted test battery (subtests from the Wechsler Adult Intelligence Scale [WAIS]), although interest was growing within the field to document the cognitive status of ALS patients. In 1989, Gallassi et al., recruited 35 controls, and patients with ALS, without clinically evident cognitive deterioration. Both groups underwent electroencephalograph, CT, and neuropsychological assessment. They reported temporal slowing on EEG, and that the CT was unremarkable between patients and controls. Gallassi et al. (1989) report a definite and stereotyped executive-based cognitive impairment on their cognitive battery for ALS patients, which appears to have contributed to a trend in profiling the cognitive performance of ALS patients on neuropsychological measures.

Within more recent literature, cognitive and behavioural changes in ALS are often described as a recent understanding, or recent phenomena. In reviewing the literature, it is clear that cognitive and behavioural features of ALS have been reported alongside clinically meaningful change since the late nineteenth centaury, with a clinical overlap between ALS and FTD considered early as early as 1932. In recent years, there has been a rapid increase in cognitive and behavioural profile associated with ALS, which will now be described in detail.

2.3 Cognition and Behavioural Change in ALS

It is now well established that a broad range of cognitive sequelae are reported in ALS. The pattern of cognitive and behavioural deficits and clinical profile of ALS are unique and distinct from those seen in other neurodegenerative diseases such as Huntington's disease,

Alzheimer's disease, pure Fronto-temporal dementia, or acquired brain injuries/disorders. Cognitive and behavioural deficits known to manifest in ALS patients are of great clinical importance as they can lead to significant disturbances in activities in daily living, peer relationships, caregiver relationships, and interactions with healthcare professionals. These deficits also provide information about the cognitive correlates of neuropathology implicated in ALS. Studying cognitive and behavioural deficits in ALS also provides information on normal cognition and brain function.

Based on a recent meta analysis of neuropsychological tests employed in ALS research, 13 cognitive domains and effect sizes (Hedges' g) were calculated for each cognitive domain and for individual tests administered in ≥5 studies (Beeldman, Raaphorst, Twennaar, de Visser,, & de Haan, 2015). Forty-four studies were included comprising 1287 patients and 1130 healthy controls. All cognitive domains, except visuo-spatial function, showed significant effect sizes compared to controls. Cognitive domains without bias due to motor impairment showed medium effect sizes (95% CI): fluency (0.56 [0.43 to 0.70]), language (0.56 [0.40 to 0.72]), social cognition (0.55 [0.34 to 0.76]), or small effect sizes: delayed verbal memory (0.47 [0.27 to 0.68]) and executive functions (0.41 [0.27 to 0.55]). Individual neuropsychological tests showed diverging effect sizes, which could be explained by bias due to motor impairment, highlighting the need to correct for motor disability. Subgroup analyses showed no influence of bulbar disease onset or depression and anxiety on the cognitive outcomes.

The cognitive profile of ALS consists of deficits in lexical fluency, language, social cognition, executive functions and verbal memory, which will now be discussed in more detail. The proportion of executive dysfunction is higher in non-demented ALS patients, compared to healthy controls. This recent meta-study illustrates the heterogeneous cognitive profile of ALS patients, showing how multiple cognitive domains can be implicated. Each cognitive domain will now be discussed in detail, with considerations made for the role of executive dysfunction on other cognitive profiles.

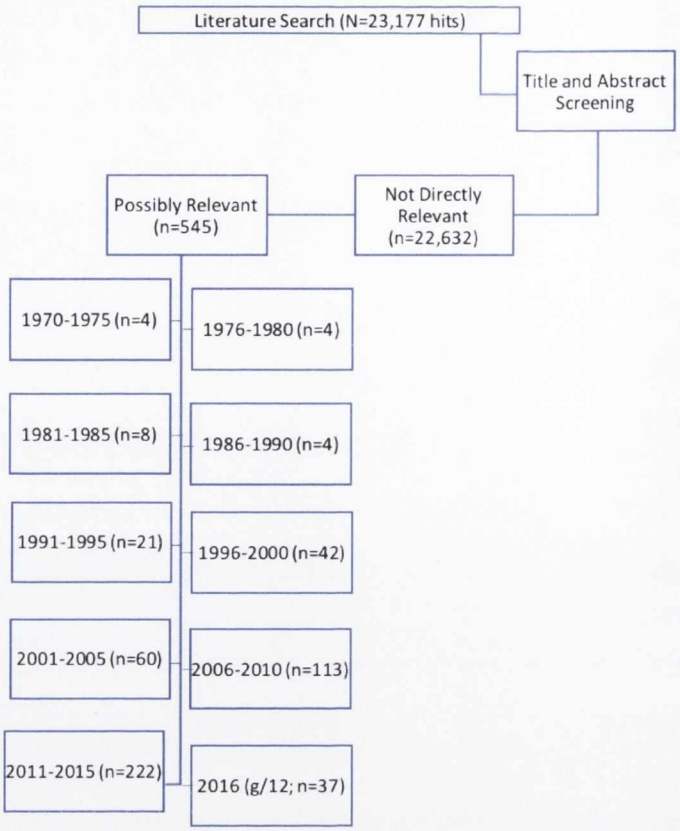

Figure 2.1: Yield from reviewing the literature for this thesis with the criteria outlined in section 2.1.

2.3.1 Executive Function

The term 'executive function' is an evolving concept in neuropsychology, which is yet to be fully delineated. In general, it is an umbrella term that refers to "higher–level" processes involved in the selection and supervision of "lower–level" mechanisms (Alvarez & Emory, 2006) that enable the planning and execution of behaviour in order to achieve prioritised goals (Lezak, 2004). Several theoretical models emphasise the dominant role of the frontal lobes in these functions, a position which is supported by lesion and neuroimaging studies (see Robbins et al., 1996 for review). However, evidence also supports the involvement of more posterior and subcortical regions in executive ability (Alvarez & Emory, 2006; Simões-Franklin et al., 2010). Given the anatomical connectivity of the frontal lobes with non–frontal regions, Stuss (2011) emphasise the involvement of 'frontal–subcortical circuits' in executive behaviour.

Throughout this thesis, the term 'executive dysfunction' will be used to refer to the presence of dysfunction in any one or a collection of higher–level processes, while 'dysexecutive behaviour' will indicate the corresponding behavioural syndrome that is associated with such dysfunction. Stuss & Alexander (2007) argue that the terms 'executive dysfunction' or 'dysexecutive behaviour' are misleading as they convey an undifferentiated disorder or syndrome. They contend that 'dysfunction' is better explained as deficits in a collection of

anatomically and functionally independent but interrelated attentional control processes, an argument presented by Stuss and Alexander (2007). The current thesis offers these terms and definitions for simplicity and acknowledges the controversy surrounding the conceptualisation of the executive function construct (Banich, 2009).

The theoretical framework considered in this thesis relates closely to work previously conducted within the area of executive function, and the results will be discussed within this framework, where relevant. In order to fully test the prospective hypotheses contained within this thesis, certain measures of executive function were employed to ensure the assessment of specific cognitive processes. To elaborate, the control-to-action model developed by Norman and Shallice (1986) distinguishes between two mechanisms. The first, contention scheduling is involved in the routine situations in which actions are automatically triggered. The second, called the Supervisory Attentional System (SAS), is a separate mechanism at the highest level of control of action, coping with novelty. This is the cognitive mechanism required where the routine selection of actions is unsatisfactory. The SAS is integral to sustaining attention, planning, inhibition, and abstraction of logical rules. ALS patients have been shown to exhibit greater executive dysfunction within these sub-domains, therefore it is likely the SAS is implicated. Suboptimal processes from the SAS may account for the secondary impact of executive dysfunction on non-executive cognitive processes, as attention is an integral feature of cognition.

2.3.1.1 Verbal Fluency

Verbal fluency impairment is the most consistently reported cognitive deficit in ALS research, a finding which is substantiated by meta–analysis (Raaphorst et al., 2010). Fluency measures typically require participants to produce as many words as possible in a given time limit and under conditions in which the response is specified by a particular restriction, such as a letter (phonemic fluency test) or semantic category (category fluency test). In addition to linguistic processes, these tests are understood to rely heavily on executive resources and recruit other cognitive processes in order to initiate appropriate responses and engage retrieval strategies in quick succession while maintaining output to avoid repetition.

Category fluency tests place fewer demands on executive processes and more demand on semantic connections (Laisney et al., 2009). Distinct neural regions for each test type have also been proposed, with category fluency performance being associated with temporal cortex and phonemic fluency performance primarily sub-served by the frontal regions, in particular the DLPFC (Birn et al., 2010; Meinzer et al., 2009; Schlösser et al., 1998). Although variable across studies, both phonemic and semantic fluency deficits have been found in ALS,

suggesting an underlying vulnerability of the cognitive and neural processes associated with the tasks in ALS (Abe et al., 1997; Abrahams et al., 2000; Hanagasi et al., 2002; Rottig et al., 2006).

Studies of verbal fluency in ALS have differed by task and modality (oral or written), which may influence the identification of deficits in patients. The most frequently used fluency tasks have included the Controlled Oral Word Association Test (COWA; Benton et al., 1978) and the (written) Thurstone's Word Fluency Test (TWF; Thurstone & Thurstone, 1938). Both tasks are timed and do not account for motor impairment in scoring. A modified version of the TWF to accommodate physical disability (Abrahams et al., 1996) introduces a second condition whereby, after the completion of the standard letter fluency task, participants are timed as they copy the words they have previously provided. A verbal fluency index (VFI) may then be calculated by subtracting the time of the copy condition from the time of the standard generation condition and dividing this by the total number of words generated. This index represents the average time taken to generate each word; higher scores indicating longer thinking times and more pronounced executive impairment. The formula is illustrated below:

$$\text{VFI} = \frac{\text{(time for generation condition)} - \text{(time for copy condition)}}{\text{Total number of words generated}}$$

Studies have varied in the adoption of this control measure, leading to a possible overestimation of fluency impairment. Abrahams et al (1996) applied these indices to their fluency measures and found that fluency impairments in the ALS group remained. The robustness of this procedure to detect fluency deficits in patients has been indicated by subsequent research (Abrahams et al., 1997; Abrahams et al., 2004; Abrahams et al., 2005a; Abrahams et al., 2005b; Abrahams et al., 2000; Stukovnik et al., 2010), suggesting fluency impairment in ALS independent of physical impairment. Although this methodology has been well adopted, brief assessments of cognitive function, such as the frontal assessment battery (FAB), are often employed, without adjusting for motor function. In 2014, Wei et al assessed a large cohort of ALS patients and compared their performance to controls. Using the FAB they evaluated executive function on 126 sporadic ALS patients and 50 healthy controls. The prevalence of frontal lobe dysfunction was 32.5 %. The most notable impairment domain of the FAB was lexical fluency (30.7 %). A binary logistic regression model was completed, which revealed that an onset age older than 45 years (OR 5.976, $p = 0.002$) and a lower educational level (OR 0.858, $p = 0.002$) were potential determinants of an abnormal FAB

(Wei et al., 2014). These data by Wei et al., (2014) are less generalizable to the wider ALS community, as there was no adjustment made for motor function.

While some studies have not found semantic fluency impairments in ALS patients compared to controls (Talbot et al., 1995), others have found that patients are impaired at generating words for 'animals' but not for other semantic categories (Abe et al., 1997; Abrahams et al., 2000; Hanagasi et al., 2002). Several studies have failed to replicate a specific 'animal' naming deficit in ALS patients (Abrahams et al., 2005b; Hartikainen et al., 1993; Palmieri et al., 2009); instead a few studies have shown fluency impairments for other categories such as, 'fruits', 'vehicles' (Abe et al., 1997) and 'supermarket goods' (Rottig et al., 2006). The semantic fluency deficits found in these patients may suggest corrupt semantic representation in ALS, or perhaps these patients also present with executive deficits; however, they do not rule out executive impairment as a source of impaired response generation on these tasks. For example, Abrahams et al (2000) compared phonemic, semantic and design fluency between 22 ALS patients and 25 controls. Working memory and word retrieval were also compared between groups. Relative to controls, patients showed impairments on the written phonemic task and the 'animal' category of the oral semantic fluency test. These deficits were found in the presence of intact phonological function and word retrieval, but impaired working memory capacity in patients. This suggests that the impoverished fluency performance demonstrated by patients was attributable to dysfunction of the executive component of working memory rather than to impairments in phonological loop functions or simple linguistic abilities.

Several imaging studies have adopted fluency tasks as activation paradigms to investigate the relationship between cognitive dysfunction and abnormal cerebral responses in ALS. The comparison of regional Cerebral Blood Flow (rCBF) of patients with and without phonemic fluency deficits in addition to healthy controls was conducted in a PET study (Abrahams et al., 1996). Reduced activation in the DLPFC, anterior cingulate (AC) gyrus, insular cortex, thalamus and premotor cortex was evident for patients showing fluency impairments. These findings are circular in a sense, as patients with impaired cognitive function showed reduced activation, although the research these conclusions corroborated previous findings from an earlier PET study (Kew et al., 1993b). The results are also in agreement with earlier PET and SPECT studies that have suggested an association between reduced glucose uptake in the frontal regions of ALS patients with impaired fluency performance (Abe et al., 1993; Ludolph et al., 1992), confirming verbal fluency is a frontal-based function.

Abrahams et al (2004) conducted an fMRI study comparing blood–oxygen–level–dependent (BOLD) changes between 28 patients and controls during a phonemic fluency task. Compared to controls, patients were impaired on this task and showed decreased BOLD responses in the PFC, such as the AC and the language–related Broca's area. The latter region has been associated with the phonological store component of working memory (Paulesu et al., 1993; Salmon et al., 1996). The study therefore highlights the involvement of language–related processes in ALS fluency performance. Structural MRI has revealed that White Matter (WM) changes in the frontotemporal regions of ALS patients are associated with fluency performance (Abrahams et al., 2004; Abrahams et al., 2005a; Pettit et al., 2013).

2.3.1.2 Attention, inhibition and working memory

Reports of directed, and sustained attention difficulties in ALS patients exist. Two large studies of neuropsychological functioning in ALS (n=146, Massman et al., 1996; n=279, Ringholz et al., 2005) have used the Verbal Series Attention Test (VSAT, Mahurin & Cooke, 1996), which includes several tasks, such as reciting the alphabet, counting backwards whilst subtracting a constant and recalling the days and months of the year in forward and reverse order. Using normative data, Massman et al (1996) found that patients' mean VSAT completion time fell at the 25th percentile. This result was unexpected, given the patients' above average premorbid IQ estimates which predicted mean scores to fall within at least the average range. Using the same task, Ringholz et al (2005) found that impaired VSAT performance was common to all patient cognitive subgroups (mild, moderate and severe impairment). This might indicate an early vulnerability of directed attentional resources in cognitively impaired patients. However, the high verbal demand of the VSAT may have contributed to poor patient performance in both studies. Indeed, dysarthria scores correlated with task completion times in Massman et al's study. On the other hand, they did not correlate with other verbal tasks, suggesting that patients were able to verbalise responses adequately under time restraints.

Studies that have incorporated non–verbal tests of attention have also indicated attentional processing impairments in ALS (Gallassi et al., 1985). On a visual search-matching task, 11 out of 50 ALS patients showed impaired attention compared to 27 age–matched controls and 23 neurological control patients (Chari et al., 1996). However, impairments in ALS patients only emerged when the attentional demands of the task increased, indicating a graded impairment effect, which is greater than that observed in controls. As such, this presents as a more specific cognitive deficit, rather than a bottleneck effect of attentional resources.

Event Related Potential (ERP) studies allow the examination of attention in ALS through the adoption of physiological data alongside neuropsychological tasks. An overview of such research can be found through recent research within the field (Gil et al., 1995; Munte et al., 1999; Poletti et al., 2016; Polich & Criado, 2006; Seer et al., 2015).

Aspects of attention can be measured by digit span tasks, and they has been reported as impaired in ALS patients (Gordon et al., 2010), and also within the normal range (David & Gillham, 1986; Ludolph et al., 1992). A distinction between forward and reverse digit span performance is evident in studies with some patients demonstrating intact performance on the former and impaired performance on the latter (Hanagasi et al., 2002; Moretti et al., 2002; Rakowicz & Hodges, 1998). This dissociation may reflect intact global attention capacity but deficient working memory processes, which are each associated with the respective subtask.

Recently, a study set out to delineate the specificity of reported working memory deficits (Hammer et al., 2011). Eleven ALS patients and healthy age–matched controls performed several working memory tasks: digit span, reading span and two N–back tasks which required the storage of figural and spatial information, separately. In the N–back task stimuli are presented serially and participants have to indicate whether the presented stimulus is identical to the one that was presented 'N' trials before (McEvoy et al., 1998). ALS patients showed comparable performance on the digit span, reading span and figural N–back tasks, but significantly impaired performance on the spatial N–back task, relative to controls. These data conflict with the commonly held view that spatial tasks, and digit-based tasks are a methodological analogue of each other. Secondly, these data suggest that spatial working memory tasks are more demanding on the executive system, which warrants further investigation, though theoretically they should be equivalent according to the widely accepted model of working memory proposed by Baddeley and Hitch (1974).

The concept of working memory proposes that a dedicated system maintains and stores information in the short term, temporally speaking, and that this system facilitates long-term retention and storage. This model is supported by the SAS model, described above, as it incorporates the idea of the SAS through a 'central executive' component. The working memory model proposed by Baddeley and Hitch (1974) has recently been updated (Baddeley, 2000). This updated model can be seen in figure 2.2. Throughout this thesis, this updated model of working memory will also be assessed, alongside the SAS.

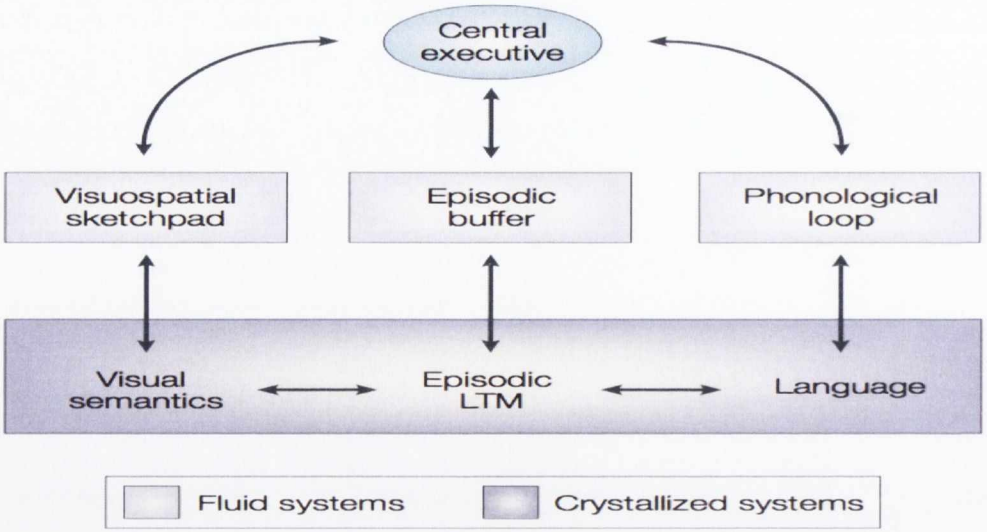

Figure 2.2: The cognitive model of working memory model by Baddeley (2000), updated from the original model proposed by Baddeley and Hitch (1974).

A detailed review can be found on the components of the working memory model (Baddeley, 2000), although, in brief, the visuospatial sketchpad refers to a cognitive schema involved in the short term retention of visual information, through 'visualising stimuli within the minds eye'. The phonological loop refers to the often, but not exclusive, sub-vocal rehearsal of auditory stimuli to aid retention.

Previous evidence suggests the involvement of the right DLPFC in spatial working memory (Bor et al., 2006); further implicating impaired functioning of this region in ALS. In addition, ERP data, which accompanied the N–back tasks, revealed that the differentiation between stimuli (target and non–target stimulus–positions) in the spatial task was more prominent in ALS patients compared to controls and showed a frontoparietal gradient. The study also found significantly reduced COWA performance in ALS patients relative to controls, further supporting Abrahams and colleagues' suggestion of a frontally–mediated working memory impairment (Abrahams et al., 2000). Baddeley (2000) provides a tentative mapping structure for the conceptualised working memory model reported above (Figure 2.2).

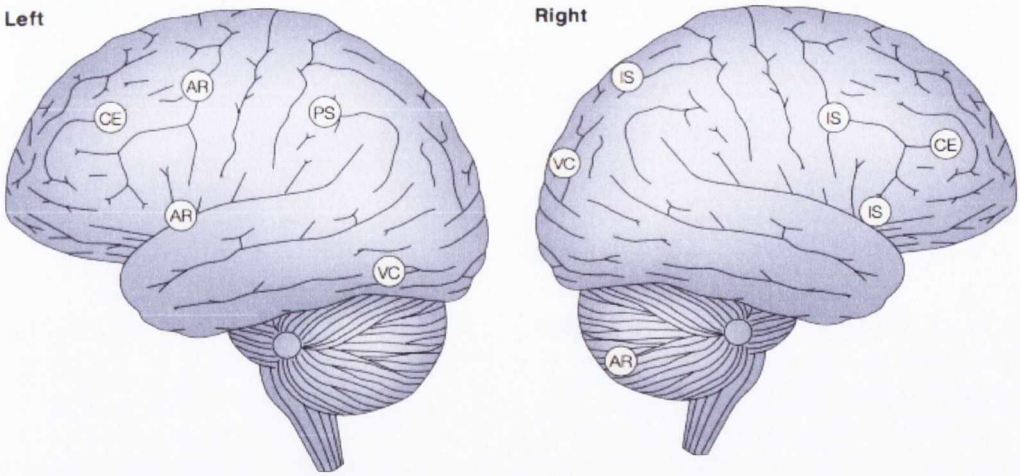

Figure 2.3: Anatomical correlates proposed by Baddeley (2000) for the model of working memory outlined in figure 2.2. Central Executive (CE); Articulatory Rehearsal (AR); Inner Scribe (IS: spatial rehearsal); Phonological Store (PS); Visual Cache (VC: storage).

According to Baddeley (2000) the functions associated with each component are not meant to represent the only functions that are served by the associated brain regions, nor are the labels outlined in figure 2.3 supposed to represent all brain regions associated with a particular function. The central executive (CE), for example, is likely to engage multiple brain regions in a functionally coherent network, including dorsolateral prefrontal cortex. AR, articulatory rehearsal; IS, inner scribe (spatial rehearsal); PS, phonological store; VC, visual cache (storage). A debate exists within the literature regarding the functional equivalence of working memory tasks, depending on their stimulus modality i.e., spatial/verbal. Currently, this model does not account for additional executive demands caused by modality specificity.

Selective attention and inhibition in ALS has been investigated using the Stroop Test (Stroop, 1935). In this test, participants are instructed to name the print colour of a semantically congruent ('red' written in red ink) or incongruent word ('red' written in blue ink). The task requires participants to selectively focus attention in order to inhibit the interference caused by the distracting information. In 'incongruent trials', naming of the ink colour typically takes longer than in 'congruent trials'. This phenomenon is known as the 'Stroop Effect'. Stroop performance is proposed to reflect functioning of frontal regions (Bench et al., 1993). Findings from this task in ALS samples have been mixed, with some studies reporting deficits (Frank et al., 1997; Gibbons et al., 2007; Hanagasi et al., 2002; Rusina et al., 2010; Sterling et al., 2010) and others showing comparable performance to healthy controls (Gordon et al., 2010). In particular, studies which have compensated for motor impairment or recorded alternative indices of performance, such as error scores, (Abrahams et al., 1997; Kew et al.,

1993a; Ludolph et al., 1992; Ogawa et al., 2009; Pinkhardt et al., 2008; Stukovnik et al., 2010) have failed to identify group differences, though these patients may have a broader categorisation of being cognitively intact. Subsequent research has used this task to compare performance across control, ALS and FTD groups (Lillo et al., 2012b). Group differences for overall and error scores on this task were statistically significant; and indicated a continuum of performance between the groups, with ALS patients performing worse than controls but better than FTD patients. Nonetheless, the overall score, which was a composite of timed responses, did not account for possible dysarthria of the ALS patients and so group differences on this score should be interpreted cautiously.

2.3.1.3 Conception formation, problem solving, set–shifting

Concept formation is the ability to identify relationships among environmental stimuli and group these stimuli into meaningful classes according to rules. This enables effective decision–making about objects and flexible responding to changes in contextual relationships (Hartman et al., 2004; Milton et al., 2009; Nyhus & Barcelo, 2009). Difficulties in concept formation and mental flexibility are often assessed in ALS using the original and modified version of the Wisconsin Card Sorting Test (WCST, Grant & Berg, 1948; Milner, 1963; Nelson, 1976). Performance on this task is strongly, but not exclusively, associated with executive and frontal lobe function (Demakis, 2003; Milner, 1963; Nelson, 1976; but see Nyhus & Barcelo, 2009). An early neuropsychogical study of ALS, found impaired performance in patients relative to healthy controls on the WCST (David & Gillham, 1986). Subsequent studies have supported these findings (Abrahams et al., 1997; Evdokimidis et al., 2002; Frank et al., 1997; Rusina et al., 2010; Strong et al., 1999); but not consistently (Gibbons et al., 2007; Ludolph et al., 1992; Ogawa et al., 2009). Poor performance on the WCST can be attributed to impaired concept formation or a tendency towards perseveration. A similar test, the Card Sorting Task (CST, Delis et al., 2000), examines these processes separately (Beatty et al., 1994). The CST possesses many unique features compared to the WCST, most notably additional sort recognition trials that assess sorting strategy under a motor–free condition.

Libon et al, (2012) found a range of test performance in 41 ALS patients on the CST. Using age–corrected scaled scores, K–means cluster analyses classified patients into three groups of impaired (n=9), average (n=20) and above average (n=15) sorting ability. Action naming and word meaning test scores predicted sorting performance on the free sorting and recognition sorting conditions, respectively. Previous reports of impaired action and object naming in ALS exist and posit the degradation of the action/semantic network in patients. The study's

findings may support this position. Letter fluency scores were related to performance on both sorting conditions, suggesting the contribution of executive resources to task performance. However, the measure used did not control for motor impairment (i.e. Abraham's protocol), and should be interpreted cautiously.

Nonetheless, in a subset of 16 patients, sorting recognition scores correlated with cortical thinning in the left DLPFC and left parietal cortices. Since PFC regions are implicated in the executive components of sorting tasks (Badre et al., 2009), recognition sorting performance in ALS may depend, in part, on the executive retrieval and mediation of lexical and semantic knowledge. In a similar study of executive function, Kasper et al (2015) investigated cognitive performance in ALS longitudinally. 93 ALS patients and 73 age-, sex- and education-matched healthy controls underwent up to four neuropsychological evaluations, separated by 3- to 6-month intervals. The focus of their neuropsychological battery was executive function. In this study, patients with ALS showed no decline over time, regardless of their baseline performance on subcomponents of executive function. The authors infer that executive deficits which develop in some ALS patients, may emerge before motor symptoms and remain stable after an initial decline. They conclude that the discrepancy between the trajectory of cognitive decline, and the trajectory of declining motor functions may be a result of differential vulnerability in prefrontal pathology associated with ALS.

Lange et al (2016) evaluated patients' performance on a computerized task-switching paradigm modeled after the WCST to elucidate the neurocognitive processes underlying their set-shifting impairments. Results revealed significant set-shifting deficits in patients with ALS, and that executive deficits were accompanied by substantial alterations of event-related brain activity.

2.3.1.4 Insight and Awareness

Insight and the awareness of deficits are increasingly recognised as a multidimensional deficit in neuropsychological processes. There are many theoretical models which distinguish between different types of deficit awareness (see Hoerold, Pender, & Robertson, 2013 for an overview of theoretical concpets). Few studies have examined insight and awareness into cognitive and behavioural change in ALS, despite anosognosia of this kind constituting a core criterion of FTD diagnosis (Neary et al., 1998). A lack of awareness for cognitive dysfunction has been indicated in one study which found that, despite impaired performance relative to controls on an executive function measure, non–demented ALS patients consistently rated their performance on the task as similar to or higher than controls (Stukovnik et al., 2010). It is not known whether these evaluations reflect reduced insight into cognitive difficulties,

denial coping strategies or the fact that the patients' executive dysfunction was not severe enough to affect their everyday cognitive performance and thus remained undetected by patients. Further research in this area is required. Most studies have focussed on insight into behavioural change, possibly because of the availability of behaviour scales and their potential to gain patients and caregiver reports for comparison.

Differences between patient and informant ratings on patient behaviour were noted in a study of 70 ALS patient–caregiver couples (Chio et al., 2010). Compared to patient evaluations, caregivers reported higher frequencies of clinically significant pre–morbid and post–illness behaviour on all FrSBe domain scores. Caregivers rated apathy as the most commonly impaired domain (55.7%), followed by executive dysfunction (45.7%) and disinhibition (25.7%). Patients, however, rated apathy as the least commonly impaired (8.6%), noting executive dysfunction (20%) and disinhibition (10%) as more frequent. These discrepancies might reflect a particular lack of awareness of apathetic behaviour in ALS or could be attributed to over–responding by the ALS caregivers. A direct comparison of insight for behavioural change between ALS patients with and without FTD suggested preserved insight in non–demented ALS patients only (Woolley et al., 2010a). Loss of insight was defined as impairments endorsed by caregivers that were at least two standard deviations greater than those endorsed by the patient on domain or total scores of the FrSBe. While ALS–FTD patients reported only mild changes on the apathy domain, their caregivers reported profound changes in apathy, executive functioning and total behaviour change. These rating differences between respondent groups satisfied the loss of insight criterion. In contrast, a comparison of ALS patients and their caregivers' ratings showed high concordance, with the patient group reporting slightly but not significantly greater change over time on all behavioural domains.

2.3.2 Social cognition and Emotional Processing

Social interaction is integral to human life. Only recently, emotional processing disorders have been shown in this disease. The interest in affective processing in ALS is growing (Sodda, 2014). Successful navigation of the social environment provides personal and evolutionary advantages (Adolphs, 1999; Gresham & Elliott, 1987; Silk et al., 2003). This interaction is reliant on two coinciding processes: the perception and processing of social cues in the environment, and the formulation and action of appropriate responses to these cues (Elamin et al., 2012). Of interest in the study of social cognition and emotion, are arousal and valence detection impairments, independently from the stimulus modality (verbal or visual); recognition of facial expressions of anger, sadness and disgust is impaired in ALS, even when cognition is preserved; clinical features such as type of onset and severity of the disease could

be the cause of the heterogeneity in emotional deficits profiles between patients; and imaging linking emotional dysfunctions in ALS.

In order for face perception to be reasoned appropriately by an individual, a number of brief, yet detailed processes must occur. Bruce and Young (1985) outline a cognitive model of facial processing, where modules feed into a centralised cognitive system, where the shallow output in the ability to accurately process an expression, a person's identity, and have semantic links in order to generate a person's name, if known. This cognitive model can be seen in figure 2.4. According to their model, facial features and configurable information engage multiple levels of processing relating to encoding mechanisms that extract information about the individual components of the face (e.g., identity, expression, gaze).
From these encoding mechanisms, face expressions are proposed to be processed independent of face identity, while the processing of facial speech is independent of other face categorizations such as emotion and eye gaze (Bruce & Young, 1986; Bruce et al., 2000; Campbell, Landis & Regard, 1986).

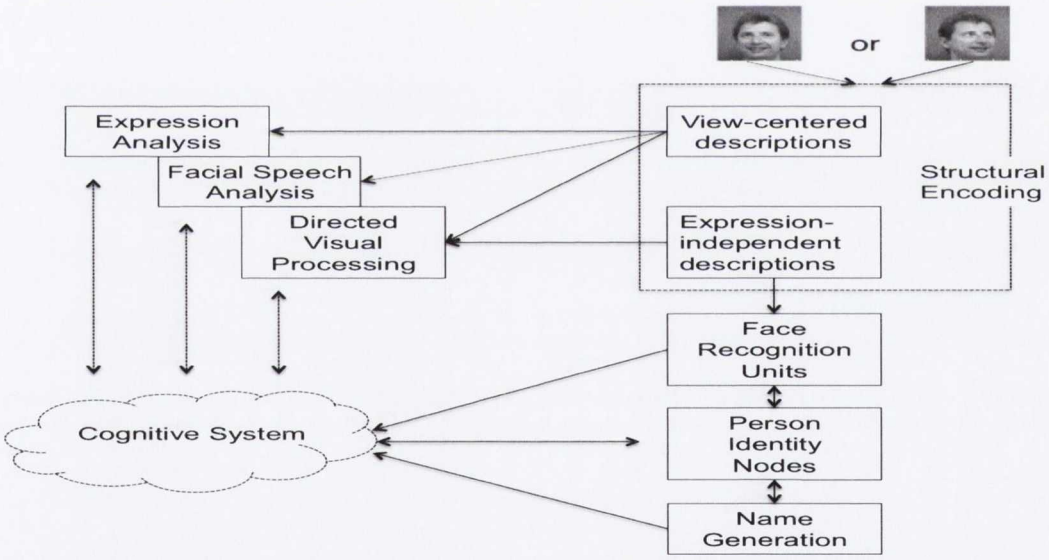

Figure 2.4: A cognitive schema for how people analyse, process, and recognise faces, facial features, and (Bruce & Young, 1985)

Bruce and Young's 1985 cognitive model of face processing has been widely accepted among the literature, with primary aspects of the model withstanding the test of time. Few models have since been developed to build on the work of Bruce and Young, although complementary models of function have been applied. Although different in many ways, the Haxby et al., (2000) model of a distributed human neural system from face perception (Figure 2.5) builds on the Bruce and Young model, and enhances our understanding of face processing by integrating emotional properties, eye gaze, expression, and lip movement. The

distributed model does more to integrate not only the initial perception of a face, or facial features, but introduces the concept of a core system i.e., the visual analysis, and an extended system i.e., other neural networks such as the limbic system. Graphically illustrated, the modules (grey boxes) and the central systems (broken line) allow the reader to infer the shallow output depending on an expected outcome.

Social cues are embedded in language, paralinguistic information (such as intonation or emphasis) and non–verbal indicators i.e., eye gaze, facial expression and gestural movement (McDonald, 2012). In social neuroscience, the concepts of emotional processing and social cognition are intractably linked and overlap greatly; distinctions between them are not often emphasised in the literature. Here, the term socio–emotional processing will be used to encompass both meanings; however, each will be defined and discussed separately in relation to their study in ALS.

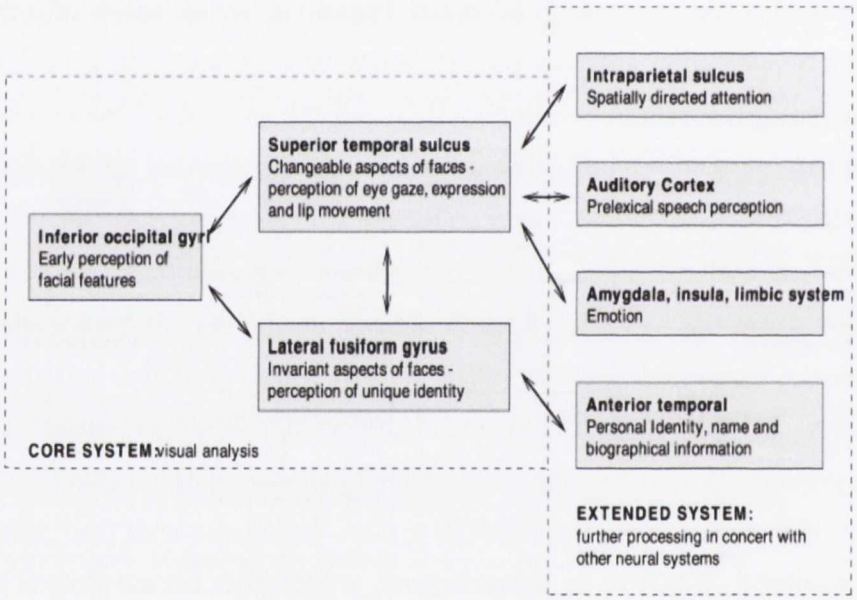

Figure 2.5: A detailed model of facial processing proposed by Haxby et al., (2000), which proposes aset of core systems (involved with visual analysis ie., fusiform regions) and an extended system (which incorporates other systems i.e., limbic-system).

Generally, emotional processing is described as the specific detection, representation and retrieval of affective information. Social cognition is a term used to refer to those cognitive processes that subserve the encoding and decoding of socially salient information in relation to the self and others (Beer & Ochsner, 2006). Important subcomponents of social cognition include Theory of Mind (ToM) and empathy. ToM is a construct that refers to the capacity to infer other peoples' mental and emotional states, allowing the prediction of, and appropriate response to, their behaviour (Baron- Cohen & Frith, 1985; Premack & Woodruff, 1978). Experimental and imaging evidence suggests a distinction between ToM for emotions

(feelings) and cognitions (thoughts, beliefs) of others (Amodio & Frith, 2006). Empathy, on the other hand, can be defined as the ability to appreciate and experience the emotional states of others (Lacoboni, 2009). It is conceptually related to ToM, with some authors also distinguishing between 'cognitive' and 'affective' components (Davis, 1983). How these various facets of social intelligence converge to enable social behaviour is of on– going scientific enquiry.

A challenge in describing the underlying neuroanatomy of psychological processes is that no such process maps cleanly onto a particular structure working in isolation (Adolphs, 2010). A widely acknowledged position suggests that a set of distributed structures constitute specialised neural systems dedicated to the processing of social information, referred to as the "Social Brain" (Brothers, 1990). Lesion and neuroimaging studies have implicated involvement of certain neural regions in the identification of emotions from faces. For example, the amygdala is suggested to support fear–processing, while anterior insula cortex is associated with recognizing disgust (Adolphs et al., 2002). Other regions such as the basal ganglia, the temporal lobes, the AC and the right somatosensory cortices have also been implicated in emotional processing (Cancelliere & Kertesz, 1990; Ojemann et al., 1992). Some of these structures share reciprocal projections to other neural regions, residing in the PFC.

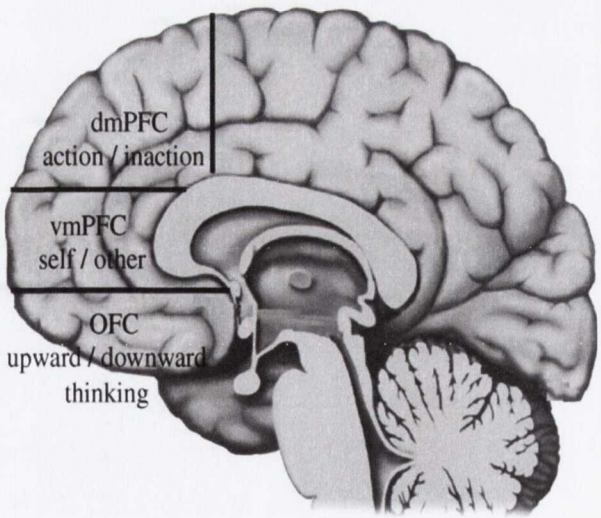

Figure 2.6: Subdivisions of the prefrontal cortex (PFC) into regions including the Orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC), and the dorsomedial prefrontal cortex (DPFC)

Subdivisions of the PFC include the OFC, ventromedial (vMPFC) and DPFC regions (Figure 2.6). The two former regions are often used interchangeably due to their partial overlap, but distinctly the OFC occupies the ventral surface of the PFC, while the vmPFC constitutes the inferior part the medial wall of the frontal lobe (Zald & Andreotti, 2010). Both have been noted for their roles in emotion processing (Heberlein et al., 2008; Hornak et al., 2003; Hornak et al., 1996), affective ToM and empathy (Gallagher et al., 2000; Shamay-Tsoory et al., 2009; Shamay-Tsoory et al., 2005; Stone et al., 1998). The DLPFC, on the other hand, has mostly been associated with 'pure' executive functioning (Lamar & Resnick, 2004).

However, there is evidence that it may be involved in affective decision–making and cognitive aspects of ToM and empathy (Hynes et al., 2006; Manes et al., 2002; Shamay-Tsoory & Aharon-Peretz, 2007).

The investigation of emotional processing in non–demented ALS has entailed the use of several paradigms sensitive to the recognition and memory for emotional and social stimuli. The use of divergent measures and the application of variable impairment detection methods (e.g. group versus individual–level analysis) across studies have led to inconsistent conclusions about the prevalence and nature of the reported deficits. The impact of traditionally small sample sizes and diverse sample compositions should also not be underestimated in this regard. Nonetheless, a heterogeneous profile of impairment has been indicated. Here, studies investigating ALS impairments in emotional processing and social cognition will be critically reviewed, in preparation for the aims of the current thesis.

2.3.2.2 Theory of Mind (ToM)

Impairments in the recognition of basic emotion extend to more socially complex emotions in ALS. Basic emotions (such as sadness, happiness, fear, etc.) have been distinguished from complex emotions (such as guilty, arrogant, or flirtatious, etc.) on the basis that the latter require the attribution of mental or emotional states that bear a social relation (Adolphs et al., 2002). Girardi and colleagues found significant group differences on both a basic emotion recognition task and the complex Reading the Mind in the Eyes (RME) tasks in 19 patients (Girardi et al., 2011). The latter task requires an attribution about mental or emotional states from immediate cues in the eye region of the face and is a well–established ToM or "mentalising" measure (Baron-Cohen et al.,1997). A subgroup of patients in the Girardi et al (2011) sample performed in the impaired range on both measures; performance on these tasks correlated strongly with each other ($r=-.76$, $p<.05$). A relationship between executive dysfunction and social cognition performance was also observed, as verbal fluency indices (thinking latencies for word generation), correlated negatively with both tasks ($r=-.83$, $p<.005$ and $r=-.66$, $p<.05$, respectively). Deficits on the RME have not been reported consistently; however, as a recent study of 15 ALS patients found no impairment on this measure, despite showing a deficit on a measure involving the prospective social interaction of cartoon characters (Cavallo et al., 2011a). While the RME is a widely used measure of ToM, it does not entail the depiction of social situations. ToM in ALS might be differentially impaired, with some patients displaying difficulty with mental attribution regardless of social (or non–social) context and others showing a select difficulty with interpreting elaborate social

interactions between individuals; this could account for the incongruous result on the RME in the latter study.

Impairments on less complex ToM tasks, involving a simple social cue such as eye gaze, have also been reported. Using the Judgement of Preference task (JOP, Baron- Cohen et al., 1995), Girardi et al found that ALS patients failed to correctly identify which picture a character "liked best", as determined by the orientation of the character's gaze (Girardi et al., 2011). No group effect was found on a condition task in which participants determined which picture the character was looking at, thereby eliminating the possibility of visual processing deficits. Distracter trials, in which an arrow pointed to a different picture than to which the face was orientated, were introduced in both control and experimental conditions. Although ALS impairment was more pronounced when distracters were present (64% of patients impaired), over a third of patients (36%) showed impairment on the less executively demanding trials involving no distracters. Error analysis revealed that patients relative to controls selected more items, which were indicated by the distracting arrow. This suggests an attentional component underlying the impairment found on these trials.

Notably however, patients also selected non–target items based on their personal preference (as indicated by a pre–experimental personal preference condition) on distracter and non - distracter trials. These error responses may imply a failure to override their egocentric responding, contributing to reduced inferential performance. Performance on this task was related to self–perceived change in levels of apathy, a frontally mediated behaviour. The assessment of ToM in ALS has also included the use of cartoons and written scenarios from which the intentions and beliefs of characters can be inferred.

Gibbons et al (2007) found a spectrum of ToM ability in their sample of 16 ALS individuals on the Happé Cartoon and Scenarios task (Happé et al., 1999). The ALS group performed significantly worse than controls on the scenario subtask, but only a trend of impaired performance was observed for the two cartoon subtasks. Lack of group differences were attributed to variation in ALS performance, which ranged from normal to significantly impaired. Impairments were more prominent in patients with bulbar symptomology, which converges with studies that posit bulbar signs as a potential susceptibility factor for cognitive decline.

Error analysis revealed that ALS participants as a group provided more descriptive responses, lacking abstract inferences. The subgroup of bulbar patients committed more concrete errors than controls; an error pattern noted in FTD patients on the same task (Snowden et al., 2003).

Notably, patients displayed no evidence of a differential impairment for ToM compared to control conditions across all subtasks.

Evidence for a selective ToM deficit has been indicated by one study which employed the Social Faux Pas test (Stone et al., 1998). This task consists of written scenarios containing characters saying and committing socially inappropriate comments or actions. Participants are required to identify and explain the faux pas through a series of questions which tap into the participant's ToM ability and awareness of social proprieties. Performance on this task by a group of ALS individuals indicated impairment in identifying faux pas scenarios, as well as an inability to qualify a correctly identified faux pas. In contrast, on scenarios not involving faux pas, ALS participants were unimpaired, indicating specific compromise in ToM ability. Performance on an oral fluency task had been co–varied out in these analyses, leading the authors to conclude that performance was not attributable to executive dysfunction (Meier et al., 2010). Although, a caveat of this procedure is that it assumes the single fluency measure entered as a covariate represents all constituents of executive function or that the nature of executive involvement is similar between tasks.

Further delineation on the nature of ToM deficits in ALS is provided by a study which investigated ToM ability under conditions of private (individual) and social (group) intentionality (Cavallo et al., 2011a). A theoretical distinction among varieties of intentions posits that private intentions necessitate individually–driven behaviour to secure a goal while social intentions involve a social goal requiring action from several individuals. Disproportionately wider prefrontal engagement in social relative to private intentions has been observed in neuroimaging paradigms (Ciaramidaro et al., 2007; Enrici et al., 2011). Using a cartoon completion task, Cavallo et al (2011a) found that ALS individuals showed a dissociation of ToM ability. Patients accurately inferred private intentions of individual characters but failed to demonstrate understanding of social intentions. This selective impairment has previously been shown in FTD patients (Cavallo et al., 2011b), further suggesting a similar nature of ToM deficits between the two diseases. Individual analysis of performance supported group comparisons with the same direction of effect in 12 of the 15 patients. The focus on distinct types of intentions under social compared to non–social contexts is a novel departure from previous studies which have typically compared general inferential ability to specific ToM ability under social and non–social contexts within the same experimental categories. As Cavallo and colleagues suggest, this may explain the heterogeneous results obtained across these studies. On the other hand, ceiling performance

on the non–social (private intention) items was found in both participant groups, implying that the social stories may have been relatively more complex than the non–social items and perhaps required greater executive demand. Executive dysfunction, therefore, may have been a source of the observed selective deficit, rather than specific difficulty with inferring social intentions.

A further dissociation of ToM ability in ALS was explored using a non–verbal cartoon completion task that entailed emotional and cognitive attribution under separate conditions (Cerami et al., 2013). Twenty ALS patients and 56 healthy controls were presented with comic strips comprising three pictures depicting a story. Participants were asked to complete the story with a picture from a choice of three possible alternatives. These alternatives depicted plausible, implausible or plausible but incorrect endings. One condition required the identification of characters' emotional states (emotional attribution), while a second condition involved the identification of characters' intentions (cognitive attribution). A control condition depicted pictures, which required the application of causal knowledge relating to the physical properties of objects. No differences were found between participant groups on the control or cognitive attribution conditions. However, significantly reduced performance in patients relative to controls was noted for the emotional attribution items. The results align with those from previous studies noting socio–emotional processing impairments which are isolated from executive dysfunction in patients. Performance differences may be explained by the heterogeneous quality of ALS ToM impairment, which itself may correspond to variation in neural damage.

Van der Hulst, Bak, and Abrahams (2014) further delineated a ToM deficit, by distinguishing between Affective and Cognitive subcomponents, and determining the relationship to behavioural change, levels of empathy and self-awareness. The Cognitive–Affective Judgement of Preference Test was administered to 33 patients with ALS and 26 controls. Furthermore, a comprehensive neuropsychological battery and detailed behavioural assessment was conducted. Patients with ALS showed a significant impairment in Affective ToM only when compared with healthy controls, with a deficit in 36% of patients; 12% showed an isolated Affective ToM deficit while 24% showed more generic ToM dysfunction. A Cognitive ToM deficit was found in 27% of patients, with 3% showing an isolated Cognitive ToM deficit. This specific difficulty in identifying and distinguishing the feelings and thoughts of another from a self-perspective may underpin the social behavioural abnormalities present in some patients with ALS, manifest as apathy and loss of awareness.

Carluer et al., (2015) aimed to clarify whether a cognitive ToM deficit is indeed associated with ALS, specify the putative link between ToM deficits and executive dysfunction in ALS, and identify the dysfunctional brain regions responsible for any social cognition deficits. Twenty-three patients with ALS and matched healthy controls were recruited, and assessed using an original false-belief task and a specially designed battery of executive tasks. Carluer et al., confirmed the presence of cognitive ToM deficits in patients compared with controls, and revealed significant correlations between ToM and executive function. Watermeyer et al., (2015) later confirmed this through a cross-sectional study, which examined ALS patients' performance on measures requiring social inference, and determined the relationship between such changes and variations in mood, behaviour, personality, empathy and executive function. Patients also performed worse on individual tests of executive function measuring cognitive flexibility, response inhibition and concept formation. ALS patients were also significantly impaired on individual aspects of social cognition assessing the attribution of emotional and mental states. Regression analyses indicated that ALS-related executive dysfunction was the main predictor of social cognition performance, above and beyond demographic variables, behaviour, mood and personality. On at least some aspects of social cognition, impaired performance in ALS appears to be secondary to executive dysfunction.

2.3.2.2 Empathy

While some behavioural inventories include items which assess empathic responding, to date, there have been no formal attempts to directly assess levels of self– or caregiver reports of empathy in non-demented ALS. This is surprising given the growing evidence for reduced empathic ability in FTD (Fernandez-Duque et al., 2009; Rankin et al., 2005), which has shown to correlate with performance on measures of social cognition (Shany-Ur et al., 2012). If changes in socio–emotional processing are indeed reflective of those apparent in bvFTD, it would follow that empathic ability in ALS might also be compromised. Further, its relationship to other constructs of social cognition, such as ToM, and emotion processing is of theoretical and methodological interest to future ALS studies. Determining the presence of reduced empathy in ALS may also benefit current understanding of behavioural change within the disease, and in addition its impact of the patient–caregiver relationship.

2.3.2.3 Emotional Processing

Compared with healthy participants, ALS patients evaluated emotional images as more positive and reported a balanced state of subjective arousal when viewing scenes that

contained social situations and facial expressions i.e., they rated calm pictures as more exciting and exciting pictures as more calm (Lule et al., 2005). A second study used fMRI to measure participants' neural response patterns to similar emotive stimuli (Lulé et al., 2007). The data revealed that ALS patients showed increased activation in the right supramarginal gyrus, a region which has previously been noted for its involvement in the recognition of basic emotion from faces (Adolphs et al., 2000) and its recruitment in the cognitive reappraisal of aversive stimuli (Ochsner et al., 2002). The enhanced neural response pattern became more pronounced at a six month follow–up, indicating increased recruitment of this area along the disease progression. Intriguingly, other areas, such as the amygdala and AC which are typically associated with altered response patterns for valence and arousal (Anders et al., 2004) did not contribute to group differences. However, 11 of the 13 ALS patients from the study showed reduced amygdala volume in a separate analysis. A possible interpretation of these findings may be that the progressive recruitment of somatosensory regions acts as a compensatory mechanism in the context of other compromised emotion–processing substrates. At the follow–up, patients also showed a reduction in brain responses from baseline in the anterior insula, an area strongly associated with arousal and subjective emotional awareness (see Craig, 2009, for review). Moreover, these reduced responses correlated with the subjective arousal reports at the initial assessment, indicating that the subjective experience of attenuated arousal may precede the underlying progressive neuropathology.

The relevance of altered socio–emotional processing in ALS is highlighted by findings of altered social perception in the context of hypothetical social situations. In a social judgement task, participants were asked to imagine a scenario in which a presented face is available to them for travel directions and to rate how approachable they believe that face to be i.e., how likely they were to ask them for directions. Although an earlier study found no difference in ratings for faces between non–demented patients and controls (Papps et al., 2005), a later study comprising of ALS and ALS–FTD patients did show evidence for altered responding relative to controls (Schmolck et al., 2007).

2.3.2.4 Emotional memory

Reduced arousal for affective material may be related to impaired recall of emotional stimuli, which has also been demonstrated in ALS samples. Papps et al (2005) found that ALS individuals failed to demonstrate enhanced recognition of emotional words relative to neutral

words, a pattern of performance typically observed in healthy individuals (Bradley et al., 1992; Brierley, 2004; Kuriyama et al., 2010). These results could not be explained by general memory impairment or fatigue effects, as the ALS individuals showed enhanced memory for neutral words relative to controls. However, a recent study which included a standardized measure of verbal memory found that a subgroup of ALS patients who failed to demonstrate enhanced emotional word recognition on the same task did display general memory impairment (Cuddy et al., 2012). In contrast to Papps et al, this study failed to find overall group differences, although heterogeneous ALS performance within a small sample size, greater equivalence in mood levels between groups and a methodological departure in measure administration, may have contributed to the dissimilar results obtained.

If the impairments found in Papps et al's study are reflective of an exclusive difficulty in the encoding, consolidation and/or retrieval of emotionally–toned material, they may implicate underlying neuropathology of the limbic structures in ALS. The aim of a recent study by Cerami et al., (2014) were to evaluate two components of empathy in non-demented ALS subjects, and to associate performance with regional grey- matter density using VBM. Twenty non-demented sporadic probable or definite ALS patients and 56 matched healthy controls participated in a non-verbal task requiring the attribution of emotional versus cognitive states to identify the correct ending of comic strips, compared with a control condition requiring identifying causal relationships devoid of social components. A subgroup of 14 ALS and 20 controls underwent the VBM study. Results demonstrated that, compared with controls, ALS patients showed defective emotional empathy attribution, related with reduced grey-matter density in the anterior cingulate cortex and right inferior frontal gyrus. Cerami et al., provide evidence of a specific impairment of emotional empathy in ALS patients, reflecting neural damage in a limbic prefrontal network involved in emotional processing. These data are highly relevant, as social cognition disorders may represent a marker of cognitive dysfunction in ALS.

Enhanced memory for emotional stimuli has been associated with amygdala activation in healthy individuals (Canli et al., 2000), while selective deficits in emotional memory recognition have previously been noted in patients with amygdala damage (Cahill et al., 1995). Although neuroimaging studies have documented amygdala abnormalities in ALS patients (Anderson et al., 1995; Kawashima et al., 2001), corresponding neuroimaging data is required to determine if the selective deficit observed is associated with damage to or dysfunction of this or other neural processes. Furthermore, it remains to be seen whether recognition deficits for emotional words can be replicated for memory of other types of

emotional stimuli, such as prose and scenes or whether it is representative of memory changes for personal emotional events.

2.3.2.6 Emotional Perception/Recognition

Studies of emotion recognition for prosodic stimuli, albeit limited, have produced varied results. An initial study found that, relative to controls, ALS patients showed a generally absent impairment for emotionally–intoned sentences (except for the recognition of surprise) in the context of significantly reduced recognition accuracy for emotional faces (Zimmerman et al., 2007). This dissociation in performance between the two tasks might suggest a selective impairment for facial information only in ALS or imply a relative insensitivity of prosodic tasks in detecting emotional processing dysfunction in these patients. In contrast to these findings, Meier et al (2010) did demonstrate a deficit using the Aprosodia Battery (Ross et al., 1997), a task requiring the identification and discrimination of emotion from asyllabic utterances and syllables in addition to sentences. This task may be more difficult or sensitive than the one used in the former study. Notably, these patients showed a deficit in recognising emotion but not discriminating between them, indicating that difficulties reflected impaired recognition of the emotions themselves, rather than perceptual deficits. Findings from studies examining the recognition of emotion from faces have been similarly inconsistent. While an early investigation found no evidence of impaired facial emotion recognition in 19 ALS individuals (Papps et al., 2005), later studies have documented significantly worse performance of patients in comparison to healthy controls (Girardi et al., 2011; Lillo et al., 2012b; Zimmerman et al., 2007). Lillo et al (2012b) employed a modified version of combined facial recognition tasks, with some faces morphed to display different intensities of affect. The authors did not analyse, or at least report, any effects of emotion intensity on recognition accuracy in their sample. Since emotional intensity has been shown to influence accuracy of emotion identification across different stimuli (Hess et al., 1997; Kumfor et al., 2011), such an analysis may have provided better insight into the degree of the recognition deficit that was found. Nonetheless, the study did include a cohort of FTD patients for comparison with ALS and healthy control samples. It was found that the ALS group performed significantly worse than controls but significantly better than FTD patients, indicating a continuum of performance across the three groups and suggesting a comparable if not attenuated recognition deficit in ALS relative to FTD.

A subsidiary consideration is whether the recognition of specific emotions is affected in ALS. In one study, basic emotions such as sadness, disgust, angry and surprise showed statistically

significant group differences (Zimmerman et al., 2007), while in other studies only group effects for overall performance accuracy have been noted (Girardi et al., 2011; Lillo et al., 2012b; Oh, Oh, Kim, Park, & Kim, 2016). In FTD studies, a selective deficit in recognising negative facial expressions is commonly reported (Fernandez-Duque & Black, 2005; Werner et al., 2007). However one study which compared subgroups within their FTD cohort found that the selective deficit was shown only for patients with predominantly temporal–lobe involvement. Patients with disproportionately more frontal–lobe atrophy showed impairments for both negative and positive facial expressions (Rosen et al., 2004). These findings suggest that frontal–lobe pathology in FTD may correspond to more profound or global impairment in emotion recognition than regionally restricted temporal–lobe atrophy. Given that ALS patients have shown simultaneous deficits in identifying positive and negative emotions and that most studies have documented impairments in overall performance accuracy rather than in specific emotions or valence–type, it is possible that the nature of the ALS deficit is in keeping with that of FTD patients with prominent frontal–lobe atrophy. Alternatively, the acknowledged anatomic heterogeneity within ALS samples in terms of the degree and pattern of patient neurodegeneration may itself have influenced the behavioural results obtained in these studies.

2.3.2.6 Affective decision–making

Decision-making under conditions of reward, punishment, ambiguity and risk has also been studied in non–demented ALS. Although no group effect was observed in one study using a similar probabilistic reversal-learning task (Meier et al., 2010); differences between ALS participants and healthy controls have been observed using the Iowa Gambling Task (IGT, Bechara et al., 1994; Bechara, Damasio, & Damasio, 2000). This task requires the selection of cards from four alternative decks, with the objective to maximise monetary reward. However, the distribution of reward and penalties between decks is such that selection from some decks leads to an overall gain, while selection from other decks leads to an overall loss; these latter decks being associated with increased risk. Using an abbreviated version of the IGT, Girardi et al (2011) found that, in contrast to controls, ALS participants continued to select from high–risk decks despite the negative consequences associated with monetary loss. Notably, ALS individuals did not display increased selection from high–risk decks with task progression, a response style noted in FTD patients (Torralva et al., 2007). Instead, performance was uniform throughout the task, indicating an executive failure to learn reward–penalty contingencies rather than a heightened risk–taking preference (Clark & Manes, 2004). In support of an executive dysfunction contribution to task performance, correlational

analyses revealed a positive relationship between this selection behaviour and higher self–reported rates of executive and overall behavioural dysfunction. However, no relationship with objective measures of executive function was found.

2.3.3 Language

2.3.3.1 Confrontation naming

In addition to the relatively robust fluency deficits demonstrated in non–demented ALS patients, impairments in confrontation naming have been reported (Abrahams et al., 2004; Cobble, 1998; Hanagasi et al., 2002; Kilani et al., 2004; Mantovan et al., 2003; Taylor et al., 2013; Wicks et al., 2009), albeit less consistently (Abrahams et al., 2000; Kew et al., 1993a; Rakowicz & Hodges, 1998; Talbot et al., 1995). Phonemic and semantic paraphasias, errors which are associated with PNFA and SD (see Chapter 1), have also been demonstrated in ALS patients on these tasks (Mantovan et al., 2003; Rakowicz & Hodges, 1998; Strong et al., 1999).

Leslie et al., (2015) employed a cognitive and voxel based morphometry study to investigate and establish neuroanatomical correlates of semantic deficits in ALS, and ALS-FTD. They also recruited patients with semantic dementia (SD) and controls. Semantic deficits were evaluated using naming and semantic knowledge composite scores from the Sydney Language Battery (SYDBAT). ALS patients were less impaired than ALS-FTD patients, who in turn were not as impaired as SD patients. However, the authors used a screening tool, which does not account for motor disability, and little reference is made to the impact of executive dysfunction on language in this study.

The clinical presentation of language deficits in ALS, such as naming, comprehension, verb processing etc., can be contextualised through the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) model proposed by Kay, Lesser, and Coltheart (1996). The PALPA is considered one of the most testable cognitive models of language available, and the proposed model adopts aspects of the central system i.e., modules relating to phonological analysis, and auditory processing.

2.3.3.2 Comprehension

Much like ALS naming studies, the assessment of receptive language has produced mixed results. An early study found significant differences between 19 ALS patients and 10 controls on the Token Test which requires the adherence to verbal commands of increasing complexity

(Talbot et al., 1995). Subsequent larger studies have failed to detect group effects using the same task (Mantovan et al., 2003; Rusina et al., 2010). Other means of assessment have included testing the ability of participants to match spoken sentences with pictures or line drawings, on trials of increasing grammatical complexity. Findings of impaired performance have like–wise been variable across small samples which have on occasion included patients with FTD–PPA (Cobble, 1998; Rakowicz & Hodges, 1998; Strong et al., 1999), thereby limiting inferences regarding comprehension difficulties in the non–demented ALS population. In a similar fashion, it has been recommended that syntactic comprehension be evaluated in bulbar-onset ALS patients, though the generalizability of recent research is implicated by inadequate sample size (Yoshizawa et al., 2014). Using the Test for the Reception of Grammar 2nd Edition (TROG-2) syntactic comprehension was assessed recently across the spectrum of ALS-FTD (ALS n=20; FTD-ALS n=15; PNFA n=27; and Controls n=23), Kamminga et al., (2016) report that syntactic comprehension deficits were detected in 25% of ALS (p=.011), 92.9% of FTD-ALS (p<.001), and 81.5% of PNFA (p<.001) patients. FTD-ALS patients were disproportionately impaired compared to PNFA. Impaired TROG performance was frequent in ALS with early bulbar involvement, but did not correlate with bulbar impairment overall.

2.3.3.3 Verb and noun processing

The selective deficit in verb processing shown in ALS–FTD, has also been demonstrated in non–demented ALS patients. Despite recent interest in cognitive changes in patients with ALS, investigations of language function looking at the level of word, sentence and discourse processing are relatively scarce. Grossman et al (2008) compared knowledge of verbs and nouns in a sample of 34 ALS patients. Participants were required to select one of two available single word choices that best matched either a presented verb (associated with an action) or noun (associated with an object). In addition, participants were asked to match one of four available action verbs or object nouns with a phrase describing either an action or an object. A pattern of impaired action knowledge (verb processing) compared to object knowledge (noun processing) was revealed in 24 ALS patients. Participants also completed a brief assessment of executive functioning and grammatical comprehension. Performance on both verb and noun processing correlated positively with grammatical comprehension, suggesting that the latter did not influence the select deficit in verb processing in these patients. Data then presented by Tsermentseli, Leigh, Taylor, Radupovic, Catani, and Goldstein (2016) support implication of the semantic system, and document the relevance of subtle language dysfunction as a marker for cognitive change prior to executive dysfunction.

2.3.3.4 Writing Errors

Increased writing errors in the form of syntactic and spelling mistakes and the omission and substitution of letters have been observed in ALS patients without overt dementiaor aphasia compared to controls (Cobble, 1998; Ferguson & Boller, 1977; Ichikawa et al., 2010; Tsuji-Akimoto et al., 2010). These errors are qualitatively similar to the agraphia, paragraphia and spelling errors reported in aphasic ALS patients (Ichikawa et al., 2008). In non–demented ALS, writing errors have been proposed as predictive of frontotemporal degeneration (Ichikawa et al., 2011). Similarly, the severity of writing errors has been associated with neuronal loss in the AC gyrus (Yabe et al., 2012).

2.3.3.5 Discourse

Discourse analysis has been used to investigate spoken language in non–demented ALS patients using the Cookie Theft picture description task (Goodglass et al., 2001) and a topic–directed interview. On both tasks, Strong et al (1999) found that ALS patients produced significantly less self–corrected errors relative to controls at baseline and again at a 6-month follow–up. Discourse deficits may reflect underlying executive dysfunction rather than discrete language disruption in ALS patients. This suggestion is supported by studies, which reveal a relationship between executive function and discourse production in several neurological conditions, including FTD (Ash et al., 2006; Coelho et al., 1995).

2.3.3.6 Language dysfunction and relation to executive dysfunction

Meta–analysis supports the presence of language dysfunction in ALS, as a significant medium effect size for language deficits based on seven studies ($n=155$, $d=0.53$, $p<.05$, 95% CI [0.09;-0.97]) has been demonstrated (Raaphorst et al., 2010). Population research indicates a higher prevalence of language dysfunction in patients (23.3%, $n=232$) than previously suggested by clinic–based investigations (Phukan et al., 2012). Nevertheless, these studies include restricted sets of language assessment, thereby limiting inference regarding the profile of impairment. Debate surrounds whether ALS language dysfunction is reflective of aphasic–type impairment or secondary to executive deficits (Bak & Hodges, 2004; Talbot et al., 1995).

2.3.4 Memory

2.3.4.1 Recall and Recognition Memory

Immediate verbal recall has been shown to be impaired in some (Gordon et al., 2010; Hammer et al., 2011; Mantovan et al., 2003; Ringholz et al., 2005) but not all studies (Hanagasi et al., 2002; Rottig et al., 2006), on measures of verbal span, word and prose

retrieval. Delayed verbal recall is, likewise, highly variable (Gallassi et al., 1989; Hanagasi et al., 2002; Hartikainen et al., 1993; Iwasaki et al., 1990; Kilani et al., 2004; Neary et al., 1990; Paulus et al., 2002). Impaired cued verbal recall has been noted in ALS patients using the Paired Associative Learning task (David & Gillham, 1986; Phukan et al., 2012) and others assessing immediate and delayed cued recall (Hanagasi et al., 2002). However, some studies measuring similar processes have failed to replicate these results (Abrahams et al., 1997; Abrahams et al., 2004; Abrahams et al., 2005b; Kew et al., 1993a).

A comparable inconsistency exists for studies assessing immediate and delayed visual memory recall. ALS patients have displayed reduced immediate recall of visual stimuli (David & Gillham, 1986; Gallassi et al., 1989; Kew et al., 1993a; Mantovan et al., 2003; Palmieri et al., 2009; Ringholz et al., 2005), but not consistently (Abe et al., 1997; Abrahams et al., 1997; Evdokimidis et al., 2002; Lakerveld et al., 2008; Ludolph et al., 1992; Wicks et al., 2009).

A minority of studies have investigated delayed visual recall, with some finding impairment (David & Gillham, 1986) but not others (Evdokimidis et al., 2002; Kilani et al., 2004). Abdulla et al., (2014) conducted a detailed study of visual and verbal memory, and tested the hypothesis that memory impairment in patients with ALS is related to hippocampal degeneration. Consecutive patients with ALS (n=58) and 29 matched controls participated in standardized neuropsychological assessment and magnetic resonance imaging. Patients with ALS performed worse in global cognitive functioning, executive function and verbal memory tests ($p < 0.05$). Verbal memory test performance correlated with the left hippocampal volume in patients with ALS ($p < 0.05$), although there was no significant correlation with tests of executive function and clinical variables underscoring the specificity of the present findings. In a similar study of prose verbal memory, Raaphorst et al., (2015) investigated brain atrophy in relation to memory function (prose). Twenty-six ALS patients without dementia and 21 healthy controls (matched for gender, age and education level) underwent comprehensive neuropsychological evaluation and T1- and T2-weighted 3T MRI brain. Grey and white matter brain volumes were analysed using VBM and age related white matter changes were controlled for. The most frequently abnormal memory test (<2 SD below normative data corrected for age, gender and education) was correlated with regional brain volume variations by multiple regression analyses with age, gender and total grey matter volumes as covariates. Immediate and delayed story recall scores were abnormal in 23% of ALS patients and correlated to bilateral hippocampus grey matter volume ($r = 0.52$ for both memory tests; $p <$

0.05; corrected for age, gender and total grey matter volume). This correlation was not found in healthy controls with similar age, education and global white matter changes.

Consonni et al., (2015) recently utilised the Rey Auditory Verbal Learning Test (RAVLT) to investigate verbal episodic memory. Immediate and delayed recall performances of 13 non-demented ALS patients with a specific mild executive dysfunction (ALSci) were investigated and compared their performances to those of 48 healthy controls, and 13 cognitively normal intact ALS patients. Compared to cognitively intact ALS and controls, ALSci patients had a selective mid-list impairment for immediate recall scores. These results suggested that subtle executive dysfunctions might influence the recall of mid-list items, possibly reflecting deficiency in control strategies at retrieval of word lists, whereas severer dysexecutive syndrome might also affect the recall of terminal items possibly due to attention deficit or retroactive interference.

Recognition for verbal information is largely reported as preserved (Abrahams et al., 2005b; Hanagasi et al., 2002; Kew et al., 1993a; Massman et al., 1996; Rottig et al., 2006), although some studies have noted impairments (Abrahams et al., 1997; Machts et al., 2014; Mantovan et al., 2003). Recognition of visual information has been assessed using varied non–verbal stimuli, such as faces (Abrahams et al., 1997; Hanagasi et al., 2002; Kew et al., 1993a; Ringholz et al., 2005; Strong et al., 1999; Talbot et al., 1995), figures and patterns (Chari et al., 1996; Frank et al., 1997; Gordon et al., 2010; Mantovan et al., 2003), again providing inconsistent results.

2.3.4.2 Nature of memory impairment in ALS

Published evidence on recall and recognition memory in ALS is highly variable. A better indication of the memory profile in ALS might be provided through meta–analysis. Raaphorst et al (2010) found significant mean effect sizes for immediate but not delayed verbal memory domains. A significant mean effect size for visual memory impairment was also found. Generally, immediate memory impairments are attributed to executive impairments related to the frontal cortex, while delayed memory recall is associated with medial temporal–related processes (Lezak, 2004). The profile indicated by this study therefore implicates a frontally–mediated memory deficit in ALS. Notwithstanding, the proposed involvement of medial temporal lobe in memory change in ALS is not irrelevant.

2.3.5 Visuoperception and visuocontructive skills

Visuoperceptual function refers to a set of processes that include object identification and recognition (Phukan et al., 2007). Sustained and directed attention are also required, which can cause secondary deficits on visual tasks. Visual processes are relatively spared in ALS,

and this model provides information on some of the intact sub-processes. These processes are largely preserved in ALS, as suggested by individual studies (Kew et al., 1993a; Massman et al., 1996; Ringholz et al., 2005; Talbot et al., 1995; Wicks et al., 2009) and meta–analysis (Raaphorst et al., 2010). However, mild impairments using a motor–free visual perception test (Strong et al., 1999); object decisions test (Robinson et al., 2006) and a line orientation task (Hanagasi et al., 2002) have been reported. Where impairments are found, it is possible that these deficits are secondary to the executive dysfunction inherent in the respective patient samples, rather than visuoperceptual difficulties per se.

Findings of similar impairments reported sporadically in FTD patients are often interpreted in light of severe executive impairment (Zakzanis, 1998). Despite a lack of impairment findings, these tests are often included to eliminate the possibility of global cognitive deficit that might influence performance in other cognitive domains.

2.3.6 Relationship between disease variables and cognition in ALS

Studies supporting the existence of neuropsychological impairment in ALS must account for disease–related factors which could reasonably explain or at least contribute to cognitive change:

1) Respiratory insufficiency is an inevitable consequence of the disease course and has been associated with cognitive dysfunction in ALS (Kimura et al., 1999; Newsom-Davis et al., 2001). Recently, comparable executive functioning was documented between patients with intact (n= 20) and compromised (n=24) respiratory function (an FVC score <80%). However, within the respiratory–impaired group, those not receiving pulmonary interventions did show greater executive impairment than those receiving treatment (Strutt et al., 2012). This supports earlier findings (Newsom-Davis et al., 2001) that respiratory insufficiency may contribute to reduced cognitive functioning, but that once treated impairment may be less evident. Cognitive assessment in ALS should monitor and control for this potential confound, but in practice the use and methods of respiratory assessment do vary between studies, and is not consistently reported. In another study, emotional well-being was shown to be negatively implicated by the impact of physical impaired in ALS (Abdulla et al., 2014b).

2) Disease severity and cognitive function, with composite scores derived for executive function and social cognition, have been investigated in relation to caregiver burden. Only disease severity and behaviour were reported to be significant (Watermeyer et al., 2015b). The study highlights the potential impact of ALS patients' functional impairment and behavioural change on ALS caregivers' psychosocial functioning. Trojsi et al., (2013)

assessed neuropsychological functioning at different stages of ALS to further delineate the occurrence of cognitive impairment alongside the trajectory of ALS i.e., disease variables. Seventy-four ALS patients were classified into four different clinical stages of disease, according to the King's staging system, and their corresponding cognitive profiles were compared. Global cognitive assessment and executive tasks (i.e., Frontal Assessment Battery and Trail Making Test B-A) and long-term memory (i.e. memory prose) were significantly different among the subsets of ALS patients, showing poorer performances with increasing clinical disability.

3) The impact of mood and fatigue on cognitive performance has received little attention, despite demonstrable relationships in other neurodegenerative disorders (e.g. Diamond et al., 2008). In one study, depression differentially affected ALS patients and controls. Neither group means met cut–off criteria for clinical depression; depression scores overall were not associated with cognitive performance in one group more than the other. Instead, depressive symptoms were negatively associated with patients' performances on delayed recall, naming and visuospatial ability, but were negatively associated with controls' performances on immediate recall and verbal fluency (Jelsone- Swain et al., 2012). Although group differences in cognitive performance were associated with the presence of depressive symptoms, they do highlight the importance of considering mood assessment alongside cognitive testing, as significant associations were found within the groups. In the same study, 'vegetative' symptoms (which comprised fatigue items) were not associated with cognitive performance in the ALS sample. A lack of effect might be attributed to better physical functioning in the group included in the analysis, although a relationship between cognitive impairment and level of physical functioning has been inconsistently reported (Gordon et al., 2010; Jelsone-Swain et al., 2012; Lakerveld et al., 2008).

4) The rate of disease progression may be a more useful predictor of cognitive impairment, as clinic and population–based research has associated executive dysfunction with more aggressive disease course (Elamin et al., 2013; Gordon et al., 2010; Phukan et al., 2012). Site of disease onset may also be relevant to neuropsychological functioning in ALS. Patients with bulbar–onset disease have shown impaired cognitive performance relative to limb–onset patients and healthy controls in cross–sectional and longitudinal analyses (e.g. Abe et al., 1997; Portet et al., 2001; Schreiber et al., 2005; Strong et al., 1999). However, these findings are not always replicated (e.g. Kilani et al., 2004; Ringholz et al., 2005; Rippon et al., 2006; Stukovnik et al., 2010; Zalonis et al., 2012). The presence of pseudobulbar palsy may also be

associated with cognitive dysfunction (Abrahams et al., 1997).

Using clinic-based information available at the first clinic visit, Elamin, Bede, Montuschi, Pender, Chio, & Hardiman, (2015) have developed a practical prognostic algorithm for patients with ALS. The ALSFRS-R was used to quantify disease specific variables, with executive dysfunction, and site of onset. A high-risk classification was associated with a positive predictive value for poor prognosis of 73.3–85.7 % and a negative predictive value (NPV) for good prognosis of 93.3–100 %. Classification into the low-risk group was associated with an NPV for bad prognosis of 100 %. A simple algorithm using variables that can be gathered at first patient encounter, validated in an independent patient series, reliably predicted prognoses in ALS patients, illustrating the importance of both cognitive and physical symptoms on patient prognosis.

2.3.7 Neuropsychological profile of ALS and emotional lability

Emotional lability (EL) has been investigated sparingly. An early neuropsychological study found that total errors on the WCST predicted the presence of EL symptomatology with 75% accuracy (McCullagh et al., 1999), although a later study failed to identify any relationship using an abbreviated version of the same task (Palmieri et al., 2009). However, different measures of EL were used and the latter study's sample comprised several MND variants (i.e., PMA, PLS patients), which may show variable EL severity and different profiles of neuropsychological change. Assessing the relationship between EL and cognitive change in ALS is confounded by the presence of other disease factors.

Some evidence indicates a relationship between episodes of crying and depression (Moore et al., 1997; Newsom-Davis et al., 1999), while another study has shown an association of EL with anxiety and emotional fragility (Palmieri et al., 2009). Other studies have noted EL symptoms in non–depressed and non–anxious patients who show cognitive change (Girardi et al., 2011; Wicks et al., 2009). Furthermore a relationship between EL and cognition may be a function of bulbar symptomatology, as EL is also more common in patients with bulbar presentation (Moore et al., 1997).

2.3.8 Cognitive impairment in large ALS cohorts

The reported prevalence of cognitive dysfunction in ALS varies among studies, presumably reflecting discrepancies in testing procedures, sample size and patient sampling. Furthermore, despite the introduction of methods to control for the confounds of motor impairment in

testing, studies diverge on their adoption. Similarly, inconsistent exclusion criteria across studies result in samples with variable co–morbid disease factors that may influence cognitive performance. Notably, different criteria of cognitive impairment are in use, further complicating comparisons between studies. In addition, referral bias from clinics, which may have a specific interest in ALS, might further distort these estimates.

The largest clinic–based neuropsychological study of ALS (n=279) to date reported that 51% of their patient sample demonstrated subtle to severe cognitive impairment; the more severely impaired meeting criteria for dementia (Ringholz et al., 2005). The study distinguished patient performance along a continuum of impairment. Mild cognitive impairment was defined as performance below the 5th percentile of the healthy control group performance on two or more neuropsychological tests. Moderate–severe impaired was specified as performance below the 2.3rd percentile of the control group on three tests. DSM–IV and McKhann criteria (McKhann et al., 2001) were used to establish dementia diagnosis. Of the 142 patients classified as impaired, 32% and 19% met the criteria for 'mild' and 'moderate–severe' cognitive impairment, respectively. Of the 'moderate–severe' patients, 15% were diagnosed with dementia. Forty–one 'demented' patients met criteria for FTD, while only 2 met criteria for AD. The study used a detailed neuropsychological battery of non–timed tasks that assessed several cognitive domains. However, measures of verbal fluency (COWA) and attention (VSAT) did not include a motor control condition, possibly inflating the prevalence of cognitive impairment obtained. Despite this limitation, the size of the study may provide a more reliable estimate of cognitive impairment in ALS than previous smaller investigations (e.g. Massman et al, 1996; Lomen–Hoerth et al, 2003; Rippon et al, 2006). The classification of patients into groups based on the severity of cognitive dysfunction underscores the continuum of impairment that can occur within the disease. Finally, the study supports the impression of a higher prevalence of FTD than other dementia syndromes, such as AD, in ALS.

This study was followed by another relatively large (n=110) clinic sample that differentiated neuropsychological performance between bulbar (n=40) and limb–onset (n=70) patients (Flaherty-Craig et al., 2006). The study used only three tests of cognitive assessment (verbal reasoning, verbal judgement and verbal fluency) and relatively less stringent criteria of cognitive impairment than Ringholz et al's study (1.5 standard deviations below total ALS group mean on the tests). Nonetheless, a comparison of patients with bulbar and limb onset revealed discrepant rates of impairment between the patient groups. Limb–onset patients showed lower prevalence of impairment on all three tests; corroborating previous reports of

an association between cognitive dysfunction and bulbar–onset disease. These results suggest that the prevalence of cognitive impairment in ALS may vary as a function of the ratio of bulbar versus limb–onset patients across patient samples. Cognitive dysfunction in ALS has been associated with shorter survival times and more aggressive disease (Elamin et al., 2013; Olney et al., 2005; Phukan et al., 2012; Rusina et al., 2010). This implies that clinic–based investigations which typically comprise prevalent cases may underestimate the incidence of cognitive dysfunction in the disease. A recent population–based study recruited 160 incident cases and found that approximately 40% of ALS sample showed cognitive impairment, predominantly but not exclusively in the form of executive dysfunction (Phukan et al, 2012). This estimate is lower than that reported by Ringholz et al's large clinic study; however, more stringent impairment criteria were applied in this study. Performance below the 2.3rd percentile of the control group (n=110) on two domain–specific tests qualified for impairment. Patients were classified according to a domain–based system rather than according to a continuum of general cognitive performance, which may also account for the lower prevalence reported.

In a large prospective cohort study reported by Oh et al., (2014), neuropsychological functioning was documented in patients without known genetic mutations in ALS. One hundred and sixty six patients were enrolled in a prospective longitudinal cohort, with six cognitive domains assessed; namely executive function, attention, language, calculation, visuospatial function and memory. ANOVA and t-tests were used to assess differences in clinical characteristics and neuropsychological parameters between sporadic ALS patients. Patients were categorised into five subtypes: normal cognition (ALS pure), cognitive impairment (ALSci), behavioural impairment (ALSbi), and frontotemporal dementia (ALS-FTD). Seventy patients (70/166, 42.2%) were cognitively or behaviourally impaired. Among the impaired patients, eight (8/166, 4.8%) had FTD-type dementia and one (1/166, 0.6%) was Alzheimer's disease-type. The ALS patients with cognitive impairment (ALSci) and with FTD (ALS-FTD) were more severely impaired in executive function, attention, language and memory than the cognitively intact ALS patients (ALS pure). The Kaplan-Meier method and Cox proportional hazard model were used for survival analysis whereby ALSci ($b = 1.925$, $p = 0.025$) and ALS-FTD groups ($b = 4.150$, $p = 0.019$) tended to have shorter survival than the ALS pure group.

Montuschi et al., (2015) investigated 207 ALS patients using a neuropsychological battery of tests; of these, 19 were excluded from the analysis due previous conditions affecting

cognition. Ninety-one (49.7%) patients were cognitively normal, 23 (12.6%) had ALS-FTD, 36 (19.7%) ALS-ECI (Executive Cognitive Impairment), 10 (5.5%) ALS-NECI, 11 (6.0%) ALS-Bi and 11 (6.0%) were deemed to be "non-classifiable", 1 had comorbid Alzheimer's disease. Patients with ALS-FTD were older, had a lower education level, and had a shorter survival than any other cognitive group, consistent with previous findings. Of the nine cases with C9ORF72 mutation, six had ALS-FTD, two ALS-ECI and one was cognitively normal. One of the five patients with SOD1 mutations and one of the five patients with TARBDP mutations had ALS-Bi. This study highlights the consistency in cognitive performance by ALS patients, the prevalence of ALS-FTD, and also the negative prognostic indicator assocated with a multisystem impairment. Notwithstanding, these studies also highlight the gross inconsistencies between cognitive categorisation terminology used, in spite of recognised consensus criteria for cognitive and behavioural impairment.

2.3.9 Longitudinal assessment of cognition in ALS

Only a few studies have assessed cognition over time in ALS. Due to the progressively debilitating nature of the disease, these studies are often confounded by high attrition rates, limited sample sizes, missing data and restricted compositions in which patients with more aggressive disease forms may be inadequately represented at follow–up. The first prospective study of cognition in ALS included 13 patients, of which only eight remained in the study at a six month follow–up (Strong et al., 1999). At baseline, only a test of visual perception distinguished patient and control performance. However, at follow–up the patient group showed relative impairments on tests of word generation, visual recognition of faces and visual perception. Bulbar–onset patients showed greater impairment than limb–onset patients at both testing points; impairments extended to working memory and cognitive flexibility for this group. Additionally, progression of cognitive impairment in the bulbar–onset group, but not the limb–onset group was evident, as involvement of cognitive domains increased between testing periods for these patients only.

In contrast to this first study, Kilani et al (2004) compared 18 patients and 19 controls over a period of 12 months and found generally preserved cognitive performance and lack of progression in their patient sample. At baseline, patients performed significantly worse than controls on a Trail–making test and the BNT, but these impairments were no more pronounced at subsequent follow–ups. Only two bulbar–onset patients were included in the study, which might explain the lack of deteriorated performance in this sample as opposed to Strong et al's study. Further, bulbar severity scores were reportedly low in the ALS patients.

Previous studies have noted a relationship of cognitive impairment with not only bulbar–onset location but severity of bulbar symptoms (Abrahams et al., 1997).

A larger prospective study directly compared bulbar (n=15) and limb (n=37) onset patients over a course of 18 months, at 4 month intervals (Schreiber et al., 2005). Unsurprising for a study of this length, only 19 of the original 52 patients remained in final follow–up assessment. Nonetheless, at baseline, neuropsychological testing revealed relative performance decrements in bulbar–onset patients compared to limb– onset patients on tests of word and design fluency. Although no profound deterioration was documented, these inter–group differences increased during follow–up, with the bulbar–onset group remaining significantly impaired. Due to the high attrition rate, longitudinal statistical analyses could not be applied to separate groups. Notwithstanding, the results, based on mean scores, do point to some decline in executive function for the bulbar–onset patients over the course of the study.

A similar profile of cognitive stability in ALS was suggested by another study using a comprehensive neuropsychological assessment of executive function, memory, language and visuospatial ability (Abrahams et al., 2005b). Only verbal fluency impairments were found in patients (n=20) at inclusion, but indices remained stable relative to controls (n=18) at the six–month follow–up. Using a computerized sentence completion test, and controlling for motor speech impairment, the study found significantly slower word retrieval response times between testing sessions for the patient group. It was noted that 50% of the patients at the second test session showed clinical signs of pseudobulbar palsy. It was not reported whether the presence or emergence of bulbar symptomatology was associated with performance deterioration. Notwithstanding, these results suggest that cognitive deterioration in non–demented ALS progresses slowly relative to the overall disease and that language function may be more vulnerable than other domains to deterioration over the course of disease.

Clinic–based studies are not only restricted in size but may also be susceptible to referral and selection bias, thus limiting the generalizability of their findings. Population–based research which follows incident cases through the disease duration may provide a better indication of the prevalence of cognitive impairment in ALS and the nature of its progression. One such study recruited recently diagnosed patients (n=186; diagnosis<12 months) from the Irish ALS register (Elamin et al., 2013). Patients and healthy controls (n=120) underwent comprehensive cognitive testing over a period of 18 months at four–month intervals. Patients who did not qualify for ALS–FTD (n=164) were designated to one of three groups, on the basis of cognitive performance at baseline. These groups were as follows: cognitively intact patients (n=94), patients with predominant executive impairment (n=47) and patients with

non–executive impairment i.e., memory and/or language dysfunction, n=28. Within the executive impairment group, some patients showed only executive impairment i.e., single–domain executive deficit, n=17, while in other patients the impairment extended to memory and/or language dysfunction i.e., multi-domain executive deficits, n=30. The majority of cognitively intact patients remained stable throughout the study, although the emergence of non–executive cognitive abnormalities, in particular language dysfunction, was noted in this group. The emergence of executive dysfunction was rare. This result resonates with earlier reports suggesting a higher susceptibility of language faculties to compromise with advancing disease (Abrahams et al., 2005b; Gordon et al., 2010). The majority of patients presenting with only executive dysfunction developed deficits in other cognitive domains. Patients with multi–domain executive dysfunction at baseline showed little progression, except for one patient who developed bvFTD. Similarly, only a small proportion of the remaining patients in the non–executive dysfunction group developed executive impairment. These results demonstrate not only that cognitive dysfunction in ALS may deteriorate with time, but that these cognitive deficits vary in presentation and progression. That is to say that ALS cognitive impairment may be characterised by distinct subtypes, each with their own clinical trajectory.

2.3.10 Behaviour Change in ALS

Relative to cognition, systematic study of behaviour in ALS has been slow in development. Unsurprisingly, the prevalence, incidence and nature of behavioural symptoms have not been fully ascertained (Lillo et al., 2010; Lillo & Hodges, 2010). Investigation is strongly influenced by the prevailing classification of the dementia subtypes associated with FTLD. This is underscored by current criteria proposing the application of FTD diagnostic features to the assessment of behavioural impairment in ALS (Strong et al, 2009). The term ALSbi is offered to denote those patients who do meet FTD diagnostic criteria, yet show mood independent change from disease onset. Research studies differ in the format (self or informant rated; questionnaire–based or structured) and type of inventory used. Furthermore, differing diagnostic criteria are applied to corroborate impairment. Despite these discrepancies, a proposed behavioural profile in ALS has emerged. The following section will outline and discuss the principal findings from the main studies of behaviour ALS, across the continuum of ALS-FTD.

2.3.10.1 Commonly reported behavioural symptoms

Direct comparisons of ALS and bvFTD patients show that, although behavioural symptoms are significantly less frequent in ALS, changes in behaviour are qualitatively similar between the two groups (Lillo et al., 2010). Apathy appears to be the most common behavioural

feature, although dysexecutive behaviour, social disinhibition and increased irritability are also reported frequently. A study of 45 patients which used the informant FrSBe found clinically significant levels of impairment on all three behavioural domains (as determined by a T–score cut–off of ≥65) following disease onset. The prevalence of impairment was highest for apathy (55.6%), followed by dysexecutive behaviour (46.7%) and disinhibition (28.9%). Only a statistically significant difference between pre– and post–illness–onset ratings was found for the apathy subscale (Grossman et al., 2007). Of note, premorbid ratings for all domains also met clinically significant criteria, suggesting that behavioural change in ALS may precede the physical symptoms associated with the disease. Alternatively, they might reflect pre–existing personality characteristics that have been previously noted in ALS by caregivers. The study design did not allow for the examination of these alternatives, but indicates an interesting avenue of investigation.

Silva et al., 2015 investigated the profile of patients across the ALS, ALS-FTD, and FTD spectrum. In total, 21 ALS, 12 FTD-ALS and 14 behavioural variant FTD (bvFTD) patients were included in the study. Moderate or severe behavioural disturbance was common in patients with ALS at baseline (47.6%), although less frequent than in bvFTD patients; patients with FTD-ALS displayed intermediate impairment. The ALSFRS-R did not correlate with the Frontotemporal dementia functional rating scale. These data are interesting as they illustrate the independence of ALS specific factors (i.e., ALSFRS-R), and show that behavioural change may be a primary marker of disease severity in ALS. Similar findings are reported by Andrews, Pavis, Staios, and Fisher (2016) using the Cambridge Behaviour Inventory, who report the domains with the strongest relationship to burden were everyday skills, and motivation.

The profile of apathetic behaviour has been noted in a larger study (n=225) using the same informant measure and clinical cut–off criteria. Relatively conservative frequencies of impairment for apathy (31.6%), dysexecutive behaviour (19.6%) and disinhibition (16.9%) were noted. Nonetheless, 40% of patients showed impairment on at least one domain subscale. Analyses of a subset of 39 patients with premorbid data revealed that all patients showed significant changes in the FrSBe subscales, including the total behavioural change score (Witgert et al., 2010). In another study, when more stringent criteria for behavioural change were applied (2 SD between premorbid and current FrSBe ratings) the results failed to find significant changes over time on any of the domains (Woolley et al., 2010a). However, in contrast to the previous study, ratings did not meet the cut–off criteria for significant

behaviour in either pre–morbid or post–illness–onset domains. Behaviour for all patients was characterised by caregivers as typical of the normal population. Thus, this small sample (n=17) may not have captured the proposed heterogeneity of behaviour in the ALS population. Gibbons and colleagues (2008) found a spectrum of behavioural change in 14 of their 16 ALS patients using the Manchester Frontotemporal Dementia Behavioural Interview (Bathgate et al., 2001; Snowden et al., 2001), an inventory which taps into a broad range of behaviours associated with FTLD. In all 14 patients, at least some change in affect and/or social behaviour was present. The most commonly reported change was increased self–centeredness and a reduction in concern for others, with over two–thirds (69%) of patients displaying these features. The authors suggested that this might reflect ego–centric behaviour typical of bvFTD. Other bvFTD–like behaviours included apathy (38%), blunting of emotion (25%), socially disinhibited behaviour (13%) and lack of awareness and concern for their disease (13%). Notably, the study also detected altered responses to sensory stimuli (50%) and repetitive, stereotyped behaviours (19%),suggestive of temporal lobe pathology associated with SD. Functional imaging in 8 patients did reveal frontal and temporal lobe abnormalities, although the imaging results were not formally examined alongside the behavioural scores.

Wei et al., (2014) employed a Chinese version of the frontal assessment battery (FAB) and frontal behavioural inventory (FBI) to evaluate 126 sporadic ALS patients and 50 healthy controls. Based on the FBI score, 46.0 % of patients showed varied degrees of frontal behavioural changes. The most common impaired neurobehavioral domains were irritability (25.4 %), logopenia (20.6 %) and apathy (19.0 %). The binary logistic regression model revealed that the ALS Functional Rating Scale-Revised scale score (OR 0.127, $P = 0.001$) was a potential determinant of an abnormal FBI. In contrast to many other studies, frontal functional impairment and the severity of frontal behavioural changes were not associated with the survival status or the progression of ALS by the cox proportional hazard model and multivariate regression analyses, respectively. In a similar study by Cui et al., (2015), irritability, logopenia, and apathy ranked highest as abnormal in their cohort of ALS patients. Correlation analysis revealed that the degree of behavioural change and frontal cognitive status were significantly associated with caregiver burden, with more extensive impact from disinhibitive behaviours.

Temporal lobe–mediated behaviours have also been detected in ALS using the Frontal System Behaviour Scale (Kertesz, 1997), however the depth to which these behaviours are being

investigated appear shallow (Radakovic, Harley, Abrahams, & Starr, 2015), prompting the need for ALS specific measures (Radakovic et al., 2016). Caregiver ratings for 198 ALS patients were identified as moderate–to–severe on bvFTD–like behaviours relating to apathy (13.6%), indifference (4.5%), perseveration (9.1%) and utilization behaviour (1.1%). However, items indicative of PPA, such as verbal apraxia and logopenia, were also identified as moderate–to–severe in 13.6% and 20.4%, respectively (Flaherty-Craig et al., 2009). The above studies delineate a heterogeneous nature of behavioural change in ALS, which may encompass milder forms of those seen across all the FTLD syndromes; possibly in accordance with underlying neuropathology. Nonetheless, caution in their interpretation is warranted. None of the behavioural measures employed across these studies have been validated in the ALS patients or adapted for the motor impairment. Responses to instrument items may be influenced by disease–related symptoms, although some studies do describe attempts to overcome this weakness through emphasizing the distinction of behavioural and physical symptoms to respondents (e.g. Grossman et al., 2007; Witgert et al., 2010). The same relates to results reported by Caga et al., (2016) who investigated whether apathy implicates survival in ALS patients. In their study, the majority of patients with moderate to severe apathy had a more rapid disease trajectory ($p = 0.003$) and had a median survival time of 21.7 months, considerably shorter than patients with mild apathy (46.9 months) and no apathy (51.9 months) ($p=0.0001$). Apathy remained a significant predictor of survival even after controlling for clinical factors and symptom duration at the time of study entry (hazard ratio 3.8, 95% confidence interval 1.9–7.5, $p = 0.0001$). These findings contradict those of Mioshi et al., (2014), who investigated patient susceptibility to neuropsychiatric symptoms in the context of progression of more classic motor symptoms in ALS and to examine the impact of neuropsychiatric symptoms on survival. Their study cohort consisted of 219 patients with ALS (limb onset n=159; bulbar onset n=60), with neuropsychiatric symptoms measured using the Motor Neuron Disease Behavioural Scale and more classic ALS symptoms assessed by the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised. A Rasch analysis and Cox proportional hazard regression models were used. The Rasch analysis demonstrated that neuropsychiatric symptoms appeared earlier than classic motor features of ALS. However, differences in neuropsychiatric scores did not affect survival: patients with abnormalities in neuropsychiatric domains did not exhibit a different rate of survival than those without.

These studies are subject to a number of methodological issues, and incongruences which may explain their differing findings. Subjective report designs and conventional methodological issues, such as recall bias and social desirability, apply. The common reliance

on informant–ratings indicates an assumption that informant reports are a reliable standard, but caregivers might underestimate patients' behavioural impairment through denial coping mechanisms and/or a lack of discernment of slowly developing changes leading to lower caregiver–ratings (e.g. Woolley et al., 2010a). Alternatively, increased distress, burden and a lowered quality of life might lead to overestimation of impairment by caregivers (Chio et al., 2010; Lillo et al., 2012a). In addition, few studies using self–report data employ a healthy control sample (e.g. Girardi et al., 2011; Wicks et al., 2009).

2.3.10.2 Behavioural change in non–demented ALS

Prevalence estimates of behavioural change in ALS vary by study, likely reflecting inconsistencies of the methodologies and diagnostic criteria used. A recent systematic review of 21 studies found that mild to moderate behavioural changes were shown in 17% – 88% of ALS patients without overt dementia (Raaphorst et al., 2012). One cross–sectional study which applied Strong et al's criteria to 23 patients and found that the prevalence of ALSci (31%) was higher than ALSbi (4%) and symptom co–morbidity (4%) (Consonni et al., 2013). However, as this sample size was small, generalisations about the relative prevalence of cognitive and behavioural dysfunctions in the ALS population are restricted. Larger studies, preferably with population–based designs, are warranted.

2.3.10.3 Mood, disease parameters and behavioural change

Whether behavioural symptoms in ALS are part of the degenerative process or simply a reaction or adaptation to the progressive and terminal nature of the illness is a matter of debate. For example, a sensible query is the contribution of depressive symptoms to elevated levels of apathy as reported by caregivers. Evidence for mood–independent behavioural change is supported by studies which have found raised apathy in non–depressed patients (Gibbons et al., 2008; Grossman et al., 2007; Lomen-Hoerth et al., 2003; Wicks et al., 2009; Witgert et al., 2010). Furthermore, in one study, depressive symptoms were present in 30% of ALS patients (n=81), but regression analysis revealed no relationship between mood symptoms and the presence of apathy (which was moderate to severe in 41% of patients), or any other behavioural symptom (Lillo et al., 2010). Again, some reported changes in ALS should be interpreted with caution due to the physically debilitating nature of the disease. Loss of functional independence may contribute to increased irritability or self–centeredness as reactive behaviours towards the illness (Gibbons et al., 2008).

Similarly, increased apathy in patients may be a response to the progressive loss of ability to engage with previous activities. Moreover, there is little study of whether behavioural change

in ALS is a manifestation of fatigue, sleep disturbance (see Lo Coco et al., 2011), or medication–use. Nonetheless, absent relationships between behavioural change and functional status or disease duration have been noted (Gibbons et al., 2008; Grossman et al., 2007; Terada et al., 2011; Tsujimoto et al., 2011; Witgert et al., 2010; Woolley et al., 2011). A recent study compared cognitive and behavioural functioning between ALS and PMA patients under the premise that the two cohorts would show similar motor dysfunction. The PMA group had longer disease duration, but groups were matched on motor disease severity.

Greater frequency of impairment in both cognitive and behavioural domains was found for the ALS group. In particular, 'aspontaneity' (or apathy) significantly differed between the two groups, with ALS patients showing a higher prevalence. Since the cognitive and behavioural profile of the PMA group was comparable to that of a healthy control group, these findings lend support to the notion that cognitive–behavioural impairment in ALS is not exacerbated by the physical limitations imposed by the disease (Consonni et al., 2013).

As with cognitive change, evidence for increased vulnerability of bulbar patients to behavioural impairment is suggested but not conclusive. The presence of bulbar symptomology has been associated with increased ratings of behavioural symptoms in some studies (Chio et al., 2010; Flaherty-Craig et al., 2009; Gibbons et al., 2008; Grossman et al., 2007), but not others (Consonni et al., 2013; Lillo et al., 2010; Witgert et al., 2010). Severity of bulbar symptoms did not show a relationship to behavioural change in one study (Grossman et al., 2007), while another showed that apathy and executive dysfunction were strongly related to presence of bulbar symptoms, more than to a bulbar disease onset (Chio et al., 2010).

2.3.10.4 Neuroanatomical basis of behavioural change in ALS

Neural correlates specific to apathetic behaviour have been suggested using DTI. Woolley et al (2011) assessed WM changes in 24 patients, 16 of whom received informant FrSBe ratings. A significant negative correlation between apathy change scores and alterations in the right AC was noted. Similar DTI data were obtained by another group investigating behavioural change in early–stage ALS (Tsujimoto et al., 2011). Twenty–one patients who were described as 'functionally independent' (defined by achieving at least a score of 2 or more on each sub-score of the ALSFRS–R) showed WM changes in the right frontal gyrus. Additionally, VBM analysis revealed that the severity of apathy was significantly correlated with atrophy in the OFC and DLPFC prefrontal cortices. An association between apathy and frontal lobe

abnormalities has also been reported in FTD (Zamboni et al., 2008). The above studies therefore affirm a view of continuity between ALS and FTD at the behavioural and neuropathological levels.

Behavioural changes in ALS might also reflect underlying genetic variation (Wicks et al., 2009). While sporadic patients showed a normal range of behaviour on the FrSBe, familial ALS (fALS) patients with and without SOD1 gene mutations endorsed significant levels of apathy following symptom onset. Additionally, non–SOD1 fALS patients showed significant post–illness–onset executive dysfunction scores. Due to the limited number of behavioural–genetic studies in ALS, consistent replication of the results is lacking and thus generalizability of these findings is restricted.

2.3.10.5 Cognitive impairment and behavioural change

The nature of the relationship between cognitive and behavioural change in ALS is not fully characterized. Significant correlations between executive deficits and behavioural change have been found (Grossman et al., 2007; Witgert et al., 2010) and co–morbidity of symptoms is reported (Consonni et al., 2013; Strong et al., 2009). However, changes are also shown to occur independently (Witgert et al., 2010; Woolley et al., 2011). Murphy et al (2007) compared cognitive function in behaviourally intact (n=11) and compromised (n=9) patients. Only patients in the latter group showed co–morbid executive dysfunction, suggesting an association between the domains. Since the impaired group included five ALS–FTD patients, conclusions about the specific relationship between cognition and behaviour in non–demented ALS patients were limited.

A larger study used K–means cluster analysis to classify a subset of 141 non–demented patients into three groups, namely intact, mildly impaired and moderately–severely impaired, on the basis of neuropsychological test performance. FrSBe scores for the three groups were compared. Greater levels of behavioural impairment were found in the moderately–severe patient group, but only apathy differed significantly between groups. Nevertheless, 68% of patients in this group showed no behavioural symptoms at all, while 16% of the cognitively intact patients exhibited behavioural dysfunction (Witgert et al., 2010). Behavioural and cognitive disturbance was therefore incompletely related, suggesting that changes apparent in non–demented ALS may occur in isolation or together.

Determining the relationship between cognitive and behavioural change in ALS is of

theoretical and clinical importance. If cognitive and behavioural impairment emerge independently this might imply distinct phenotypes; presumably with unique neuropathologies, within ALS. Alternatively, the possibility of symptom comorbidity extends the proposed spectrum of neuropsychological change within the disease. Furthermore, the identification of separate or concurrent symptomology in ALS patients may present unique challenges to the care of patients, and consequently to their respective caregivers.

2.3.11 Mood and personality in ALS

2.3.11.1 Depression

One of the earliest reports of psychological status in ALS patients reported an absence of depressive symptoms in their small cohort (n=10, Brown & Mueller, 1970). Despite subsequent failure to replicate these findings with larger samples (Houpt et al., 1977; Montgomery & Erickson, 1987, although see Clarke et al 2001), the view that ALS patients remain resilient to depression in the face of their illness persists. A 2007 review of 28 studies reported a range of depression prevalence, varying from 0% – 100%. The weighted means for studies reporting means and standard deviations indicated a normal or only mild level of depression, depending on the measure used (Averill et al., 2007). Another review in the same year noted that larger studies (n ≥100) reported estimates of between 11% – 15%, double that of the general age–consistent population (McLeod & Clarke, 2007). Most psychological studies in ALS rely on self–report measures which are not formerly diagnostic of a major depressive disorder. Where studies have employed structured clinical interviews, such as the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition , population rates of major depressive disorder are estimated between 0% – 11% (Ganzini et al., 1998; Hammer et al., 2008; Rabkin et al., 2005; Rabkin et al., 2000). A recent study using DSM–IV criteria estimated a much higher prevalence of major depression in their sample (n=37) at 21.6% (Ferentinos et al., 2011). This might have been due to the fact that patients were interviewed relatively sooner after diagnosis than in previous studies, as some evidence indicates that depressive symptoms are inversely related to time since diagnosis (Hillemacher et al., 2004).

The great variability reported in the literature is likely to be an artefact of the methodological disparity between studies, as different psychometric tools, assessment procedures (questionnaire; structured interview; postal survey), diagnostic or cut–off criteria, sample sizes and composition (cognitive status; MND phenotype; disease duration) and designs (cross–sectional or longitudinal) have been employed. Indeed, a survey study comparing prevalence rates of depression using different mood questionnaires in the same ALS sample

(n=104) found a greater severity of mild to severe depressive symptoms using the Beck Depression Inventory (56%) (BDI, Beck, 1996) than the Hospital Anxiety and Depression Scale (25%) (HADS, Zigmond & Snaith, 1983) (Wicks et al., 2007). A more recent study of Greek patients (n=37) obtained a similar pattern of results with their selection of inventories, which also included the BDI and HADS (Ferentinos et al., 2011). Discrepant estimates between generic assessment tools may reflect their dissimilar emphasis on physical symptoms of depression which share an overlap with ALS symptoms (e.g. fatigue, sleep disturbance). Some, but not all, studies have attempted to circumvent these confounds by omitting biased 'somatic items' from analyses (e.g. Abrahams et al., 1997; Goldstein et al., 2002; Wicks et al., 2007), but the psychometric properties of these modified mood measures have not been examined. Recently, a Rasch Analysis of the original HADS conducted for 298 ALS patients, found that the removal of two items, one from each of the depression and anxiety subscales, improved the fit of each remaining 6–item subscale to the Rasch model (Gibbons et al., 2011). The modified version showed satisfactory reliability and good internal construct validity, making it suitable for use in the ALS population. New cut–off criteria indicating "caseness" for depression and anxiety were also calculated. The suggested prevalence of case–level depression and anxiety was 11.1% and 22.5%, respectively. A comparison of these prevalence estimates with those that would have been derived from the original cut–off criteria (HADS D: 15.1%; HADS A: 18.8%) suggested that the original HADS slightly overestimated caseness for depression and slightly underestimated caseness for anxiety, relative to the modified version.

The notion that severe depression is not a frequent feature of ALS is supported by indirect comparisons with other neurodegenerative conditions such as PD, MS and Huntington's disease (HD). A caveat of comparing prevalence rates between these disorders is that the neuropsychological, physical and pathological differences between them might impact depression differently in each condition. Moreover, assessment of depression between these disorders encompasses the same methodological variability apparent in ALS research. To overcome these limitations, one study compared the prevalence and severity of depression in ALS patients to that of patients with similar disease profiles (Taylor et al., 2010). Prevalence rates obtained from the BDI–II, HADS and Major Depression Inventory (Olsen et al., 2003) were comparable between groups, although higher than that estimated in the general population (Mojtabai & Olfson, 2004; Steffens et al., 2000). These results challenge the assumption that ALS patients are exceptionally resistant to mood disorder.

Longitudinal studies typically fail to show increased depression and anxiety over the course of disease, even at the late–stage of illness (Cupp et al., 2011; Goldstein et al., 2006b; Rabkin et al., 2005). One study did report increased depression from baseline to a 9–month follow–up in 31 patients, but symptoms remained in the non–depressed range (Gauthier et al., 2007).

Although fatigue has been previously associated with depression (Lou et al., 2003), a recent study found that 65% of their sample of ALS patients (n=223) endorsing fatigue were not depressed (McElhiney et al., 2009), suggesting the two conditions may occur independently. Other correlates of depression include reduced quality of life (Kubler et al., 2005; Lule et al., 2008; Tramonti et al., 2012); lack of social support (Ganzini et al., 1999; Goldstein et al., 2002; Rabkin et al., 2000); anxiety (Atassi et al., 2011), pain (Rabkin et al., 2000; Tedman et al., 1997); reduced survival (McDonald et al., 1994) and perceived burden placed upon their respective caregiver (Gauthier et al., 2007; Rabkin et al., 2000). These relationships underscore the importance of on–going psychological assessment in ALS patients. Although inconsistent, they also point towards associated disease variables that may improve identification of patients at risk of developing depression.

2.3.11.2 Anxiety

The presence of anxiety has received little study in ALS, yet many studies incorporate measures of anxiety into their assessment, or use it to evaluate treatment programs (Díaz, Sancho, Barreto, Bañuls, Renovell, & Servera, 2014; Pagnini, et al., 2014). Prevalence estimates of ALS individuals meeting criteria for significant anxiety range from 11% – 26% (Clarke et al., 2001; Ferentinos et al., 2011; Goldstein et al., 1998; Goldstein et al., 2002; Moore et al., 1998). Findings parallel those in the depression literature, in which the varied use of mood measures across studies lead to inconsistent estimates. Wicks et al (2007) compared estimates from the HADS with the State and Trait Anxiety Inventory (STAI, Spielberger et al., 1968, 1977) and found that while only 8% of the 104 patients were classified as anxious on the STAI, 18% met criteria for 'caseness' of anxiety on the HADS. A more recent study which adopted the Brief Symptom Inventory (Derogatis & Spencer, 1993) found that anxiety subscale scores in ALS patients (n=51) were significantly higher than those of a non–clinical normative sample (n=685). In comparison to a psychiatric outpatient reference group (n=999), ALS anxiety scores were not statistically different. This suggests that anxiety in ALS patients might be as severe as that in psychiatric patients receiving treatment in outpatient mental health services (Felgoise et al., 2010). In contrast, another study found no difference between patients (n=40) and controls (n=40) using the STAI

(Pagnini et al., 2012). However, as with depression, similar methodological differences between studies apply. A distinction is made between state anxiety, an unpleasant emotional reaction in response to perceived threat, and trait anxiety, stable anxious feelings in anticipation of threatening situations. Vignola et al (2008) examined both constructs in 75 ALS patients using the revised STAI (Spielberger, 1983) at the time of diagnosis and at a follow–up phase later in the disease course. Results from the diagnostic phase indicated that 31% qualified for high state anxiety and 14% showed high trait anxiety. At the follow–up phase, these figures decreased to 11% and 2% respectively. These results suggest that trait anxiety may be low in ALS patients and that state anxiety declines with disease progression, following high levels during the initial diagnosis period. State anxiety at the time of diagnosis was related to depression, lower life satisfaction and shorter survival. Both state and trait anxiety correlated with QoL at the two time points, highlighting the important relationship between anxiety and patient perceptions of wellbeing. Furthermore, anxiety has been correlated with speech and eating abilities, as well as the social consequences of experiencing impairments in these domains (Hogg et al., 1994). Other studies have noted associations between anxiety and emotional functioning, mental health, fatigue and pain (Olsson-Ozanne et al., 2011; Olsson et al., 2010; Tedman et al., 1997).

2.4 The Impact of Cognitive and Behaviour Change on Patient QoL

In ALS, deficits may present pre-clinically or early in the disease course. Within ALS based research and clinical practice there is an increasing recognition of the importance of categorising a broad spectrum of cognitive impairments associated with the disease. However, there is a dearth of studies investigating the specific role of cognitive impairment on QoL. Quantifying the detrimental impact that cognitive and behavioural changes have on an individual's functional ability, lifestyle, and social interactions can be of value as there is an evolving recognition that cognitive and behavioural changes are likely to negatively impact on personal relationships and consequently threaten social support and reduce QoL.

To date, there has been an absence of longitudinal QoL research that assesses the degree to which burden is influenced by changes in cognitive dysfunction and behavioural change. There may be several reasons for this. Cognitive deficits are conceived as a cumulative loss of function supported by specific systems, and the impact of heterogeneous losses is difficult to study. A further factor is that cognitive deficits are rarely static and are often influenced by the natural history of disease. Longitudinal studies of cognition in ALS indicate that selective cognitive impairment, in the form of verbal fluency deficits, indicating executive dysfunction,

appears very early on in the course of the disease, and language functions become more vulnerable as the disease progresses. However, performance on cognitive testing close to the diagnosis of ALS is not predictive of burden or low QoL. Within cross-sectional studies QoL scores, correlate positively with the existence of confiding and emotional support and also correlate negatively with the presence of self-rated everyday cognitive difficulties, as described above.

2.5 The Impact of Cognitive and Behaviour Change on Caregivers QoL

The heterogeneity of caregiver-patient relationships adds an additional dimension to understanding the complexities associated with the impact of cognitive and behavioural change in neurological conditions on QoL. In general, relationship strain has been correlated to a number of factors including the premorbid relationship quality of patients and caregivers. Loss of intimacy, reduced social contacts, and the extent of change caused by the disease increase tension, worry, and stressful situations for both patient and caregiver (Tramonti, Bongioanni, Leotta, Puppi, & Rossi, 2015).

Family members are increasingly being asked to perform complex tasks similar to those carried out by paid health or social service providers, often at great cost to their own well-being and great benefit to their relatives and society as a whole (Cipolletta, & Amicucci, 2015).

Caregiving presents difficult, sometimes intractable problems, and although through other neurodegenerative conditions, we have learned a great deal about how to describe and characterize the challenges of caregiving, assess its impact on family members, and identify promising intervention approaches, yet more needs to be done. Understanding caregiving stages across the disease trajectories may enable us to develop stage-appropriate preventive intervention strategies that protect the caregiver from adverse outcomes.

Caregiver burden is a multidimensional construct and encompasses both *objective* and *subjective* aspects. Cognitive, behavioural, and neuropsychiatric symptoms are significant factors that contribute to caregiver burden negatively impacting QOL. ALS caregivers with high QOL and low psychological morbidity (i.e., anxiety/depression) are those with a positive problem orientation (viewing problems as opportunities rather than threats) and those whose behavioural response style was rational rather than impulsive, careless, or characterized by avoidance. There is also evolving evidence that caregivers' psychological status may also influence the mental and physical outcome of patients. Calvo et al., (2011) showed that, compared with controls, children with a parent who had ALS had several clinically significant

adverse emotional and behavioural consequences, with emotional and behavioural problems, internalizing problems, anxiety and depressive symptoms.

The existing caregiving literature in wider neurodegenerative conditions tells us a great deal about who is at risk for negative health outcomes (Hsieh et al., 2013). The significance of caregiving has resulted in extensive research within this area, much of it focused on dementia caregiving. In AD, for example, cognitive deficits and behavioural symptoms of dementia account for approximately 25% of the variance in caregiver distress regardless of how this is measured. Female caregivers reported higher levels of burden than male caregivers.

In general, the various dimensions of caregiver burden are exemplified by ALS, which differs from other neurodegenerations as it can develop at any stage of life, and onset is often insidious, has a rapid decline, and variability in cognitive and behavioural phenotypes (Creemwes, de Morée, Veldink, Nollet, van den Berg, & Beelen, 2015). These factors render the multidimensional determinants of caregiving uniquely complex in ALS compared to other neurodegenerative diseases.

Existing data suggests that behavioural change is of great importance as a mediator of caregiver burden and Quality of Life in ALS caregivers (Tremolizzo, et al., 2016). The influence of cognitive change, poses a significant burden to both patients and their carers. However, the presence of cognitive/behavioural changes in ALS patients is often under-recognized by healthcare professionals, and the burden of care associated with these changes is not currently addressed in clinical practice. Moreover, the relentless disease progression typically seen in ALS exemplifies how the factors maintaining and precipitating strain and caregiver burden could change alongside the disease trajectory.

Relatively little is known about transitions into, and out of, the caregiving role. It is therefore necessary to develop methods by which burden and strain in patients or caregivers can be predicted to ensure adequate supports and referral pathways exist.

In ALS, caregiver burden and reduced caregiver Quality of Life is modulated by patients' cognitive and behavioural status, but does not significantly impact patient survival. Assistive technology can improve patient quality of life, and also that of caregivers (Hwang, Weng, Wang, Tsai, & Chang, 2014). Highly stressed caregivers show remarkable signs of recovery after the death of their loved one, suggesting that much of the work of dealing with loss

occurs before the death. However, during the illness, caregivers are at high risk of developing stress, anxiety, and depression. Anxiety and depression in caregivers have been repeatedly shown to independently affect their QoL. Identifying predictors of anxiety and depression in people with ALS is also important because affective state may be amenable to psychopharmacologic and psychotherapeutic interventions, and depression may contribute to QoL (Pagnini, Philips, Bosma, Reece, Langer, 2016). The concordance between caregiver and patient distress tends to be high. Caregiver mental status can in turn have a great influence on patients. This suggests that attention to the mental health needs of caregivers may not only relieve caregivers' distress but also alleviate patient distress, and improve QoL.

2.6 Summary

In conclusion, there is some evidence to indicate that a subset of ALS patients show impairment across a variety of tests of emotional processing and social cognition. The nature of these deficits is similar and milder to the impairments observed in FTD. However, the evidence is neither consistent nor conclusive. Studies have predominantly relied on static stimuli and abstract social situations, which may limit inferences regarding the everyday difficulties patients experience with social interaction. Study sample sizes are typically small, further limiting generalizability to the ALS population.

Other aspects of social cognition, such as empathy, are yet to be explored in the disease. In addition, the role of executive function in these impairments is controversial. Detailed investigation of the relationship between executive dysfunction and socio– emotional processing change in ALS would improve understanding of the underlying mechanisms of these reported deficits.

Cognitive, and especially behavioural changes, significantly impact on QoL of patients with neurological disease and on their carers. This is congruent with other areas of medicine where perceived memory difficulties, poor concentration and impaired problem solving are important predictors of low QoL. In the neurodegenerative conditions, cognitive and behavioural impairment can present at different stages of a disease, and can manifest in varying forms, depending on the region of brain involvement and the nature of the underlying pathology. For example, executive impairment may implicate other cognitive processes if compromised, as disruptions to the supervisory attentional systems can negatively impact memory via encoding, lexical fluency, and orientation. Similarly, patterns of behavioural change are a function of the neurological pathways that are affected by the illness, and can range from extreme apathy to disruptive disinhibition, and accordingly require different types

of tailored intervention. While a range of interventions have been described that can help to support the QoL of patients and carers, there is no "one size fits all", and there is an urgent need for further research into the longer term impact of cognitive and behavioural change on QoL of patients and carers, such that an evidence base for effective targeted interventions can be generated.

2.7 Primary aims, hypotheses and objectives of the thesis

A gap exists within the literature pertaining to cognitive and behavioural changes associated with ALS. Further to this, little is known about the impact of cognitive and behavioural decline on primary caregivers. The overall objective of this thesis is to examine the cognitive and behavioural profile of ALS in detail, and to investigate the impact of cognitive and behavioural impairment on caregivers. An aim of this thesis, given the lack of research on social cognition in ALS, will be to examine social cognitive processes in tandem with executive function, in order to make a meaningful contribution to both the literature, and clinical practice.

2.3.15.1 **Primary Hypothesis**: *Executive dysfunction will negatively implicate social cognitive processes in ALS.*

The current study examines the hypothesis that patients with ALS will show executive impairments relative to controls in the area of executive function, and that social cognitive processing will also be compromised. To test this hypothesis, patients will be stratified based on their cognitive classification and compared to healthy controls a measure of social cognition.

2.3.15.2 **Hypothesis Two:** *The contribution of cognitive, behavioural, and physical impairment as significant predictors of caregiver burden*

This thesis will address this hypothesis by analysing disease specific functionality, cognitive outcomes, and behaviour change, considering caregiver burden scores. Analyses will consist of regression based methods, and inferential statistics.

To investigate these hypotheses, and number of additional aims and objectives have been proposed. The objective to test is listed, followed by the rationale and proposed method:

2.3.15.3 *Executive tasks can be repeated overtime without compromising performance.*

The current study examines this through the use of control data by comparing performance at baseline to a follow-up time-point. Control data will be maximised to the point that statistical power allows i.e., if a large enough cohort exists at the third time-point then this shall be used over initial repeat testing.

2.3.15.4 *Measures of working memory through different modalities are functionally equivalent.*

The current study investigates this study objective using a between groups design. Participants with ALS patients, who completed a battery of neuropsychological tests employing an auditory modality or working memory, will be compared to a cohort that completed a visual analogue of this task.

2.3.15.5 *The contributions of executive dysfunction to visual memory processes across the ALS-FTD continuum.*

The current thesis will address this study objective by stratifying patients based on the prevalence and severity of executive dysfunction, and regression analyses will be conducted. This will allow for interferences to be made regarding the impact of executive performance, and individual tests on visual memory.

2.3.15.6 *Cognitively intact patients ALS patients perform significantly lower than controls on executive and verbal memory tasks.*

The current thesis will consider this study objective through cognitive status stratification, and then between group analyses of performance on verbal list-learning tasks.

2.3.15.7 *Some cognitively intact ALS patients are significantly declining over time*

The current thesis will investigate this study objective through the cognitive stratification based on cognitive performance, and those whom are classified as cognitively intact will be selected. Healthy control data will be used to investigate the standard error and variance expected with the chosen metric or neuropsychological measure, and this will be compared to the variance seen within the patient cohort.

2.3.15.8 *Profiling behavioural change in ALS patients*

The current study tests the study objective that ALS patients will show increased behaviour change in the domains of apathy, dysexecutive behaviour, and disinhibition, as measured by a standardised scale.

2.3.15.9 *Social cognitive performance will differ based on disease-onset.*

The current study will consider the current literature, which proposes that bulbar-onset patients experience greater cognitive deficits than spinal-onset ALS patients. This study objective is also based on the caudal model of neurodegeneration proposed by Bak and

Chandran (2012), which proposes that bulbar-onset patients may have more cortical regions implication at their disease-onset.

2.3.15.10 *A more rapid disease trajectory negatively influences caregiver burden*

To consider this study objective within this thesis, survival data will be obtained from the national register of motor neuron disease in Ireland. Information on caregiver burden will be extracted from the dataset and linked to survival data. Survival plots will then be generated, using level of burden as a dichotomising variable.

2.3.15.11 *The relationship between caregiver burden and caregiver QoL is linear*

To consider this study objective fully within this thesis, caregiver and quality of life data will be gathered and correlated. As burden is not a one-dimensional concept, the features of burden captured within the scale will be explored i.e., role strain, personal strain, and guilt. These individual metrics of burden will undergo k-means clustering in order to determine appropriate cut-off scores for high/low categories. Post-hoc analyses will be conduct thereafter to investigate whether there is a significant difference in quality of life, based on levels of personal strain, role strain, or guilt.

3.0 Methodology

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3.1 Study Design

This research employed a population-based case-controlled cross-sectional design, with an exhaustive purposive sampling method. This was achieved through screening and recruitment through the national ALS multidisciplinary clinic based at Beaumont Hospital, a Health Service Executive (HSE) Centre of Excellence for the care of MND patients, and through the national register for MND in Ireland, the longest running single-disease register in the world. The design of this study incorporates integrated single-case, case-control, and longitudinal design. For the purpose of investigating the hypotheses contained within this thesis, cross-sectional case-control population-based data are quintessentially reported.

Data collection took place during the ALS multidisciplinary team clinic held at Beaumont Hospital if the participant expressed interest in neuropsychological testing on the same day as their medical consultation. Home visits were also conducted at patient request in order to reduce research burden on patients, and to make participation more amenable to patients who were experiencing increasing mobility difficulties. The data collected included clinical, neuropsychological and demographically relevant information. Testing was scheduled at 4-6 month intervals, although patients could withdraw from the study at any point without reason or their medical care being affected. Although motor disability is a pertinent feature of ALS, many of the tests selected were 'disease free', that is to say that patients can give verbal responses or write/point.

Statistical analyses included descriptive interpretation of the demographic data, between-group analysis of patients, and also healthy case controls, and within-group analysis of patient groups.

3.2 Recruitment

All ALS patients diagnosed in Republic of Ireland within the study approval period were identified on an incidence basis through the Irish ALS Register, and invited to participate in this research. A dedicated member of the Irish ALS research team maintains the register and it is an information network benefiting from multiple medical informants, with links to the Irish Motor Neuron Disease Association. The data from the ALS register allowed for direct comparison of basic demographics between study participants and non-participants, which provided an estimation to which the study sample was representative of the national ALS population.

Patients were approached during their clinic visit to their respective clinic. Interested patients in whom no apparent reason for exclusion was apparent were given a 'Patient Recruitment

Package' (Appendix 2). This included a 'Patient Information Leaflet', a 'Return Post Card' and a stamped envelope addressed to the researcher. The Patient Information Leaflet described the study and indicated the voluntary nature of the study, informing them that refusal to participate would not impact their treatment, and that they were free to withdraw from the study at any point without explanation. It also provided patients with contact information should they wish to clarify anything.

On receiving the return postcard, or confirmation of the patient's interest in participation via other means, the researcher contacted the patient by phone to confirm interest, answer any remaining queries, and arrange a suitable date and time for assessment. Patients were also given an appointment for the imaging and neurophysiological assessment aspects of the research. Patients who indicated a lack of interest in taking part were noted, and this information was stored within their psychology file to avoid being approached in future.

Unless the patient requested otherwise, a letter was posted to the patient's general practitioner to inform him/her of the patient's participation in the study with an enclosed poste for advertising the recruitment of healthy controls. This allowed for a more geographically matched control sample to be recruited for comparative reasons. In case of identification of major cognitive or behavioural abnormalities the patient's treating neurologist were informed, where appropriate. For particular aspects of this thesis, follow-up visits were conducted every 4-6 months in patients who were alive, continued to consent, and were able to participate in a manner which would not cause unnecessary distress to the patient or their caregiver. Patients were contacted by telephone prior to the follow-up visits to confirm their continued interest in participation.

Endpoints of this research were:

(1) The patient declines further participation

(2) In the event of patient death

(3) Progression of physical disability to the extent that participation is no longer ethical

(4) Progression of a dementia process to the extent that participation is no longer ethical.

3.3 Case Ascertainment, Inclusion and Exclusion criteria

Case ascertainment was supervised and the final exclusion of any patient was decided through consultation with the study supervisors and principal investigators (NP and OH). Patients who

gave consent had their charts reviewed to ensure they did not meet the exclusion criteria detailed below. Due to the range of physical disabilities in the ALS cohort, not all patients completed all aspects of all tests. In addition, due to disease progression not all patients were able to undertake repeated assessments. Missing data were excluded from individual analyses but the cases were retained. ALS patients were screened for the C9orf72 expansion routinely as part of the clinical care, and adjustments to analyses were made accordingly. Participants who tested positive for the C9orf72 expansion were excluded from group analysis, although cases were retained.

Inclusion criteria

- Probable or definite ALS according to the El Escorial Criteria
- Diagnosis from January 2013
- Negative for C9orf72 expansion analysis

Exclusion criteria

- History of major head trauma
- History of other health-related/neurological conditions that could affect cognition:
  - Major hemispheric stroke
  - Traumatic brain injury
  - Intellectual/Learning disability
  - Severe active epilepsy
  - Alcohol dependence syndrome
- Current use neuroleptic medications / high dose psychoactive medication
- Current/Active psychosis.

In cases where a reason for exclusion became apparent at the stage of data collection, information which may not have been detailed in the medical chart, data collection was completed, and then the case was discussed at a later stage with the supervisors in order to make the final decision regarding patient exclusion. During data collection, incidental findings were noted on a small number of participants (n=3). They were excluded as a result of this. On assessment, one participant presented with unexpected clinical symptomatology, which was later clinically diagnosed as vascular dementia with comorbid ALS. A second patient's diagnosis was clarified and refined, and was no longer suitable. The third patient had underwent intense treatment for a previous neurologically related condition, where the treatment method may have neatively implicated cognition.

3.3.1 Healthy Controls

An age-, gender-, education-, and IQ-matched control sample were ascertained, with geographical variables and socioeconomic status considered where possible. This cohort was recruited through poster advertisement and advertisements placed in publically appropriate areas as outlined by the Medical Research Ethics Committee approved protocol. Once the potential control participants expressed interest they were provided with a 'Control Information Leaflet' and contacted after an appropriate amount of time had lapsed. This allowed participants time to consider their participation (See Appendix 2). Where possible, healthy controls were requested to present to the Department of Psychology, Beaumont Hospital for assessment, in line with the Standard Operating Procedures (SOPs) in place for the safety of participants and researchers. In line with the consent procedure, controls were amalgamated with previously recruited healthy controls that had overlapping performance data in order to maximise participant contributions. At the time of consent, healthy controls are requested to consent for the data to be used in future research, once it has been appropriately codified. Inclusion criteria for healthy controls were age more than 18 year and age, sex and education similar to recruited patients. The same exclusion criteria outlined above were applied to healthy controls. No controls were excluded.

3.3.2 Minimum Case Ascertainment and Power

The statistical power of a test is the long-term probability, given the effect size, the significance criterion (alpha) and *N* required, in rejecting the null hypothesis. The *N* necessary to attain the desired power for the specified hypothesis increases with the greater power desired. In this instance, *N* is the necessary sample size for *each* group.

According to Cohen (1992), each group is required to have a minimum of 17 participants to find significant between group differences with Power = .80 and Alpha =.10 (Large effect size). However, based on the incidence rate of ALS, a minimum sample of 52 across all groups (i=3) will be recruited to achieve a medium effect size, Power = .80 and Alpha set at .05. This is a more stringent set of criteria, which will allow significant results to be interpreted more robustly. If more participants than expected consent to take part in the research, a posteriori analysis (post-hoc) test will be conducted to assess the impact of the additional participants. Table 3.1 reports the a priori power calculations conducted to ensure suitable sample recruitment.

Table 3.1 A Priori Power Calculations

Effect Size Category	Minimum Participant per group	Total Group	Actual Power	Effect Size (f)	α Error Probability	Groups	Non-centrality parameter λ	Critical *F*
Large	17	52	.8071	.4	.05	3	8.320	4.038
Large	26	52	.8074	.4	.05	2	8.320	4.034
Medium	42	128	.8014	.25	.05	3	8.00	3.916
Medium	64	128	.8014	.25	.05	2	8.00	3.916
Small	261	787	.8000	.1	.05	3	7.87	3.853
Small	393	787	.8000	.1	.05	2	7.87	3.853

3.4 Ethical Approval and Data Protection

Ethical approval has been obtained from Beaumont Hospital Medical Research (Approvals 06/79, 08/90 and 10/20). Procedures involving experiments on human participants were undertaken in accord with the ethical standards of the Committee on Human Experimentation of the Institution in accord with the Helsinki Declaration of 1975 (See appendix 1 for approval letter).

Participants completed written consent forms where possible. If a patient was too impaired to complete the form, their spouse/partner was asked to complete it on their behalf, or their next of kin. Consent was taken at the time of assessment to ensure the patient was content on the day of testing. Data was collected through traditional means of paper-based questionnaire with the added inclusion of the computerized measures. The data was then transferred to a coded database using SPSS. All identifiable information was treated according to the requirements outlined in the conditions of ethical approval, and also conformed to Irish Data Protection Acts 1988 and 2003. The 'legend' document contained the identifiable data, which was strictly kept separate from patients' clinical, demographic and neuropsychological data. A copy of the 'legend' was also made available to both supervisors. Paper based copies of the data were stored within the Research Office within the Academic Unit of Neurology, Trinity College Dublin, in secure locked filing cabinets. An independent member of the Academic Unit of Neurology, to ensure congruency between softcopy data files and hardcopy data, audited these data.

Only members of the Irish ALS research team working within the department had direct access to the data. To further protect the identity of patients who took part in this research, data was analysed for publication as group results. Identifying information was never

published and did not benefit a third party.

3.4.1 Potential Ethical Issues

Participants may experience a significant increase in fatigue due to the length of the test battery. As such, the battery was designed to be a concise as possible to address the research questions within this thesis. Considering the potential impact of fatigue, the battery was reverse administered on a pilot cohort to ensure that test-order was not implicated by fatigue. Stress, and anxiety resulting from the prospect of a neuropsychological assessment were addressed prior to beginning. To address these potential ethical issues, the following measures have been put in place:

I. Participants will be given time to read the project's information leaflet and ask any relevant questions prior to consent;

II. Researchers will explain the nature of the assessment to the patients;

III. Researchers will reiterate the fact that participation is voluntary, has no consequences with regard to clinical care, and that the participant can withdraw at any time from the project;

IV. Participants will also be informed that data will coded and stored securely;

V. Assessments will be conducted within the patient's home to maximise comfort;

VI. Participants will be afforded breaks if required, and reminded of this throughout the assessment.

It is unlikely, but possible, that major cognitive or behavioural abnormalities could be identified in a healthy control participant. As part of the consenting procedure, the healthy participant's general practitioner and/or relevant treating consultant will be informed, if appropriate, with any such incidental findings. Follow-up arrangements are then made by the GP, guided by the Department of Psychology at Beaumont Hospital, should the need arise.

3.5 Demographic and Clinical Data

3.5.1 Clinical Interview

The following demographic and clinical variables were documented in all participants:

- Date of birth;
- Gender;
- Handedness;
- Education in Years;
- Occupation;
- Marital status;
- List of medications;
- Exclusion criteria;
- El Escorial Criteria Status.

3.5.2 TOSCA 500

Arterialised tissue capillary blood gas tensions were measured during the home-visits using a non-invasive transcutaneous sensor (TOSCA 500, Radiometer Copenhagen; Masimo Set ®). The sensor was attached to the patient's ear lobe with the use of disposable individual ear clips and electrolyte gel solution. The sensor functioned via a transcutaneous electrode system that involves a thermostatically controlled heating element to maximise local tissue blood perfusion. Although patients experienced a warm sensation the point of contact of the sensor with the ear lobe (temperature is set to 42.5 degrees C.), no pain was experienced and importantly, the skin was not punctured. The sensor is connected to a mobile monitor on which, after an interval of 10 minutes, there is a stable display of the patient's pulse rate, arterial oxygen (%SpO^2) and Carbon dioxide (PCO^2) levels. Arterialised capillary blood gas tensions were documented at time of assessment, and these data were used for within patient group comparisons.

3.5.3 The ALS Functional Rating Scale – Revised (ALSFRS-R)

Disease severity was estimated during a patients clinic visit, and also during at the time of assessment using the revised version of the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R; Cedarbaum, & Stambler, 1997). The ALSFRS-R is a validated functional scale in which scores range from 0 to 48, with lower scores indicating greater disability, where the symptoms are tailored to features of Motor Neuron Disease (MND).

The structure of the ALSFR-R lends itself to evaluating different regions of the body relative

to the presence/absence and degree of bulbar involvement (slurring of speech, drooling of saliva and swallowing difficulties). The total score of these three questions constitutes the "bulbar ALSFRS-R sub-score" (maximum 12 points for normal bulbar function). The sum of the next three questions constitutes the "respiratory ALSFRS-R sub-score" of the ALSFRS-R (maximum 12 points obtained in case of normal respiratory function). This specifically investigates the presence of shortness of breath, orthopnoea (a shortness of breath when lying flat) and use of non-invasive ventilation.

The remaining questions evaluate limb function by enquiring on fine and gross motor function, in the context of activities of daily living such as walking, climbing stairs, writing, the ability to feed and dress. The total score of these questions constitutes the "Limb Function subs-score" with a maximum of 24 points obtained in case of normal upper and lower limb function. The total sum of this scale thus reflects the severity of the disease, and the impact on activities of daily living.

3.6 Neuropsychological Assessment

The battery of neuropsychological measurements was designed to minimize the effect of fatigue, motor and bulbar disability. The majority of tasks in the battery were untimed to avoid the confounding effect of physical disability. The utilization of the CANTAB Research Suite also provided electronic versions of validated measures, which otherwise would have been excluded for patients with severe bulbar features.

Some of the tasks were timed; however scoring algorithm standardized the scores to adjust for features of motor disability. The battery was carried out in fixed order due to the delayed recall paradigms of the memory tests. The test battery was piloted, and designed to take less than 2 hours, inclusive of breaks.

A 15-minute break was incorporated into the battery, approximately midway through the testing, though patients were afforded breaks at natural points during the assessment. A natural point for a break within a battery of tests is considered where a participant could take a break without causing disruption to a subsequent test i.e., an immediate, delay and recognition memory paradigm.

Neuropsychological assessments, scoring and analysis were conducted under the direction and supervision of a Principal Clinical Neuropsychologist (NP), as well as cognitive categorisation. Controls underwent the same neuropsychological assessment as ALS patients.

The rationale for using healthy controls was to create culturally relevant normative data for the Irish population of same age and sex as the ALS patients. These normative data were then used to identify appropriate cut offs for abnormal performance on the undertaken neuropsychological tasks, which determined whether a patient, or control, was impaired. An independent member of the Academic Unit of Neurology, Trinity College Dublin, audited data collected throughout this thesis once all data collection was finalised. The auditor then reported back to the Research Manager within the Academic Unit, inline with the quality control protocols within the School of Medicine, Trinity College Dublin.

3.6.1 The Test of Premorbid Function

The Test of Premorbid Function – UK edition, (TOPF; Wechsler, 2011) is a time-effective task employed for this study, which takes less than 10 minutes to complete. It is comprised of a list of 70 words that have atypical grapheme to phoneme translations and is an effective method for predicting full-scale IQ and memory performance. Through the generation of indices, the TOPF enables clinicians to estimate an individual's level of intellectual functioning before the onset of injury or illness relative to their Processing Speed (PSI), Working Memory (WMI), Verbal Comprehension (VCI), Performance Reasoning (PRI) and it also provides clinicians with an estimate of Full Scale IQ (FSIQ). The measure requires verbal engagement from the participant, though correlates >.9 with non-verbal measures of current function, also adopted within this research.

Scoring: The patient is scores one point for each correct pronunciation to yield a maximum of 70 points. The raw scores are converted to age, gender and education adjusted standardised scores. This is preferred over the WTAR where scores are subsequently converted to Full Scale Intelligence Quotients (FSIQ) only.

3.6.2 Ravens Matrices

Raven's Matrices are a validated measure of current function/intelligence designed in 1936 as a non-verbal test. This study employed a single 36-page test coloured booklet presented one page at a time, with progressive difficulty (Raven, 1947). Each page contained a large figure or pattern with a missing section. Below the large pattern were six small figures one of which completed the figure or pattern. The subject was required to select from correct figure from the six possible options. The 36 items were placed in 3 sets of 12 items and the difficulty of the sets was progressive. The use of Raven's Matrices has several advantages for assessing ALS patients. It requires no verbal input and minimal motor input. Patients with severe physical and bulbar disability often can still undertake the test by simply pointing to the

responses. The patient score is then compared to age matched population based Irish norms, and a standardized score is created.

3.6.3 The Florida Affect Battery *rev.* (Bowers, Blonder, & Heilman, 1998)

3.6.3.1 Facial Identity Discrimination

The patients were shown pairs of unfamiliar faces and were required to determine whether the faces were the same or a different person. The stimuli are gender specific throughout, each with a neutral facial expression. Hair is excluded from these pictures initially to reduce non-racial cues of identification. This task serves as a 'control' for future tasks to ensure there is no facial processing deficit, which is often seen in right posterior temporal stroke patients.

3.6.3.2 Affect Identification and Discrimination

Patients were required to verbally determine whether two faces depicted the same or different emotional expressions. Each trial consisted of two photos. On half the trials the stimuli were the same i.e., happy and happy., and on the alternate trials the stimuli were different i.e., happy and angry. Patients were then required to verbally label emotive facial expressions in this task. They were shown 20 stimuli and asked to depict if the expression was happy, sad, angry or neutral.

3.6.3.3 Affect Selection

The task assesses patients' ability to select target expressions named by the examiner. On each trial, patients were shown five pictures of different women, each expressing different facial emotion. They were then asked to identify the picture of the face that corresponds to the emotion named by the examiner (i.e., "point to the angry person").

3.6.3.4 Matching Facial Affect

In this task, patients were asked to match the picture of an emotional face to another face with the same emotional expression. He was shown a stimulus page consisting of multiple photographs. On the left side of the page, there is a single photograph of a target emotional face. To the right of the page, there are pictures of five women, expressing different emotional expressions. Patients are prompted by the examiner to match the target expression with its counterpart on the right.

3.6.3.5 Non-Emotional Prosody Discrimination

This task measured a patient's ability to process propositional prosody and serves as a control for the affective prosody tasks, much like the Facial Identity Discrimination task above. Patients were played 16 pairs of sentences, spoken in either an interrogative (The boy went to the store?) or declarative tone of voice (The boy went to the store!). On half the trials, two sentences convey the same propositional prosody (i.e., both statements are questions). For the remaining trials, the two sentences differ in their propositional prosody (i.e., one a statement and one a question). Patients must indicate whether the sentence pairs are the same or different in terms of prosody. This task is not a forced-choice response, and patients have to complete the task under time pressure. The gap between sentences was prolonged for patients with bulbar onset, if required.

3.6.3.6 Emotional Prosody Discrimination

In this task, patients were presented pairs of semantically neutral sentences that are spoken in the same or different emotional tone of voice. They were then required to judge if the affective prosody was the same or different in both sentences. Half the items were "same" (10 trials) and half are "different" (10 trials).

3.6.3.7 Emotional Prosody Identification

This task assesses the ability to verbally label affective prosody. Patients were required to listen to semantically neutral sentences spoken in one of five affective tones of voice (happy, sad, anger, etc.). They were then asked to name the emotional prosody of each item. Twenty trials are given, with four repetitions of the five affective choices.

3.6.3.8 Conflicting Emotional Prosody

Patients further listened to affectively intoned sentences whose semantic content may differ (i.e., conflict) or be parallel the prosodic message. Thirty-six sentences were given, and patients were asked to judge the affective tone of voice of the speaker in each. In half of the trials, the semantic content and prosody conflict (i.e., "all the puppies are dead" said in a happy tone of voice; Incongruent).. In the remaining sentences, the semantic content and prosody are Congruent (i.e., "all the puppies are dead" said in a sad tone of voice).

3.6.3.9 Cross-modal Matching

Patients are shown a picture of an emotional face for this task, and at the same time, they listened to three sentences, each spoken in a different emotional tone. They were then asked to indicate which sentence best corresponds to the facial expression. Because this task entails some "memory load", each set of three sentences is presented twice.

3.6.4 Reading the Mind in the Eyes Test

Facial cues are the preferential focus in order to extract complex meaning regarding motives, feelings, and intentions about others. Specifically the ocular region of the face encompasses many features if interpreted correctly allow people to make inferences about mental states. The Reading the Mind in the Eyes Task (Baron-Cohen, Wheelwright, Hill, et al., 2001) is a measure which utilizes these features to evaluate affective theory of mind abilities i.e. the ability to infer how other individuals are feeling or mental states.

The participants were presented 36 black and white photographs of the eye region of male and female actors depicting complex emotions or mental states such feeling "sad" or "reflective". The subject was required to choose from four presented options, the word that most accurately described the mental state of the individuals depicted in photographs. Due to the pivotal role of this measure within the thesis, an example of the stimuli is presented in figure 3.1. The Reading the Mind in the Eye has good convergent validity with social–cognitive tests of theory of mind, as well as cross-cultural validity, with excellent sensitivity and specificity relative to autistic participants (Adams et al., 2010, Baron-Cohen et al., 1999, Adolphs et al., 2002). Additional advantages of this task include the fact that it is untimed and that it is not affected by severe physical disability as patients can simply point to their selected response.

The main disadvantage of this task is that some of the words used to describe emotions are relatively difficult (e.g. "despondent", "aghast") which may cause confounding effect. To overcome this, prior to the administration of the task, participants were informed that s/he could enquire on the specific meaning of any word, and this was then read to the participant from an appendix supplied with the measure. Performance on the Reading the Mind in the Eyes Test has been linked to brain regions known to be integral in social cognitive functioning, as shown above, including the medial prefrontal cortex, orbitofrontal cortex, and temporal lobes, particularly the superior temporal sulcus (Gallagher and Frith, 2003, Baron-

Cohen et al., 1999, Adams et al., 2010).

3.6.5 The Stroop Colour Word Interference Test

The Stroop CWI Task (Trenerry, Crosson, Deboe, & Leber, 1989) measures multiple dimensions of executive control including error monitoring, working memory, selective attention, and inhibitory control (Royall et al., 2002). *Part-A* (the 'rule attainment' task) the patients were presented with a list of colours which were printed in the intuitive colour i.e., red was printed in red ink, and asked to read the printed words as quickly as possible, while being timed.

Part-B (the inhibitory/interference subtask), the patients were presented with another list of colours where the colours they were printed in were incongruent i.e., red was printed in blue. The patients were then asked to name as quickly as possible the *colour of ink* in which each word is printed and inhibit calling out the word printed. Although the task is predominantly a test of executive function, other cognitive skills are also recruited to complete the task. This can be said for many aspects of cognitive functioning.

3.6.6 Letter Fluency

Patients were tested using the version of the task described by Abrahams and colleagues (Abrahams et al., 1995) as it incorporates a method for adjustment for features of spinal and bulbar motor neuron disease. The method, termed the verbal fluency index (VFI), involves three subtasks detailed below, with the formula outlined in detail in Chapter 2. For convenience, the formula is restated as:

$$\text{VFI} = \frac{(\text{time for generation condition}) - (\text{time for copy condition})}{\text{Total number of words generated}}$$

The first subtask required the subject to retrieve as many words as they can think of starting with the letter "S" in a period of five minutes. In the second subtask the subject was allowed four minutes to generate as many four letter words starting with the letter "C" as s/he can think of. The rules of the task prohibited the use of names of people and places (i.e., proper nouns) or the use of identical words with different endings (e.g., sad and sadly). Numbers were also excluded from these tasks. For both subtasks the examiner kept the time for scoring reasons. The subject either wrote down the words on a piece of paper, or spoke the words while then the examiner wrote them down legibly. The choice of modality (written or spoken) in ALS patients depended on their disabilities.

If a written-modality was selected, then the participant was asked to copy all the words s/he

generated as fast they can, while the examiner recorded the time. If the chosen modality was "spoken" then the subject was asked to read all the words s/he generated, while the examiner recorded the time.

3.6.7 Categorical Fluency

The category fluency task, also termed the semantic verbal fluency test, requires the subject to retrieve words that belong to a particular semantic category such as "fruits", "furniture" or "animals".

In the version used in this study subjects were instructed to name as many "animals" as they could think of in a pre-set time of one minute (Delis, 2001). Only a spoken form of this task was undertaken, thus patients with severe bulbar involvement were excluded. While access to the temporal lobe-based semantic knowledge is essential for normal performance on this task, it is also sensitive to frontal lobe dysfunction because, like phonemic verbal fluency, it captures several components of executive functioning such as planning, strategy making, error monitoring, and inhibition of words not conforming to the rules.

3.6.8 Cambridge Neuropsychological Test Automated Battery

3.6.8.1 Intra-Extra Dimensional Set Shift

Intra-Extra Dimensional Set Shift (IED) is a test of rule acquisition and reversal. It features: visual discrimination and attentional set formation maintenance, shifting and flexibility of attention This test is primarily sensitive to changes to the fronto-striatal areas of the brain. This test is a computerised analogue of the Wisconsin Card Sorting test, and is sensitive to cognitive changes associated with schizophrenia, Parkinson's disease, and dopaminergic dependent processes. Two artificial dimensions are used in the test: colour-filled shapes and white lines. Simple stimuli are made up of just one of these dimensions, whereas compound stimuli are made up of both, namely white lines overlying colour-filled shapes. The participant starts by seeing two simple colour-filled shapes, and must learn which one is correct by touching it. Feedback teaches the participant which stimulus is correct, and after six correct responses, the stimuli and/or rules are changed. These shifts are initially intra-dimensional (e.g., colour filled shapes remain the only relevant dimension), then later extra-dimensional (white lines become the only relevant dimension). Participants progress through the test by satisfying a set criterion of learning at each stage (6 consecutive correct responses). If at any stage the participant fails to reach this criterion after 50 trials, the test terminates. This test has eighteen outcome measures, assessing errors, and numbers of trials and stages completed.

3.6.8.2 Spatial Span and Reverse Spatial Span

There is evidence suggesting that backward but not forward digit span is impaired in ALS patients. (Hanagasi et al., 2002, Moretti et al., 2002) This is likely to be related to the extra demands placed on both working memory and inhibitory control in case of spatial working span (Royall et al., 2002, Hanagasi et al., 2002). In this study the subjects' performance on the spatial span and spatial working memory were included in the assessment of their executive functioning. Spatial Span (SSP) assesses working memory capacity, and is a visuospatial analogue of the Digit Span test. White squares are shown, some of which briefly change colour in a variable sequence. The participant must then touch the boxes which changed colour in the same order that they were displayed by the computer (for clinical mode) or in the reverse order (for reverse mode). The number of boxes increases from 2 at the start of the test to 9 at the end, and the sequence and colour are varied through the test. This test has six outcome measures, covering span length (the longest sequence successfully recalled), errors, number of attempts and latency.

Subsequent to this, the Reverse Spatial Span was administered which further assesses patients' working memory, executive function and their capacity to retain information. This measure is a visual analogue of the Backward Digit Span which is sensitive to cognitive decline in neurodegenerative diseases due to the extensive network which is utilized when completing the task.

3.6.9 Rey Osterrieth Complex Figure Test

The copy trial of the Rey Osterrieth Complex Figure Test (ROCFT) was used to screen for visuo-constructive abnormalities (Taylor, 1979). The ROCFT is a widely used test as it evaluates both visuo-constructive abilities and non-verbal memory. Both executive function and perceptual processes are closely involved in the accurate copy and reproduction of the complex figure. The version of the task used in this study consists of four tasks: "Copy trial" in which the subject was asked to copy a complex figure as accurately as they can; An "Immediate Recall Trial" in which the subject was instructed to reproduce the figure from memory immediately after copying it and without previous indication of this trial, and a "Delayed Recall Trial" in which the subject was asked to reproduce the figure again from memory after a 20 minutes delay. Subsequent to the delayed recall, the patient completes a recognition paradigm. This trail requires a patient to correctly identify the components of the figure, which they recognize, and to reject the items that are novel. The ROCFT was the only task used to test memory in patients with severe bulbar impairment, as there was no verbal

component. The task is a largely motor task, as it requires the ability to draw. To avoid any confounding effects of physical disability the time taken to produce the drawings was not factored in scoring, and those with severe limb weakness were not tested.

3.6.10 Boston Naming Test

A 30-item version of the Boston Naming Test (BNT) was used to screen for language deficits (Graves, Bezeau, Fogarty et al., 2004). The BNT is a test of confrontational naming in which the subjects were presented with simple line drawings of objects and asked to produce the name of the objects. The BNT test was selected for screening for language problems because it is a brief and highly informative test. It includes both high and low frequency items and as such has a graded difficulty.

The BNT can also yields rich and detailed information on lexical abilities that extend beyond the severity of word finding impairment. Qualitative examination of the errors, for example semantic errors versus problems in phonological processing, can help generate hypothesis for type of language deficits experienced by the patients. Patients were awarded one point per each correctly named object. When the names were written down (bulbar patients) spelling mistakes were noted but no marks were omitted as long as the intended word was clear.

3.6.11 The California Verbal Learning Test-II

The California Verbal Learning Test-II (CVLT-II: Delis, Kaplan, Kramer, & Ober, 2000) examines both recall and recognition over immediate and delayed memory trials. List A is composed of 16 words, four from each of four semantic categories (furniture, vegetables, ways of traveling, and animals). Words from the same semantic category are never presented consecutively. A 16-word interference list (List B) is then presented for one trial, followed by short-delay free-recall and short-delay cued-recall trials of List A. After a 20-minute delay, free-recall, cued-recall, and yes/no recognition trials of 'List A' are administered.

3.6.12 Logical Memory; Prose

Logical Memory (LM) a subset of the Wechsler Memory Scale-IV (WMS-IV; Wechsler D., 1997) that examines the ability to recall and recognise multiple elements in a logical story sequence. The patient was required to repeat two short vignettes immediately after an auditory presentation. The patient was then informed that they will be required to recall the vignettes at later stage. After an interval of 30 minutes (during which other tasks in the neuropsychological battery are administered) the patient was required to complete a delayed free recall. In addition the patient was required to answer 30 questions regarding the vignettes

with "Yes" or "No" options to test his/her ability to recognize components of the story. All of the subtest components were standardized using age matched normative data.

3.7 Mood and Behaviour

3.7.1 The Hospital Anxiety and Depression Scale

Mood disturbances, specifically anxiety and depression, were assessed in this study using the Hospital Anxiety and Depression Scale (HADS: Norton, Cosco, Doyle, Done, & Sacker, 2013; Zigmond, & Snaith, 1983). Based on previous research in movement disorders, one item, "I feel slowed down" causes concern regarding the physical overlay of this question. This question was not omitted from both patient and control scores. Data presented by Taylor, Wicks, Leigh, & Goldstein (2010) suggests that the original HADS does not lead to an overrepresentation of depression-like symptoms. Further to this, Wicks et al., (2007) compared the convergent validity of commonly used questionnaires to detect neuropsychiatric symptoms i.e., anxiety/depression, and found that results were not significantly influenced by scores on physical symptom items. Lastly, by employing an original HADS our data is supported by the robust factor structure, validity, and reliability coefficients of the HADS reported by Moorey, Greer, Watson, et al., (1991). A total score was calculated by combining the anxiety and depression scores as this is reported within the literature to be indicative of 'total distress'.

3.7.2 The Frontal Systems Behaviour Scale

The Frontal Systems Behaviour Scale (FrsBe) scale (Grace et al., 1999) is comprised of a Self-Rated form (to be filled by the patient) and a Family Rated Form (to be completed by patient's carer). Both forms pose the same 46 items differing only in pronoun used, for example the item "I am disorganised " in the Self-Rated Form becomes "s/he is disorganised" in the Family-rated Form. On each form the items are scored in the range 1 = almost never, 2 = seldom, 3 = sometimes, 4 = frequently, and 5 =almost always) according to their accuracy in describing the patient's behaviour both "Before Illness or Injury" (to establish pre-morbid behaviour) and "At Present Time" (to estimate any change due to the current illness). The 46 items were designed to cover three behavioural clusters often observed in patients with frontal lobe lesions: apathetic behaviour, disinhibition, and dysexecutive behaviour. Both the Self and Family rated forms yield separate "Before Illness" and "At Present" scores in the aforementioned scales. Raw scores were converted to age, sex and education adjusted T-score.

3.8 Categorizing Cognitive and Behavioural Impairment

3.8.1 Cognitive Status

Data from the cognitive measures was standardized and compared to Irish normative control data, as well as published data. For all groups, if their score fell greater than two standard deviations below the mean (z=>-1.96), their performance on testing was considered impaired. Patients were categorized then based on whether there was 'No Cognitive Abnormalities Detected', 'Single Test Impairment', 'Single Domain Deficit', 'Multiple Domain Deficits', or 'Mild Cognitive Impairment'. If a patient profile was indicative of a dementia process on repeat testing, this was reported to their consultant physician. Associated behavioural disturbance would also be reported. This method complements the Strong et al., (2009) criteria for cognitive classification, though utilised a more stringent cut-off score to define impairment (z= -2.00).

3.8.2 Behaviour Categorisation

A 'Behaviour Impairment' categorization was created based on whether a patient scored two standard deviations below the control mean. On the FrSBe, patients' results were compared to standardized normative data and T-scores within the clinically significant range were considered abnormal. Patients' impairments were classified based on elevated Apathy, Disinhibition and Dysexecutive behaviours.

4.0 Results

The following chapters will address each of the main research questions posed in Chapter 2, through the methodology discussed in Chapter 3. The research described herein is comprised of studies presented in journal manuscript format, with a preceding paragraph provided to link each study together. Manuscripts published, or under review, are indicated appropriately.

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4.1 Practice Effects and Executive Assessments

The objective of this study was to investigate whether it was reliable to administer measures of executive function repeatedly over time. The aim was to quantify whether control cohorts experienced a statistically significant change in their performance if the same test battery was administered within a 6-month follow-up period.

This paper has been published in the Irish Journal of Psychology:

Burke, T., Wynne, B., O'Brien, C., Elamin, M., Bede, P., Hardiman, O. & Pender, N. (2015). Retrospective Investigations of Practice Effects on Repeated Neuropsychological Measures of Executive Function. The Irish Journal of Psychology.

1.1 Practice Effects

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  - 1.1.2.1 Variation on Neuropsychological Assessment
  - 1.1.2.2 Practice Effects and Executive Functioning
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4.1.1 Abstract

The present study aimed to investigate the degree to which serial testing may impact neuropsychological test scores following serial evaluation of executive function. Healthy control data were retrospectively analysed, recruited as part of a longitudinal study of cognitive impairment in Amyotrophic Lateral Sclerosis. As part of a larger battery of tests, participants were assessed using The Brixton Spatial Anticipation Test (n=31), Backward Digit-span (n=22), The Stroop Colour -Word Test (n=30) and Phonemic Fluency (n=29). Participants completed the tests on three occasions at 6-month intervals. Results showed no statistically significant difference between any of the measures of executive function over the three time points. Further covariate analyses showed that IQ was not a confounding variable when investigating practice effects, as previously reported in literature. In an Irish cohort, participants did not show statistically significant changes over time on neuropsychological tests, either positively or negatively. Although these findings should be considered exploratory due to sample size, the wide age range and the retrospective nature of analysis, the data suggests practice effects did not significantly influence the test results in this cohort when assessed at 6-month intervals. Implications relative to these findings are discussed.

4.1.2 Introduction

Standardised neuropsychological testing is commonly used to assess individuals' cognitive abilities in diverse clinical and non-clinical settings. Neuropsychological tests can be used to monitor change in patients' underlying condition over time, or to measure responses to treatment-based interventions. However, there is growing concern that a patient's scores may be artificially inflated due to practice effects during serial testing. Practice effects are defined as increases in a person's test score from initial presentation to subsequent presentations, in the absence of intervention (Wilson, Watson, Baddeley, Emslie & Evans, 2000).

4.1.2.1 Variation on Neuropsychological Assessment

Variation on test performance is particularly important in longitudinal studies of neurodegenerative diseases, where practice effects may mask cognitive deterioration, leading to a false perception of stability over time. Concerns relate to novelty and strategy formation, as this can be an important attribute of a test of executive function (Burgess et al., 2006). Such concerns exist as one may perform suboptimally on initial assessment, and utilise a more effective strategy on repeat assessment, inflating their results due to familarity. Lowe and Rabbitt (1998) assessed two groups using selected measures of executive function, memory, processing speed and fluency. They illustrated how improvement with practice in these tests happens abruptly when a strategy or rule has been discovered, resulting in participants' performance increasing.

Rapport, Brines, Theisen and Axelrod (1997) employed a test re-test paradigm over 2-week intervals. Of particular interest were their findings relative to participants IQ. They reported that the higher a participants' IQ, the higher the gain through practice or repeated testing. However, this is not consistently reported within the literature (Basso, Bornstein, & Lang, 1999). Bartels, Wegryzn, Wiedl, Ackermann and Ehreneich (2010) claim that practice effects may result from reduced anxiety or increased familiarity with the testing environment, recall effects, improvement of underlying functions, or procedural learning (Calamia, Markon & Tranel, 2012). Practice effects, therefore, may add error which complicates test interpretation (Duff et al., 2005; McCaffrey, Duff & Westervelt, 2000).

The psychometric properties of standardised tests adjust for common, predictable sources of error, but it is imperative that clinicians also evaluate the impact of less common sources of error such as mood (Choi, Padmala & Pessoa, 2011), effort (Green, 2004), fatigue (Strober & Deluca, 2013), pain (Jamison et al., 2003) or age (Duff et al., 2010). Variables such as these

have taken special position in neuropsychology literature and are commonly referred to as secondary influence in testing procedures (Arnett, 2013).

Multiple testing is common within neuropsychology and comparison at varied testing time-points can be used for many purposes; the most common of which is to document the progression or resolution of injury or illness which can be critical to differential diagnosis and treatment (Duff, Westervelt, McCaffrey & Haase, 2001). Serial testing can also be used to assess the clinical efficacy of pharmacological (Loring & Mendor, 2004), educational (Feifer, 2008) and surgical interventions (Ghogawala, Westerveld & Amin-Hanjani, 2008) in patient and healthy populations. Repeat testing is useful in monitoring progress over time (Shapiro, Lockman, Balthazor & Krivit, 1995) as well as determining whether initial findings of concern were accurate and definitive and not a result based on individual difference. Practice-related improvement is thought to reflect the action of a number of variables such as familiarity and recall of task specific content, instructions or improvements in test taking strategy (Goldberg et al., 2007; Payne & Gwynne-Jones, 1957).

4.1.2.2 Practice Effects and Executive Functioning

While the impact of practice is a concern for all neuropsychological assessments, there is particular risk of encountering practice effects on measures of executive function (Hessen, Lossius & Gjerstad, 2013). Executive functioning is defined as a set of cognitive and behavioural skills that enable us to manage novel environments, engage in goal-orientated behaviour and modify behaviour by integrating feedback (Beglinger et. al., 2005). Executive functioning is necessary for problem solving, social behaviour, successful adaptation to novel stimuli and situations, and completing activities of daily living. These collective functions enable an individual to process and manipulate novel concepts (Toplak, West, & Stanovich, 2013), where no previously learned behaviour or strategy is available to draw upon (Shallice, 1990).

Burgess, Alderman, Evans, Emslie, and Wilson (2006) raised the concern of serial testing executive functions and noted that by definition novelty decreases with repetition and therefore a frontal task should only be used once. This raises serious concern for clinicians and academics alike regarding the efficacy of executive tests in repeated assessment and, in particular, the need for alternative forms and versions of executive tests. Furthermore, Duff (2012) noted that once experienced, tests of executive functioning do not regain novelty through disuse, even over periods as long as seventeen years (Rabbitt, Diggle, Holland &

McInnes, 2004). To this end practice effects appear to be an important variable, which may influence select measures of executive functioning, consistently over time.

In undertaking repeated neuropsychological evaluations of executive functioning in a longitudinal population based research, concern arose due to the growing body of literature cited regarding the impact of repeated testing on executive function over time (Abner et al., 2012). Most consistently reported within longitudinal research is that scores reported on some measures increase over time, though statistically significant practice effects do not always occur (Basso et al., 1999).

4.1.3 Methodology

4.1.3.1 Research Design

Data from a convenience sample of healthy volunteers utilized in a prospective investigation into the heterogeneous cognitive profiles of people with Amyotrophic Lateral Sclerosis (ALS) were retrospectively analysed. These participants were assessed sequentially at 6-month intervals, twice after the initial baseline assessment. This was completed to investigate whether test scores increased, or decreased, over time due to serial assessment, with non-directional hypotheses. The design of the aforementioned study has been well described previously (Bede et al., 2013; Elamin et. al., 2013; Phukan et al., 2012). Although attrition is expected in longitudinal research (Gustavson, von Soest, Karevold & Røysamb, 2012), due to the retrospective analyses participants' were only included for analysis if they completed the assessment at each time point. Further details on the attrition can be found in the parenting study (Elamin et. al., 2013).

4.1.3.2 Participants and Sampling

Healthy Controls were recruited through a volunteer network and the sample included individuals without any medical diagnoses. The age range of the participants was 51–85 years, with a mean of 65.69 (S.D. ±9.08), and 51.6% were males. Their mean 'estimated premorbid Full Scale Intelligence Quotient' (FSIQ) was 107.41 (S.D. = ±7.73) with the mean years of education as 13.35 (S.D. = ±3.29). Participants who completed the assessment at each time-point were included in the analysis (Backward Digit-Span, n=22; Verbal Fluency, n=29; The Brixton Test, n=31; Stroop Colour Word Interference, n=30).

4.1.3.3 Neuropsychological Measures

The neuropsychological battery was designed to assess heterogeneous cognitive profiles in ALS, as previously mentioned. These measures are of particular interest as one can adjust for disability caused by either upper or lower motor neuron degeneration (See Phukan et al. (2008) for details). Participants' estimated premorbid FSIQ (Holdnack, 2001), working

Table 4.1: Description of Measurements

Test	Description	Scoring
Wechsler Test of Adult Reading	This is a measure of premorbid IQ that requires the participant to read 50 words aloud. The difficulty increases as the trial continues.	A score is converted to estimates of premorbid intellectual ability based on the number of correctly pronounced words[1].
Wechsler Adult Intelligence Scale-III : Digit-Span Backwards	This is a measure of working memory where an individual must repeat a string of digits presented to them by the examiner, in the reverse order. There is an increment every second trial.	A score is complied based on the total of correct responses relayed to the examiner[2].
The Brixton Spatial Anticipation Test	This is a visuospatial non-verbal sequencing task measuring rule attainment, mental flexibility and spatial anticipation[3]. One is required to detect rules in sequential set of stimuli.	The total sum of errors are cumulated and converted to a standardised score, where a low error rates are indicative of high executive function.
Phonemic Fluency	Phonemic fluency is a measure of executive function where an individual must generate words on the basis of specific criteria. This requires the creation of strategies and lexical access[4]	The total number of words generated, which fit the criteria of the task, are counted to create a total score. A brief statistical conversion is used to create a Verbal Fluency index score
Stroop Colour Word Test	This version of the Stroop is a two-trial measurement of directed attention, interference control and response inhibition. Trial 1 contains 112 colour-words (red, blue, green and tan) randomly arranged. Each word is printed in an incongruous ink colour i.e., the word red is printed in blue. The participant is required to read the words as quickly as possible. For Trial 2, the examinee is instructed to name the colour of the ink[1].	The score for each task is the number of correct responses or items completed, minus incorrect responses.

Reference to the table in order of appearance:

[1] Strauss, Sherman and Spreen (2006); [2] Van den Berg et. al., 2009; [3] Perret, 1974; [4]Abrahams et al. (1996)

memory (Wechsler, 2000), phonemic lexical fluency (Abrahams et al., 1996), and executive functioning (Burgess & Shallice, 1996; Trenerry, et al.1989) were assessed using the measures outlined in Table 4.1.

4.1.3.4 Procedure

Participants completed a comprehensive test battery, which was administered and scored by an Assistant Research Psychologist, under the supervision of a Principal Clinical Neuropsychologist (NP), within the Department of Psychology at Beaumont Hospital, Dublin, Ireland. Scaled Scores, Percentiles and Index Scores were computed in accordance with standardized procedures. Assessments were conducted at baseline (T1), and then at 6-month intervals (T2 & T3).

4.1.3.5 Data Analysis

The means and standard deviations at each time point were documented with respect to the reported test statistic, and all measures met homogeneity of variance and normality specifications respectively. Analyses were conducted to identify whether there was a significant statistical difference over time. This was completed using Repeated Measures Analysis of Variance (ANOVA). According to Cohen (1992) a three-time point analysis over 18 months, with an alpha of .05, must have a sample above 21 to robustly detect statistical significance.

Multiple Analysis of Covariance (ANCOVA) were employed to investigate whether intelligence is a mediating factor in serial assessment. Statistical analyses were performed using SPSS version 20 (IBM Corp: Released 2012). The alpha value was set at .05.

4.1.4 Results

Table 4.2 illustrates that there were no statistically significant differences in the results over time using Repeated Measure ANOVA. There were no significant main effect for analyses of the Digit-span Backwards $F(2, 20)=.834$, $p=.15$; The Brixton Test $F(2, 29)=.960$, $p=.55$; Phonemic Fluency $F(2, 27)= 1.01$, $p=.35$ or the Stroop Colour-Word Test $F(2, 28)=.696$, $p=.08$.

Multiple ANCOVA were conducted to investigate whether participants' scores increased over time using pFSIQ as a covariate. Predicted IQ was determined based on the WTAR. There was no significant main effect found when IQ was controlled as a covariate on Backward Digit Span $F(2, 19) = .348$, $p = .70$; The Brixton Test $F(2, 28) = .665$, $p = .51$; Phonemic Fluency $F(2, 26) = .589$, $p = .55$ and the Stroop Colour Word Test $F(2, 12) = .237$, $p=.56$.

Furthermore the relationship between these variables were considered with only small correlations noted on Stroop Colour Word Interference r = .076, n=30, p=.686 and Fluency r = -.262, n=29, p=.265. Medium correlations were noted on The Brixton r = .306, n=31, p=.095 and Backward Digit-span r = .581, n=24, p=.003.

Table 4.2: ANOVA summary table

Neuropsychological Tests	Wilks Lambda	F	p	Eta^2	T1 Mean(SD)	T2 Mean(SD)	T3 Mean(SD)
Digit Span Backwards (n=22)	.834	$F(2, 20)= 1.99$	.16	.166	11.78 (2.87)	12.18 (3.01)	13.41 (2.85)
The Brixton Test (n=31)	.960	$F(2,29)=.603$	.55	.040	5.33 (1.91)	5.60 (1.82)	5.54 (1.80)
Verbal Fluency (n=29)	.930	$F(2, 27)= 1.01$	.37	.070	8.11 (4.79)	6.85 (4.77)	6.12 (3.13)
Stroop CWI (n=30)	.953	$F(2, 28)= .696$	.08	.507	48.61 (32.69)	52.02 (35.43)	51.38 (31.84)

4.1.5 Discussion

In the present research, we retrospectively analysed data to investigate the effects of serial testing on commonly used measures of executive function. The results suggest that no practice effects were evident on the select measures of executive function, in a healthy cohort over a 12-month period, when assessed at baseline, and on two further occasions.

In addition, the results show there was no effect of serial testing, even when controlling for IQ. Intuitively, one might expect when considering strategy formation, that individuals within the 'High Average Range' of intelligence, as measured by the WTAR, might experience positive practice effects compared to an individual within the 'Low Average Range', however this hypothesis was not supported.

Small correlation effect sizes were noted on measures of Fluency and The Stroop Colour Word Test relative to IQ as measured by the WTAR. Medium effect sizes were noted on Backward Digit-span and The Brixton. No large effect sizes were noted. These findings challenge the assumption that executive function tests lose their efficacy over time (Burgess & Shalice, 1996) as participants neither significantly improved, nor worsened over time. A proposed consideration is that measures of executive functions incorporate novelty as part of

testing, and though novelty could not be as salient on repeat measurement, participants' initial scores may reflect optimal performance, which was consistent over time.

A concern with this study is that the time interval between T1-T3 may have minimized potential practice effects noted by previously cited research, as previously cited literature commonly employ test paradigms over weekly intervals. Notwithstanding same, a 6-month test-retest paradigm is common among clinical practice (Weschler, 2008). Furthermore, this does not negate the fact that other studies have noted procedural effects up to seven years later even as long as seventeen years after initial assessment (Rabbitt et al, 2004). This is of interest as it highlights a key issue that procedural effects may confound neuropsychological assessment even if the aforementioned protocols are in place to reduce the effects of practice (Goldberg et al, 2007). The current study found that IQ, and previous exposure to the neuropsychological assessments, had no statistically significant impact on serial testing. Shorter testing time intervals may have yielded similar results to Rapport et. al. (1997) who assessed participants at two-week intervals, and this is certainly worth exploring in future research. This research would implicate that these measures are suitable for repeated serial testing in clinical practice with an Irish cohort. It remains important to measure and examine practice effects in local populations to more accurately interpret results.

4.1.6 Limitations

When assessing practice effects on a commonly used repeatable measure, Duff et al., (2005) found that age was the most frequent factor to be considered in regression based analyses, certainly one limitation to the argument is that participants' performance may have been compromised due to age related cognitive decline, and practice effects concealed this. This however, is a consideration to be cautious of in any longitudinal research. Secondly, a limitation is certainly the retrospective analyses. Future research should employ a prospective sequential design, to investigate the effect of serial assessment. Future studies may investigate whether there is a correlation between age-related decline, practice effects and functional decline relative to activities of daily living.

4.1.7 Conclusion

We retrospectively analysed control data collected as part of a longitudinal study investigating cognitive decline in ALS (Elamin et al., 2013; Phukan et al., 2012). Our findings, exploratory in nature due to a limited sample, suggest that participants' scores neither increased, nor decreased significantly as a result of serial testing. Future research may also look at practice effects on executive functions over shorter testing intervals, and also population groups with

compromised executive function i.e., specific traumatic brain injury patients. Moreover, future research could assess whether cognitive performance is consistent over time and whether individuals' effort and response time correlate.

4.2 Social Cognitive Decline and Executive Dysfunction in ALS.

Following on from the previous study of practice effects in longitudinal assessment, we sought to investigate the psychometric properties of the reading the mind in the eyes test. This measure was initially chosen as more ALS research studies are incorporating it, as well as wider neurodegenerative research (Elamin et al., 2012). There is a need for Irish population based normative data on this measure, and also an understanding of the difficulty of each item. Furthermore, it is of interest to investigate whether the reading the mind in the eyes has an adequate ability to discriminate between those who do well on the test i.e., cognitively intact ALS, and those who do not i.e., ALS-FTD. This was investigated using the cumulative reading the mind in the eyes score, as well as the individual items. This will be investigated under the following headings:

4.2.1 Abstract
4.2.2 Introduction
4.2.3 Materials and Methods
  4.2.3.1 Participants
  4.2.3.2 Cognitive Measures
4.2.4 Ethical Considerations
4.2.5 Statistical Methods
  4.2.5.1 Reliability and Validity
  4.2.5.2 Item Difficulty
  4.2.5.3 Difficulty Coefficient
4.2.6 Results
  4.2.6.1 Control Demographic and Psychometric Reliability
  4.2.6.2 ALS Demographics and Comparative Performance
  4.2.6.3 Psychometrics in ALS patients
4.2.7 Discussion

This paper has been published in PlosOne:

Burke, T., Pinto-Grau, M., Lonergan, K., Elamin, M., Bede, P., Costello, E., Hardiman, O., & Pender, N. (2016). Measurement of Social Cognition in Amyotrophic Lateral Sclerosis: A population based study. PlosOne, Early Online; doi:10.1371/journal.pone.0160850

4.2.1 Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disease. Executive dysfunction is common in patients with ALS, with up to 50% of patients performing within an impaired range. There is evidence that social cognitive deficits associated with ALS are a function of deficits in executive function. The 'Reading the Mind in the Eyes' Test is a recognized test of social cognitive function, although the psychometric properties, or validity, of this instrument remains to be established within an Irish cohort.

Methodology: Patients with ALS (n=106), and age and IQ matched controls (n=50) were recruited and asked to perform the Reading the Mind in the Eyes Test as part of an on-going population-based study of cognitive function. ALS patients were sub-stratified based on the presence, and/or extent of executive dysfunction.

Results: Cronbach's Alpha of .73 was observed, indicating good reliability on this measure. Split-half reliability analysis further confirms these findings (p= 0.826). The Reading the Mind in the Eyes test had excellent psychometric properties when discriminating between ALS patients who are cognitively intact, and those who have executive impairment, with an overall medium difficulty. There was a large magnitude significant difference between patients and controls (p< 0.001; η^2= .19). Post-hoc analysis revealed that controls performed significantly higher than patients with executive impairment (p< 0.001), and patients with single executive deficits (p= 0.002).

Conclusion: Executive dysfunction impacts on social cognitive performance. This study contributes not only to the psychometric knowledge of this measure, but also to the usability, efficacy, and reliability of social cognitive assessment in ALS. Using population-specific normative data, we confirm the Reading the Mind in the Eyes Test is a reliable measure of social cognitive processes in ALS.

4.2.2 Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and fatal neurodegenerative disorder. Cognitive impairment, specifically executive dysfunction is common in patients with ALS, with up to 50% of patients performing within an impaired range (Elamin et al., 2012). Behaviour changes are also known to occur in ALS, with apathy as the most commonly reported symptom (Burke, Elamin, Galvin, Hardiman, & Pender, 2015). Recently, an in-depth study of the social cognitive changes in ALS found that performance in social cognitive function varies based on the measure used (Giradi et al., 2011).

Social cognition can be defined as the ability to represent and attribute affective and cognitive mental states (Abu-Akel & Shamay-Tsoory, 2011). It integrates cognitive processes such as the ability to follow eye-gaze, share attention, recognize emotion, and to distinguish between self and other (Adolphs, 2009). Initial social cognition research focused on disorders where social skills were implicated as a core feature (Baron-Cohen et al., 2001; Segura, Pedreño, Obiols et al., 2015). However, in recent years the relationship between neurodegeneration and social cognitive processes has gained much attention (Cavallo et al., 2011) and assessments of neuropsychological and social cognitive performance are more routine in neurologic conditions where muscular atrophy is the dominant feature (DiRosa, Soraru, Kleinbub, et al., 2015).

Performance on measures of social cognition in ALS has been associated with fronto-striatial dysfunction. ALS-related executive dysfunction has been reported to be the main predictor of social cognition performance when compared with demographic variables, behaviour, mood and personality (Watermeyer, Brown, Sidle, et al., 2015). Social cognitive deficits are also a well-recognised feature of Frontotemporal dementia (Bertoux, de Souza, O'Callaghan, et al., 2015). ALS with a comorbid FTD is known to occur in 10-15% of patients (Byrne et al., 2012), with a strong clinical and pathological overlap between these conditions (Burrell, Halliday, Kril et al., 2016). Cognitive features, such as impaired social cognition of FTD may therefore be evident in people with ALS, who do not meet the criteria for a comorbid dementia syndrome.

A commonly used social cognition task in neurodegenerative research is the Reading the Mind in the Eyes Test (Elamin et al., 2012; Giradi et al., 2011; Watermeyer et al., 2015). The Reading the Mind in the Eyes Test (RMET) comprises photographs of eye regions of human faces where participants are required to infer their mental/emotional state given four possible

choices (Baron-Cohen et al., 2001). The RMET was chosen as a measure of affective social cognition within this cohort, as individuals can respond verbally or by pointing. Although the RMET was not specifically developed for use with an ALS cohort, it accounts for potential bulbar/spinal motor disability. The RMET has also been used with a wide variety of clinical populations with neurological conditions, including patients with ALS (Jelsone-Swain, Persad, Burkard, & Welsh, 2015), Kennedy's disease (DiRosa et al., 2015), Huntington's disease (Mason, Zhang, Begeti, et al., 2015), Lewy body dementia (Heitz, Vogt, Cretin et al., 2015), Parkinson's Disease (De Ferrari, Lagravinese, Pelosin, et al., 2015), Epilepsy (Boucher, Rouleau, Lassonde, Lepore, Bouthillier, & Nguyen, 2015), as well as psychiatric populations (Gawęda, Krężolek, Olbryś, Turska, & Kokoszka, 2015), children (Levy, & Milgram, 2014; Nentjes, Bernstein, Arntz, van Breukelen, Slaats, 2015) and healthy cohorts (Cassels, & Birch, 2014; El Haj, Raffard, & Gély-Nargeot, 2015; Khorashad, Baron-Cohen, Roshan, et al., 2015). However the reliability of the measure has been subject to criticism. Notwithstanding, recent evidence suggests that the RMET has good validity (Lodder, Scholte, Goossens, Engels, & Verhagen, 2015), and is unaffected by the test-taker's gender in some but not all instances (Ahmed, & Stephen, 2011; Fernandez-Abascal, Cabello, Fernandez-Berrocal, & Baron-Cohen, 2013). Conflicting reports of reliability may be due to cultural differences in interpreting the stimuli.

The aim of our study was to investigate the reliability of the RMET using a control cohort, to sub-stratify ALS patients based on cognitive categorisation criteria (Phukan et al., 2012) and to compare cohorts of multi-domain executive deficits (cognitively impaired), single executive deficits, and no cognitive abnormalities detectable on testing. We further investigated the difficulty and discrimination coefficients associated with this measure in an Irish population-based cohort of ALS patients and healthy controls.

4.2.3 Materials and Methods

4.2.3.1 Participants

A total of 108 population based ALS patients were included in this study. The research design, case ascertainment, procedure, and information on the population-based register have been previously reported in detail (Elamin, Phukan et al., 2012; Elamin, et al., 2012; Phukan et al., 2012; Strong et al., 2009). ALS patients were classified into groups specific to cognitive status, based on cognitive domain-based criteria. This methodology has previously been reported in detail (Phukan et al., 2012), and is based on internationally accepted consensus

criteria for cognitive impairment (Strong et al., 2009). This method further complements these criteria as a more stringent cut-off was used to define abnormality. Using these criteria, patients were sub-stratified based on whether they had 'no cognitive abnormalities' (n=70), a 'single executive deficit' (n=19), or 'multi-executive deficits/cognitively impaired' (n=19).

Due to ALS patient stratification based on severity of executive impairment, we completed a priori power analyses to ensure our findings with *F* statistics would be robust with smaller groups. A standard alpha error probability of .05 was employed, with a 1-β power of .8 recruited for a 4 group design. This yielded a non-centrality parameter λ of 12.16, critical F at 2.73, and actual power of .82, which required a minimum of 19 per group.

Inclusion criteria for this research were a diagnosis of a possible, probable or definite ALS based on the El Escorial criteria (Brooks et al., 2000), with supported neurophysiology for diagnostic accuracy. Exclusion criteria included the presence of co-morbid neurological and/or psychiatric condition such as stroke, psychosis, traumatic brain injury, or an active or positive history of chronic substance abuse. Clinic- and home-based assessments were used to gather clinical and neuropsychological data. In addition, 50 healthy age- and education-matched controls were recruited considering the aforementioned exclusion criteria.

The Medical Research Ethics Committee of Beaumont Hospital, Dublin, Ireland, has approved this study. Informed consent was obtained from all participants in this study.

4.2.3.2 Cognitive Measures

The Reading the Mind in the Eyes Task is a 36-item assessment where photographs of eye regions are presented, and participants are required to infer the mental/emotional from four choices e.g., terrified, upset, bored, irritated.

Participants were also assessed using a battery of standardized neuropsychological measures and cognitively categorised as noted above (Phukan et al., 2012). Variables of interest were extracted for the purpose of this study, which included the Wechsler Test of Adult Reading (WTAR: Holdnack, 2001), a measure of premorbid function yielding a predicted Full Scale IQ (pFSIQ). Ravens Progressive Coloured Matrices investigated current function through verbal/non-verbal trials (Raven, Raven, & Court, 1998).

4.2.4 Ethical Considerations

The Beaumont Hospital Medical Research Ethics Committee approved this study. All procedures were conducted in accordance to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all participants in this study.

4.2.5 Statistical Methods

Demographic characteristics between ALS patients and controls were analysed using independent samples t-tests (age and years of education), with χ^2 used to test dichotomised variables. ANOVA were used to compare multiple dependent variables. The threshold for statistical significance was set at $p<0.05$ as per our power calculations. All statistical analyses were conducted using SPSS, Version 22.0.

4.2.5.1 Reliability and Validity

Classification for good internal consistency, using Cronbach's alpha, remains at the internationally accepted value of >.70. Split half reliability was also assessed using Spearman-Brown coefficient for equal length measures, to complement analyses of internal consistency.

4.2.5.2 Item difficulty

We computed the difficulty and discrimination coefficient of each item in order to test if it yielded the necessary degree of reliability and validity (Linda, & Algina, 2006). This methodology has previously been employed when investigating the psychometric properties of a translated version of the RMET. We infer that a reliable and valid item should be able to appropriately distinguish between those with a higher total score and those with a lower total score on the RMET. We defined the higher score and lower score groups as the upper 27 % and the lower 27 % of participants, according to their total score on RMET consistent with previous studies (Khorashad et al., 2015).

4.2.5.3 Difficulty Coefficient

The proportion of participants who answer a test item correctly relative to the test taking population measures the difficulty of an item. The higher this proportion is, the lower the item's difficulty.

To calculate the difficulty of an individual test item, the number of participants who answered the item correctly (from both the upper and lower proportions) is divided by the total number of participants who took the test. It is represented as the following formula:

$$Pi = (Ai/Ni \times 100)$$

whereby Pi = difficulty index of item; Ai = number of correct answers in upper 27 % added to the number of correct answers in the lower 27 %; Ni = the sum of total test takers in the upper 27 % and lower 27 % groups.

Difficulty levels are classified in the following way (Kelley, 1939): very difficult (Pi < 30%); moderately difficult (31% - 50%); medium difficulty (51% - 70%); moderately easy (71% - 90%); and very easy (Pi > 90%). The ideal distribution of difficulty follows the basic principles of normal distribution.

4.2.5.3 Discrimination Coefficient

Items of a valid and reliable test must be able to appropriately differentiate between participants who are relatively strong from those who are relatively weak; otherwise, the test is lacking sensitivity and specificity. Through the use of healthy controls, we investigated the RMET's overall discrimination coefficient. We then also applied this methodology to our ALS cohort whereby the proportion of patients who scored in the upper range reflects patients with a 'no cognitive abnormality detected' status, and the proportion of patients who scored in the lower group represents the 'multi executive deficits' apparent on testing group. Using this method we calculate the ability of this task to discriminate between ALS patients who are cognitively intact, and those who are cognitively impaired based on internationally accepted criteria.

It is calculated through the following formula:

$$Di = (Pu - Pl) \times 100$$

whereby Di: index of discrimination of item; Pu: the proportion of those in the upper 27 % group who correctly scored on the item relative to the sum of test takers; Pl: the proportion of those in the lower 27% group who correctly scored on the item relative to the sum of test takers. The following guidelines have been published to interpret the Di values: D ≥40 = Excellent; 39 – 30 = Good; 29-20 =Mediocre; 19 - 0 = Poor; D < -1 = Worst.

4.2.6 Results

4.2.6.1 Control Demographics and Psychometric Reliability

Control participants at the time of assessment were 61.4 years SD± 9.1, with 12.7 years of education SD±2.9. This cohort consisted of 30 males (60%). Prior to conducting reliability analyses, we investigated whether participant gender was equally distributed within our control cohort. The distribution of gender within the control cohort was found to be homogenous (p= 0.203). We investigated whether there was a significant difference in performance based on gender, with a 2-tailed hypothesis. With equal variance assumed, we report that there was no difference identified on the score of the RMET, based on gender stratification (p= 0.113).

We proceeded to conduct reliability statistics, and considering the full 36-items of the RMET, a Cronbach's Alpha of .73 was observed. The reliability of each individual test item, and how it correlates to the overall measure can be seen in Table 4.3. Split-half reliability analyses were conducted using Spearman-Brown Coefficient, and equal length statistics confirm the reliability of this measure (p= 0.826).

Each item was analysed to investigate a difficulty coefficient (Pi) and was classified accordingly. A discrimination coefficient (Di) and classification were employed to investigate whether the individual items are accurate at discriminating between controls who performed well compared to those with a low score on the test. Overall the RMET is reported to be of medium difficulty (68.8%), with good psychometric properties for discriminating healthy controls based on performance (Di=31.7). The breakdown of individualised items can be found in Table 4.4.

Table 4.3: Itemised Reliability Statistics

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
Playful	24.38	22.48	.340	.712
Upset	24.64	20.92	.566	.694
Desire	24.38	22.77	.252	.716
Insisting	24.74	23.38	.021	.730
Worried	24.62	21.54	.428	.704
Fantasizing	24.62	22.15	.290	.713
Uneasy	24.34	23.73	-.032	.727
Despondent	24.42	23.10	.129	.722
Preoccupied	24.44	22.86	.184	.719
Cautious	24.42	23.96	-.099	.733
Regretful	24.58	21.59	.430	.704
Sceptical	24.40	22.08	.436	.707
Anticipating	24.44	22.74	.216	.717
Accusing	24.44	22.29	.336	.711
Contemplative	24.48	22.25	.318	.712
Thoughtful	24.48	22.25	.318	.712
Doubtful	24.50	23.27	.062	.726
Decisive	24.74	23.70	-.046	.734
Tentative	24.62	23.71	-.045	.733
Friendly	24.46	22.13	.363	.709
Fantasizing	24.66	22.43	.223	.717
Preoccupied	24.34	22.55	.379	.711
Defiant	24.62	23.26	.050	.728
Pensive	24.66	22.10	.295	.712
Interested	24.58	23.14	.079	.726
Hostile	24.80	21.59	.406	.705
Cautious	24.62	21.58	.419	.704
Interested	24.44	21.96	.425	.706
Reflective	24.44	24.12	-.140	.735
Flirtatious	24.36	22.11	.491	.706
Confident	24.82	22.96	.109	.724
Serious	24.72	22.36	.233	.716
Concerned	24.56	22.21	.294	.713
Distrustful	24.60	22.61	.193	.719
Nervous	24.60	23.02	.104	.724
Suspicious	24.44	23.06	.130	.722

---- Split-half reliability section break

Table 4.4: Control Difficulty and Discriminatory Performance

Q	Pi	Pi Classification	Di	Di Classification
1	75.0%	Mod. Easy	35.80	Good
2	46.4%	Mod. Difficulty	78.60	Excellent
3	82.1%	Mod. Easy	21.50	Mediocre
4	60.7%	Medium	21.40	Mediocre
5	53.6%	Medium	64.50	Excellent
6	67.9%	Medium	50	Excellent
7	96.4%	Very Easy	7.10	Poor
8	75.0%	Mod. Easy	7.20	Poor
9	82.1%	Mod. Easy	35.70	Good
10	85.0%	Mod. Easy	-14.30	Worst
11	60.7%	Medium	64.30	Excellent
12	78.6%	Mod. Easy	42.90	Excellent
13	75.0%	Mod. Easy	35.80	Good
14	78.6%	Mod. Easy	28.60	Mediocre
15	71.4%	Mod. Easy	42.90	Excellent
16	71.4%	Mod. Easy	28.60	Mediocre
17	71.4%	Mod. Easy	14.30	Poor
18	50.0%	Mod. Difficulty	14.20	Poor
19	60.7%	Medium	7.20	Poor
20	71.4%	Mod. Easy	42.90	Excellent
21	60.7%	Medium	35.70	Good
22	85.7%	Mod. Easy	28.60	Mediocre
23	82.1%	Mod. Easy	7.10	Poor
24	50.0%	Mod. Difficulty	42.80	Excellent
25	67.9%	Medium	35.70	Good
26	35.7%	Mod. Difficulty	57.20	Excellent
27	57.1%	Medium	57.10	Excellent
28	75.0%	Mod. Easy	50	Excellent
29	78.6%	Mod. Easy	0	Poor
30	82.1%	Mod. Easy	35.70	Good
31	46.4%	Mod. Difficulty	21.40	Mediocre
32	57.1%	Medium	42.90	Excellent
33	67.9%	Medium	35.70	Good
34	67.9%	Medium	21.60	Mediocre
35	64.3%	Medium	28.60	Mediocre
36	85.7%	Mod. Easy	14.30	Poor
$\bar{X}$	68.82%	Medium	31.77	Good

Pi = Item's difficulty; Di = Item's ability to differentiate between those who are high and low

4.2.6.3 ALS Demographics and Comparative Performance

Considering the reliability of the measure, we investigated the serial performance of controls on each item, as well as the scores of ALS patients. Patients at the time of assessment were 60.4 years SD± 10.8, with 12.8 years of education SD±3.3. ALS patients were mostly spinal onset (73.5%) and male (71.6%).

Figure 4.1 illustrates that control performance was highest (n=50; X =25.24 ± 4.87), followed by ALS patients with no cognitive abnormalities (n=70; X =22.9 ±6.46), followed by patients with a single executive impairment (n=19; X=19.42 ±6.71), and patients with multi-executive impairments had the lowest performance (n=19; X =16.15 ±6.22). Fig. 4.1 highlights cumulative performance of each group using the RMET with evident decline associated with grouping based on executive performance.

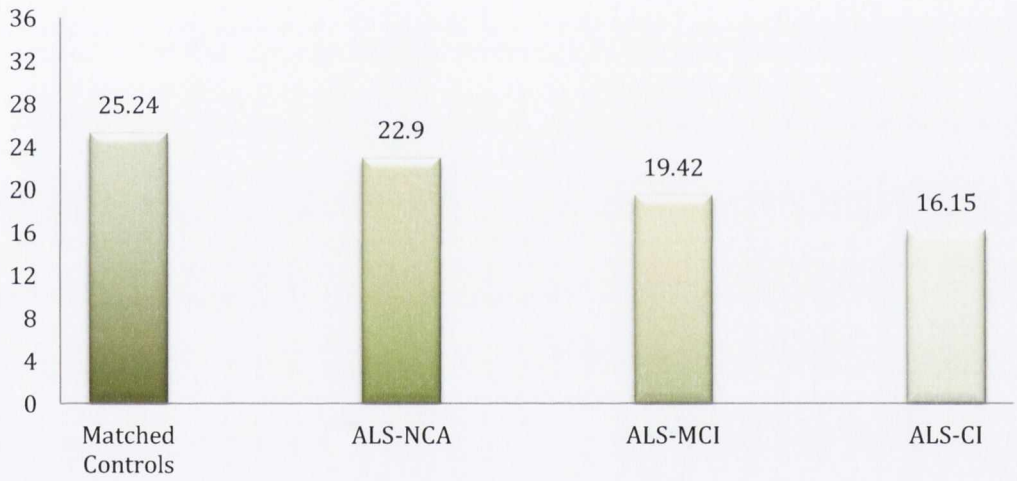


Figure 4.1: Distribution of Scores on the RMET. Patient and Control Performance on the Reading the Mind in the Eyes Test, stratified by cognitive categorisation.

Individual patient groups' performance was compared to healthy controls, with groups matched for age at assessment (p= 0.622), and years of education (p= 0.940). Homogeneity of variance was satisfied (p= 0.115), and an ANOVA was conducted as per our power calculation. There was significant difference with large magnitude reported from the ANOVA (p< 0.001; η^2= .19).

To elucidate this further, a post-hoc analysis was employed. Controls performed significantly higher than patients with executive impairment (p= 0.001), and patients with single executive deficits (p= 0.002). Controls did not significantly differ from ALS patients with no cognitive

abnormalities (p= 0.157). By contrast, ALS patients without cognitive deficits did not differ from ALS patients with single executive deficits (p= 0.118), yet did perform significantly better than ALS patients with multi-domain executive impairment (p= 0.001). Interestingly, ALS patients with single executive deficits did not differ from the patients with multi-domain executive impairment (p= 0.341).

4.2.6.3 Psychometrics in ALS patients

Itemised group performance can be seen in Table 4.5, where scoring patterns remain consistent based on executive grouping. The Reading the Mind in the Eyes test appears to have 'Excellent' psychometric properties when discriminating between patients who are cognitively intact, and those who have executive impairment (Di = 43.5), with an overall 'Medium' difficulty (54.7%). Individual item difficulty and discrimination for ALS patients are presented in Table 4.6.

Table 4.5: Individual Item Performance (% correct)

Item	Healthy Controls (N=50)	Cognitively Intact ALS (N=70)	Single Cognitive Impairment (N=19)	Multi-Executive Impairment (N=19)
1	86	74	63	42
2	60	63	57	52
3	86	71	68	42
4	50	60	47	36
5	62	64	57	57
6	62	74	42	52
7	90	70	57	47
8	82	74	68	57
9	80	71	42	42
10	82	59	68	47
11	66	70	73	47
12	84	69	47	26
13	80	66	42	36
14	80	70	57	36
15	76	69	31	26
16	76	77	78	52
17	74	63	63	52
18	50	53	47	26
19	62	53	47	36
20	78	73	68	73
21	58	53	31	42
22	90	76	52	52
23	62	57	47	21
24	58	61	31	26
25	66	60	63	63
26	44	49	52	36
27	62	59	47	52
28	80	71	52	36
29	80	63	78	36
30	88	69	52	47
31	42	43	36	26
32	52	47	47	52
33	68	54	47	57
34	64	56	36	42
35	64	60	57	57
36	80	70	73	68

Table 4.6: ALS Difficulty and Discrimination Performance

Q	Pi	Pi classification	Di	Di Classification
1	53.12%	Medium	56.20	Excellent
2	56.25%	Medium	37.50	Good
3	52.77%	Medium	56.30	Excellent
4	50%	Mod. Difficulty	50	Excellent
5	56.25%	Medium	12.50	Poor
6	56.25%	Medium	62.50	Excellent
7	71.87%	Mod. Easy	31.30	Good
8	56.25%	Medium	62.50	Excellent
9	50%	Mod. Difficulty	75	Excellent
10	46.87%	Medium	6.30	Poor
11	68.75%	Medium	25	Mediocre
12	50%	Mod. Difficulty	37.50	Good
13	56.25%	Medium	62.50	Excellent
14	56.25%	Medium	50.20	Excellent
15	43.75%	Mod. Difficulty	87.50	Excellent
16	65.62%	Medium	31.20	Good
17	56.25%	Medium	37.50	Good
18	40.62%	Mod. Difficulty	31.20	Good
19	46.87%	Mod. Difficulty	43.70	Excellent
20	68.75%	Medium	37.50	Good
21	46.87%	Mod. Difficulty	56.30	Excellent
22	56.25%	Medium	87.50	Excellent
23	56.25%	Medium	50	Excellent
24	40.62%	Mod. Difficulty	68.80	Excellent
25	56.25%	Medium	37.50	Good
26	53.12%	Medium	31.20	Good
27	59.37%	Medium	43.70	Excellent
28	59.37%	Medium	43.70	Excellent
29	56.25%	Medium	37.50	Good
30	62.50%	Medium	37.50	Good
31	37.50%	Mod. Difficulty	0	Poor
32	43.75%	Mod. Difficulty	37.50	Good
33	46.87%	Mod. Difficulty	43.70	Excellent
34	56.25%	Medium	37.50	Good
35	68.75%	Medium	25	Mediocre
36	68.75%	Medium	37.50	Good
Ave	54.76%	Medium	43.58	Excellent

Pi = Item's difficulty ; Di = Item's ability to differentiate between those who are high and low

4.2.7 Discussion

Our primary aim was to investigate whether the Reading the Mind in the Eyes Test (RMET) is a reliable measure. Secondary aims included addressing its efficacy and validity as a measure against a patient population, where executive dysfunction is categorised with high accuracy. These data suggest that the RMET is a reliable measure of social cognition for use with healthy and ALS cohorts (Cronbach's alpha .73 ; Split-half reliability p= .826). Our data further support previous work that the RMET score is not affected by gender (p= 0.113).

Overall the RMET is reported to be of medium difficulty (68.8%), with good psychometric properties for discriminating between controls that perform in the upper and lower ranges (Di=31.7). This analysis was applied to an ALS cohort, as a total group. The lower 27% of the patient group had a range of executive deficits, and the upper 27% were cognitively intact. This allowed us to infer whether this measure is useful in dichotomising executive dysfunction in ALS. These data suggest that this measure has 'Excellent' psychometric properties (Di = 43.5) for discriminating between patients with cognitive impairment and those who are cognitively intact, with an overall 'Medium' difficulty (54.7%).

Consistent with previous literature, there was significant difference with large magnitude reported between patient groups and the control cohort (p< 0.001; η^2= .19). Post-hoc analysis revealed that controls performed significantly higher than patients with executive impairment (p= 0.001), and patients with single executive deficits (p= 0.002) but not cognitively intact ALS patients (p= 0.157). Of interest were the scores of ALS patients with single executive deficits, as they did not differ from the patients with multi-domain executive impairment (p= 0.341) or cognitively intact ALS patients (p=0.118). This pattern of performance demonstrates that ALS patients without cognitive abnormalities are similar to controls, and to those with single domain cognitive impairment (See Figure 4.1). Patterns of social cognitive deficits such as these are consistent with both the subtle deficits of executive function, which may present early in the disease, as well as the more severe impairment known to occur in some cases. The lack of significant difference in performance on the RMET between groups i.e., no cognitive abnormalities and single executive impairment, could be attributed to difficulties in detecting subtle cognitive impairment in this cognitive domain.

This study has limitations. Given the lower scoring profile of cognitively intact ALS patients, longitudinal follow-up would be advantageous. This point is further generalised to the other ALS cohorts to quantify the rate that social cognitive processes decline alongside the disease

trajectory, with respect to executive dysfunction. Given the relevance of these findings in relation to executive function, future research could investigate the impact of social cognitive deficits on patient survival, the relationship of social cognitive deficits to behavioural presentations, and the extent to which patients differ on test performance considering genetic expansions known to implicate cognitive function i.e., C9orf72. Future studies could investigate the relationship between social cognitive performance and behavioural features associated with ALS; could determine whether social cognitive decline has a negative impact on caregiver burden in ALS; and whether there are additional negative implications on the psychological wellbeing of patients and caregivers.

In conclusion, our data confirm the Reading the Mind in the Eyes Test is a reliable measure of social cognitive processes, and illustrate how executive dysfunction mediates performance on this measure. These data provide clinically relevant normative data for use in clinical and research settings. Moreover, by stratifying by level of executive impairment here, these data provide a useful reference point in terms of severity of social cognitive deficit. Clinically these data support the routine inclusion of social cognitive measures in standardised batteries of neuropsychological tests. Furthermore, considering the RMET as a valid measure of social cognition for use with ALS patients, their overall performance on this measure should be considering in light of ALS-FTD comorbidity.

4.3 Social Cognition In Huntington's Disease: A Case Study.

This study was included within this thesis as it demonstrates that executive dysfunction can decline at a different trajectory to social cognitive processes. This study reports the single case study of a patient with Huntington's disease who underwent detailed assessment of social cognitive processes and executive function. This study reports a proof of concept in investigating executive dysfunction and social cognition in ALS patients, and does so through the following sections:

1.1 Social Cognition in Huntington's Disease: A Case Study

- 1.1.1 Abstract
- 1.1.2 Introduction
- 1.1.3 Case Presentation
- 1.1.4 Neuropsychological Assessment
  - 1.1.4.1 D-KEFS: Delis Kaplan Executive Function System
- 1.1.5 Discussion

This paper has been published:

Burke, T., Healy, D., Casey, P., Hardiman, O. & Pender, N. (2015). Atypical Affective Processing In Premotor Huntington's Disease: A Single Case Study. The Irish Journal of Psychological Medicine

For a more detailed overview of Huntington's disease see:

Burke, T., Doherty, C., Koroschez, W. & Pender, N. (2016). Huntington's Disease. In Hardiman, Elamin, Doherty & Bede (Eds.), Neurodegenerative Disorders: A Clinical Guide (2nd Ed.) Springer, UK.

[Note] This study is of particular relevance to the presented thesis, as it demonstrates how aspects of social cognition can be impaired in some patients with neurodegenerative conditions, while executive function remains relatively intact i.e., within the Low Average – High Average range. This study is a proof of concept for investigating social cognition in neurodegenerative diseases, whereby this concept was then applied to an ALS population to investigate further.

4.3.1 Abstract

Background. We report the case of a 52-year old male with pre-motor HD who has undergone detailed clinical and neuropsychological examination. This patient's negative symptomatology and behavioural change are having a detrimental impact on his social, occupational and interpersonal life, in the absence of motor symptoms.

Method. The patient has undergone repeat neuropsychological testing (T1 aged 50; T2 aged 52) with particular focus on executive function and social cognition on repeat testing.

Results. This case details a specific manifestation of HD relating to behavioural, psychiatric and social affective deficits.

Conclusion. This case illustrates how social cognitive changes can occur in HD, months and even years prior to the onset of motor features and how such unrecognized deficits can have an deleterious impact on an individual's functional ability and lifestyle, before the disease is traditionally considered to have become manifest.

4.3.2 Introduction

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder characterized by chorea, cognitive decline and psychiatric illness, with associated behavioural difficulties (Walker, 2007). HD is reported to have an incidence of 6·4/100,000 in Northern Ireland (Morrison et al., 1995), although prevalence is unknown in the Republic of Ireland. HD is caused by a trinucleotide repeat expansion (CAG) in the *huntingtin* gene located on chromosome 4p16·3 (Huntington's Disease Collaborative Research Group, 1993). Subtle cognitive decline has been reported prior to the onset of motor features in patients with genetically confirmed HD (Henley et al., 2012; Paulsen et al., 2013), although the focus herein is on social-affect deficits, specifically as social cognition can deteriorate over the course of the disease (Sprengelmeyer, et al., 2006), (for a review of global cognitive decline in prodromal HD see Paulsen et al., 2013).

Social cognition refers to the cognitive processes associated with social interaction, which encompass the ability to recognize, process and express emotions (Ekman 1992; Ekman 1993). These have been shown to be problematic in neurodegenerative diseases (Müller & Bekkelund, 2013) including HD (Johnson et al., 2007). Some studies maintain that poor performance on tasks that examine the recognition of emotional stimuli, by patients with HD, may be due to task difficulty rather than specific social affective dysfunction associated with emotional processing (Milders et al., 2003). However, impairment has been noted in the recognition of certain emotions in patients with HD, such as sadness and disgust, using a range of stimuli in different modalities (Snowden et al., 2008). Modalities such as facial recognition of emotion (Calder et al., 2003) and prosodic tone in an individual's voice (Snowden 2003) have evidenced deficits in emotive processing in patients with manifest HD (Henley et al., 2012).

Social cognition is theorized to be a sub-element of the executive system (Damasio & Maurer, 1978), however, there is an increasing body of evidence suggesting that social cognition is characterized by its own sub-components referred to as 'Theory of Mind' (ToM; Sprengelmeyer et al., 2006). ToM is further categorized into 'Cognitive' and 'Affective' subtypes. Cognitive ToM governs the recognition that others may have knowledge and beliefs, which are different to ones' own (Abu-Akel & Shamay-Tsoory, 2011), whereas affective ToM is the ability to infer another's emotional state and modulate socially appropriate behaviour accordingly (Shamay-Tsoory & Aharon-Peretz, 2007).

Social breakdown and interpersonal difficulties are common features of HD, and these may be mediated by cognitive dysfunction. Within the literature it is unclear as to whether a common underlying executive deficit mediates impairment on tasks of social cognition. A limitation of many studies in HD is the use of single modality testing, and sampling of manifest HD who exhibit co-morbid executive function. A minority of individuals with HD have cognitive decline prior to the onset of motor features (Paulsen & Long, 2014). Recent findings demonstrate how cognitive deterioration can be seen in persons with HD with no overt motor signs or symptoms, suggesting that subtle cognitive onset may precede motor features (Paulsen & Long, 2014).

Behavioural decline may occur prior to the onset of motor features, due to neurodegeneration in basal ganglia circuitry. The fronto-striatal system has been noted, in imaging studies of prodromal HD, to show local and global atrophy in the fronto-striatal tracts over a decade before symptom onset (Rees et al., 2013; Paulsen & Long, 2014).

Detailed neuropsychological assessment is required with patients in order to delineate differential deficits in the expression, identification and recognition of emotion, as patients may present with heterogeneous neuropsychological deficits over time (Hart et al., 2013; Novak & Tabrizi, 2010). We describe the case of genetically confirmed pre-manifest HD patient with specific social-affective deficits, prior to the onset of motor features.

4.3.4 Case Presentation

The patient was a 50-year old, right-handed Caucasian Irish male with 12 years of education and genetically confirmed HD (expansion of 41±1 CAG repeat). The patient had initially been assessed using Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) and scored 27 of 30, within the Average range for an Irish cohort (Kenny et al., 2013), when he initially presented in early 2011.

The patient, 'Mr. A' reported feeling "flat", reported no disturbance of sleep, appetite or subjective low mood. He displayed insight into his lack of motivation for social activities, family and home life. Prior to presenting at his local services in early 2011, according to his wife, he had become more intolerant, he was difficult to interact and live with, and he could suddenly present as "acutely irate" over small things, and then return to a 'flat' state. She referred to her husband as "lacking emotion", stating that his symptoms were new, and that "he was not the man she married 20 years ago", indicating a large change from his premorbid personality. Together they have two children, although both report that he has become much

more distant from them recently.

Mr. A was not formally employed at the time of his initial examination. He continued to earn an income by managing property although he commonly reported interpersonal difficulties with his clients. Collateral interview, with his wife of over 20 years confirms this, and she further reported that these hostile interactions as new onset. Mr. A's wife reports that his behaviour antagonizes clients, instigates interpersonal difficulties, and there is often little resolution.

Mr. A's father and paternal uncle were genetically diagnosed with HD. On examination, by an expert movement disorder specialist in 2012, our patient was described as physically unremarkable, and prodromal by traditional clinical characterization. Clinically, a major concern was effective treatment options for our patient, based on whether his new onset presentation was a reactive depression, or a premotor pathological decline in his HD.

Our patient had been attending a consultant psychiatrist, with a working diagnosis of idiopathic depression. After a multidisciplinary team and family meeting in late 2012, his anti-depressive medications were ceased and psychotherapeutic intervention commenced, as the patient was not experiencing any relief from medication. At that time, the evidence supported a severe apathetic profile, although our patient was not endorsing depressive or anxiety symptoms on empirical assessment.

The patient was referred for further psychotherapeutic, neuropsychological and neurological review in early 2013. At this time he completed an initial neuropsychological screening assessment (See Table 4.7). The patient was initially tested using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), which is reported to be reliable in the clinical assessment of cognition in HD (Duff et al., 2010). The patient continued, and continues, psychotherapeutic intervention. He reported that his symptoms have not been alleviated dramatically, and endorsed feeling flat, severely lacking empathy, and low tolerance for family, friends or social engagement.

After approximately one year, in early 2014, the team re-assessed the patient and his clinical presentation remained unchanged. During his annual follow-up assessment, the patient was assessed on an alternate form of the screening tool outlined below. Published normative age-matched data were used to compile standardized scores represented in Table 4.7. One should interpret the differences in percentile scores with caution, and consider the accompanied

Reliable Change Indices. The patient appears to have dropped from the 74th to the 32nd percentile, however *this is reflective of a drop of one raw score on repeat assessment.* Due to the fluctuations in the scoring pattern, Reliable Change Indices (RCIs) were calculated for each of the measures, with none reaching significance. At the time of this assessment, he was further assessed

Table 4.7. Results from Clinic Based Neuropsychological Assessment. (Percentile Scores)

Repeatable Battery for the Assessment of Neuropsychological Status	T1	T2	*RCI
List Learning	83	29	-·20
Story	82	65	-·40
Figure Copy	90	90	·00
Picture Naming	74	32	-·17
Semantic Fluency	15	21	·17
Digit-Span	41	41	·00
Coding	35	70	1·38
List Recall	92	50	-·50
List Recognition	30	30	·00
Story Recall	80	90	·17
Figure Recall	14	77	·93

*Reliable Change Index

on measures investigating executive processes and social cognitive processes in detail.

4.3.4 Neuropsychological Assessment

Mr. A's estimated premorbid Full Scale IQ (pFSIQ), using the Test of Premorbid Function (TOPF-UK), was estimated to be within the Average range, standard score 107, functioning at the 68th percentile. On the Unified Huntington's Disease Rating Scale our patient scored at maximum level, at both time points, indicating no functional disability (100/100). Mr. A had not been evaluated on this measure prior to cognitive testing, as he did not present clinically with motor symptoms. On the Frontal Assessment Battery (Dubois et al., 2000) he scored 17 of 18, with a reduced fluency score, congruent with the MoCA completed in 2011.

Scores were within the sub-clinical range for Alexithymia, Depression, Anxiety and Dissociative Disorders on self-report questionnaires. On the Personality Assessment

Inventory (PAI; Morey, 1991) the patient scored within the clinical range for Depression with elevation on the 'Non-Support' scale. A *t*-score >65*t* is considered in the clinically significant range.

The Frontal Systems Behaviour Scale (Grace & Malloy, 2001), a self- and proxy-report, measured Apathy, Executive Function and Disinhibition differences prior and subsequent to onset of illness, with a self- and proxy-report (Figure 4.2).

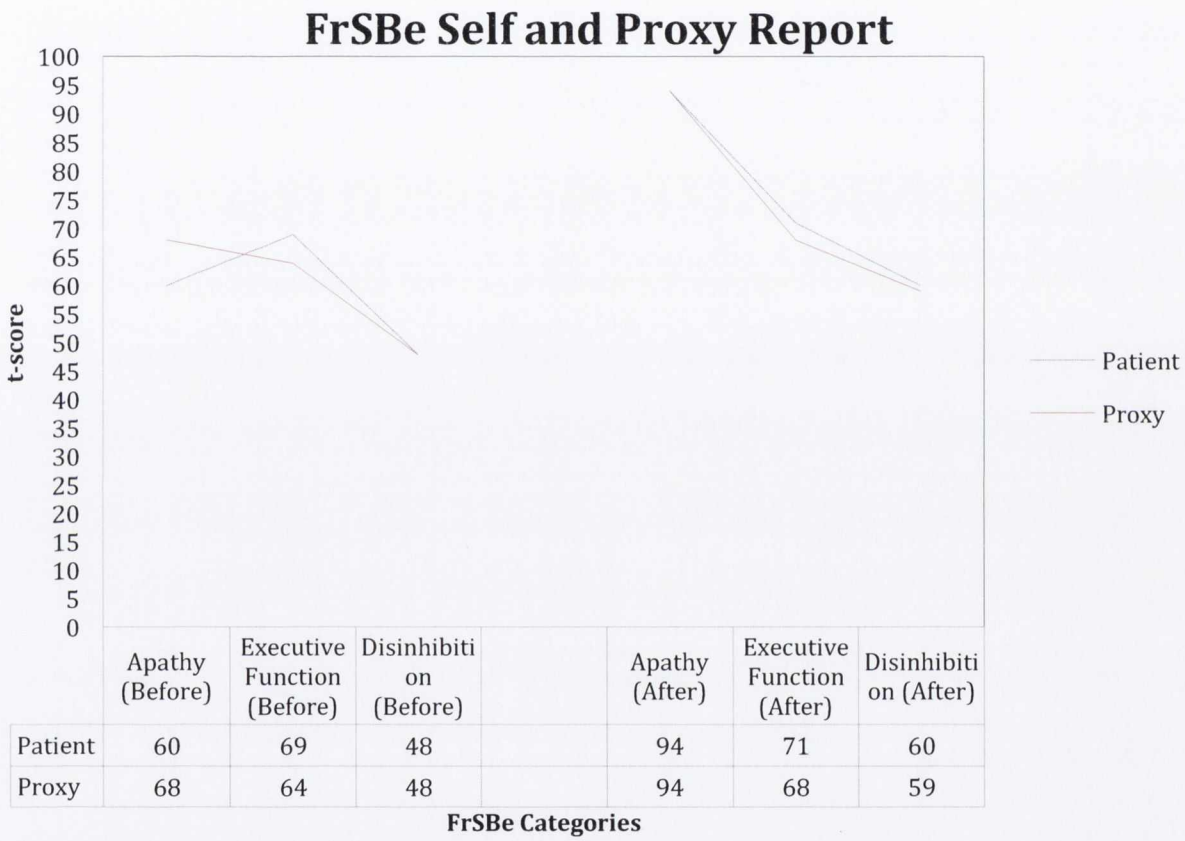
Executive functions were assessed using the Delis-Kaplan Executive Function System (DKEFS; Delis et al., 2004). Our patient performed within the expected range for tests of executive function, based on premorbid estimations. Scores were evidenced within the Borderline Impaired range on measures of phonemic fluency (See Table 4.8), although no set-loss or repetition errors were evident.

On the Social Faux Pas Recognition Test (Stone et al., 1998), a measure of cognitive theory of mind, our patient scored accurately on the experimental and control subtests. The Florida Affect Battery (Bowers et al., 1998) was used to assess this man's ability on identity discrimination, emotional discrimination, and emotional processing through facial, prosodic, and cross-modal tasks.

Table 4.8: Supplementary Investigations at T2: Social Affect and Executive Function Scores (Percentiles)

Social-Affect		
Facial Tasks	Identity Discrimination	26
	Affect Discrimination	8
	Name Affect	25
	Select Affect	<1
	Match Affect	<1
Prosody Tasks	Non-Emotional Prosody Discrimination	<1
	Emotional Prosody Discrimination	<1
	Naming Emotional Prosody	2
	Conflicting Prosody: Congruent	84
	Conflicting Prosody: Incongruent	1
Cross-modal Tasks	Matching Emotional Prosody to Emotional Face	2
	Matching Emotional Face to Emotional Prosody	<1
Executive Function (D-KEFS) [29]		
Trail Making	Visual Scanning	36
	Number Sequencing	36
	Letter Sequencing	25
	Number-Letter Sequencing	9
	Motor Speed	50
Colour-Word Interference Task		
	Colour Naming	36
	Word Reading	50
	Inhibition	36
	Inhibition/Switching	9
Verbal Fluency		
	Phonemic	50
	Semantic	36
	Categorical	36

Our patient scored within the Average range on a measure of facial identity processing. Subsequent to this he was asked to verbally label emotive facial expressions in this task and his score was within the Average range. Mr. A was then asked to identify the picture of the face that corresponds to the emotion named by the examiner (i.e., "point to the angry face"). His score was reflected within the Impaired range. Our patient was asked to match a target expression from presented choices, and his score was reflected within the Impaired range.



	Apathy (Before)	Executive Function (Before)	Disinhibition (Before)		Apathy (After)	Executive Function (After)	Disinhibition (After)
Patient	60	69	48		94	71	60
Proxy	68	64	48		94	68	59

Figure 4.2: Self and Proxy Frontal System Behavioural Scale (FrSBe)

In the emotional prosody discrimination task, the patient was presented pairs of semantically neutral sentences that are spoken in the same or different emotional tone of voice. He achieved a score within the Impaired range. On an emotional prosody identification task, assessing the ability to verbally label affective prosody, he achieved a score within the Impaired range.

4.3.4.1 D-KEFS: Delis-Kaplan Executive Function System

The patient further listened to affectively intoned sentences whose semantic content may

differ (i.e., conflict) or be parallel the prosodic message. On the incongruent task, our patient achieved a score in the Impaired range. Interestingly, on the congruent task our patient scored within the High Average range achieving a score at the 84th percentile, as seen in Table 4.8.

Lastly, the patient was shown a picture of an emotional face, and at the same time, he listened to sentences spoken in a different emotional tone. When the patient was asked to indicate which of three facial stimuli best represented an emotional tone, he performed within the Impaired range.

4.3.5 Discussion

This case-report describes a patient with genetically confirmed HD who is clinically in the pre-manifest stage. Comparing clinic-based assessments, our patient showed subtle cognitive and behavioural change over an annual period, consistent with HD, although not to a clinically or statistically relevant degree.

He presents with severe apathy, and evidenced specific deficits relating to social affective processing, which was recorded using both visual, auditory and cross-modal measurements, in the absence of any motor symptoms. Mr. A had an elevated 'Non-support' scale score, whereby a score above 70*t* may represent combative family relationships, where friends are also unavailable or unhelpful. This is unsurprising considering the aforementioned social context this man is operating within.

On assessment, the patient showed a discrepancy between elements of social-affective processes, with impairments noted at the 1st percentile, compared to social-cognitive and executive tasks within the Average range.

Social-affect deficits were found on facial, prosodic and cross-modal measures of emotional processing. Lower scores were noted on the more executively loaded subtests of the D-KEFS, which may be indicative of a progressive disease trajectory typically seen in HD, however, Mr. A has consistently scored poorly on measures of phonemic fluency, reporting 'he was never good with words'.

This profile is suggestive of a specific social-affective cognitive deficit, likely to be secondary to prodromal Huntington's disease, based on this man's confirmed genetic diagnosis and new cognitive symptomatology. It may also be plausible that this patient's disease is becoming

more manifest, amplifying specific deficits, which were subclinical until recently. It is for this reason auxiliary cognitive processes, such as executive functions, may appear relatively intact at this time. This case highlights a behaviourally interesting, and scarcely reported domain-specific cognitive impairment within a pre-motor HD case, consequently creating dramatic behavioural implications in his life. Although limitations exist when reporting any single case, it is felt that this case delineates aspects of the behavioural and neuropsychological profile of genetically confirmed prodromal HD.

A limitation of this case report is that the patient had no extensive assessment prior to his more detailed neurocognitive evaluation in 2013, with a focus on executive function and/or social cognitive functioning. This may have been beneficial in categorizing the trajectory and rate of overall cognitive decline and behavioural features of this case, however such an assessment was not initially indicated given his lack of overt symptoms at that point.

In future, it may be of clinical benefit to investigate social-affective deficits in prodromal HD, and other clinical presentations, where an idiopathic/organic depressive syndrome is possible, yet the presentation is unclear. Future clinic-based screening assessments should aim to delineate premorbid characteristics, functional decline and to empirically quantify the difficulties experienced by patients with genetically confirmed HD in the pre-manifest stage. Lastly, the emerging deficits in social cognition may explain the considerable interpersonal difficulties noted in early HD patients, which may in turn contribute to the behavioural profile, as these may often be masked by ancillary difficulties as the disease progresses. To this end clinic based assessment should routinely include measures of social cognitive processes, and clinicians should refer patients with neurodegenerative conditions for full neuropsychological assessment.

4.4 Social Cognition in ALS stratified by disease onset.

The previous chapters have established that executive tests can be repeated over time without the risk of increased performance caused by practice effects. We then demonstrated that the Reading the Mind in the Eyes Test (RMET) is a psychometrically valid tool for use with ALS patients, and published reference control data. The following study investigated whether performance on the RMET differed in ALS, based on whether a patient had spinal-onset ALS, or bulbar-onset ALS, under the following headings:

4.4 Social Cognition in ALS stratified by disease-onset

- 4.4.1 Abstract
- 4.4.2 Introduction
- 4.4.3 Materials and Method
  - 4.4.3.1 Participants
  - 4.4.3.2 Neuropsychological assessment
  - 4.4.3.3 Mood and Functional Assessment
  - 4.4.3.4 Statistical Analysis
- 4.4.4 Results
  - 4.4.4.1 Clinical, Neuropsychiatric, and Functional Data
  - 4.4.4.2 Neuropsychological Assessment
- 4.4.5 Discussion

This paper has been published:

Burke, T., Elamin, M., Bede, P., Pinto-Grau, M., Lonergan, K., Hardiman, O., & Pender, N. (2016) Discordant Performance on the Reading the Mind in the Eyes test based on disease onset in Amyotrophic Lateral Sclerosis. Amyotrophic Lateral Sclerosis and Frontotemporal Dementia.

4.4.1 Abstract

Objective: Executive Dysfunction is a core feature of Amyotrophic Lateral Sclerosis (ALS) and is associated with brain atrophy in cortical and subcortical regions. Social cognitive deficits may also be a prominent feature of ALS. This study investigated executive, and social cognitive performance, in a population based cohort of patients with ALS, stratified by disease onset.

Methods: Participants were recruited as part of a population based study investigating cognitive decline in ALS. Patients carrying pathogenic *C9orf72* hexanucleotide repeat were excluded. Participants were stratified based on bulbar (n=20) or spinal (n=39) disease onset (N=59). Matched healthy controls were used to generate culturally specific comparative data for within-patient analyses (N=59).

Results: ALS patients performed significantly worse than controls on a number of measures of executive function. When sub-stratified by disease onset, there was a significant difference between bulbar and spinal onset patients with respect to the 'Reading the Mind in the Eyes' test scores ($p< 0.001$). Conversely, standardized scores of executive function did not differ between the patient groups.

Conclusions: Patients performed significantly lower than matched controls on measures of executive function. Bulbar-onset ALS patients evidenced more social-affective deficits compared to spinal-onset patients, with matched performance on measures of executive function.

4.4.3 Introduction

Cognitive impairment as an integral part of some forms of Motor Neuron Disease (MND), has been interpreted as the fifth major clinical presentation of MND, alongside bulbar, cervical, thoracic, and lumbosacral (Bak, & Chandran, 2011). Cognitive impairment, primarily in the executive domain, occurs in up to 50% of incident patients with Amyotrophic Lateral Sclerosis (ALS), with deficits in language, emotional processing and social cognition also documented (Elamin, Phukan et al, 2012; Giradi et al., 2011; Kiernan, Vucic, Cheah, et al., 2011; Phukan et al., 2012). Additional impairment of language has also been reported in prevalent cases, particularly in those with bulbar onset disease (Abrahams et al., 1997). The presence of executive impairment is associated with poor outcome, including a more rapid decline in motor function as measured by the Amyotrophic Lateral Sclerosis functional rating scale (ALSFRS-R), and is associated with cortical atrophy on neuroimaging (Elamin et al., 2012; Elamin et al., 2013; Kilani et al., 2004; Mioshi et al., 2013; O'Callaghan et al., 2014; Sterling et al., 2010; Turner et al., 2012).

Executive dysfunction is known to occur secondary to ALS, and there is increasing evidence of impairment in social cognition in ALS implicated by frontal and temporo-parietal lobe dysfunction associated with social cognitive processes (Apperly, et al., 2004).

Social cognition can be studied using instruments such as the social faux pas recognition test, the Judgment of Preference Task, The Reading the Mind in the Eye Task, and through the use of social vignettes. The social faux pas recognition test evaluates the appropriateness of responses in a social context based on reading individual stories and answering questions posed by the examiner. ALS patients have been found to be significantly impaired when compared to control participants on this measure, and it is also time-consuming, without appropriately controlling for motor disability. However, in many instances, patients are also impaired on other measures of dorsolateral prefrontal functioning, including verbal and written fluency, which could be a confounding factor (Meier et al., 2010).

The Reading the Mind in the Eyes Task (RMET) is a reliable measure (Fernández-Abascal et al., 2013) which comprises photographs of eye regions of human faces where participants are required to infer the mental/emotional state of others. In one study, ALS patients showed a trend towards significantly lower scores compared to controls, although an absence of statistically significant difference between groups might have reflected low statistical power in the study design (Giradi et al., 2011). This measure has further been used alongside an extensive battery of executive and social cognitive tests within ALS, and was negatively implicated by executive dysfunction (Watermeyer et al., 2015). However, patients were

considered as a total cohort and not stratified by disease onset. Social understanding, measured by providing patients with a series of social vignettes describing everyday situations, has also been shown to be impaired in ALS (Cavallo et al., 2011).

The Judgement of Preference Task assesses the ability to make a preference judgement based on the eye gaze of a cartoon face, where four semantically similar objects are present i.e., fruit. The task is comprised of three conditions, the pre-experimental condition, the experimental condition and the control condition. In the experimental condition the participant is required to indicate which object does the face like best. Recently van der Hulst and colleagues investigated social cognitive processes in ALS, by distinguishing the cognitive and affective subcomponents of the Judgement of Preference task, with additional measures of behaviour and cognition (van der Hulst et al., 2015). Patients with ALS showed a significant impairment on the affective component of this task only, when compared to healthy controls. However, the ALS patients self-reported significantly higher depression, and performed significantly worse on letter fluency (written letters S-C; spoken letters P-R-W), visual processing, and naming.

The aim of this work was to investigate whether social cognitive deficits are evident as part of a wider impairment of executive function, whether they occur in isolation, and whether site of onset is preferentially associated with social cognitive impairment.

4.4.3 Material and Method

4.4.3.1 Participants

Protocols for recruitment of patients and healthy controls have been reported previously (Elamin, Phukan et al., 2012). Patients were recruited though a national ALS population-based register (O'Toole et al., 2008). Inclusion criterion was a diagnosis of a possible, probable or definite ALS based on the El Escorial Criteria, with supported neurophysiology for diagnostic accuracy. Exclusion criteria included the presence of comorbid neurological and/or psychiatric condition such as stroke, psychosis, traumatic brain injury, chronically uncontrolled diabetes or an active or positive history of chronic substance abuse. Home-based assessments were used to gather clinical and neuropsychological data.

This study has ethical approval from Beaumont Hospital Medical Research Ethics Committee. Informed written consent was obtained from all participants in this study.

4.4.3.2 Neuropsychological Assessment

Participants were assessed using a previously designed battery of standardized neuropsychological measures (Table 4.9). The assessment battery included the Wechsler Test of Adult Reading (WTAR), which is a measure of premorbid function yielding a predicted Full Scale IQ (pFSIQ; Wechsler, 2000). Ravens Progressive Matrices Subtest (Huber, Shuttleworth, Paulsen, Bellchambers, & Clapp, 1986) investigated current function through verbal/non-verbal trials. Executive and language functions were measured using both timed and untimed tasks. Timed tasks incorporated **letter** and **category** fluency to assess dorsolateral and prefrontal function. For the lexical fluency task, a Verbal Fluency Index (VFI) score was created (Abrahams et al., 1996). Creating a VFI consists of the total time given for the test, subtracted from the time taken to copy all the words generated, divided by the total number of words generated. A high VFI score represents a longer time required to generate a word, reflecting greater impairment. These indices allow for potentially confounding variables such as variation in motor speed and articulation difficulties, allowing for multimodal responses.

An untimed measure of executive function included The Brixton Spatial Anticipation Test (Burgess & Shallice, 1996). Digit Span and Backward Digit Span from the WAIS-III were also used to assess working memory and sustained attention (Wechsler, 2000). The Stroop Colour-Word Interference (Trenerry et al., 1989) task was also employed as a measure of executive function, with the Stroop Executive Factor (SEF) used to determine performance while accounting for motor disability (Phukan et al., 2012).

To assess social cognitive processes, the Judgement of Preference and The Reading the Mind in the Eyes Test (RMET; Baron-Cohen et al., 1995; Baron-Cohen et al., 2001) were used. These measurement tools were chosen as patients can respond verbally or by pointing to target stimuli, and have been previously used with ALS patients as greater physical impairment, either bulbar or spinal, does not implicate the ability of the test taker to perform the task. The RMET has good discrimination properties (Ahmed & Stephen, 2011), test re-test reliability (Fernández-Abascal et al., 2013), and is not confounded by gender (Khorashad et al., 2015).

Table 4.9: Details of the Neuropsychological Measures

Stroop Colour-Word Test	(a) Priming trial: patients presented with a multi-coloured list of colour names and asked to read as many words as they can in 2 minutes. (b) Inhibitory trial: a similar list is presented but colour names (e.g., 'blue') are printed in an ink colour not denoted by the name (e.g., red). Correct responses in two minutes are recorded.
Stroop Executive Factor (SEF)	Non-executive factors (including bulbar disability) contribute equally to both trials. The difference in scores between the two trials represent the number of responses 'lost' due to the delay imposed by the extra executive demands in the inhibitory trial.
Brixton Spatial Anticipation Test (SAT)	A rule attainment based task whereby the rule in operation, cannot be identified by any perceptually salient aspect of the stimuli. It consists of pages showing the same basic array of 10 circles set in two rows of five, with each circle numbered from one to 10. The changes in position are governed by a series of simple rules, which vary without warning.
Digit span	A measure of auditory attention and working memory. This test is composed of trials where examinees are read strings of digits and are asked to repeat them back aloud. The length of the digit strings is incrementally increased over successive trials.
Category fluency	Patients were asked to name as many animals as they could think of in 1 minute (spoken only).
Letter Fluency	Written/spoken, number of words starting with letter 'S' generated in 5 minutes and number of four letter words starting with letter 'C' generated in 4 minutes. Verbal Fluency Index used to adjust for disability.
Reading The Mind in the Eyes Test	This measure of social-affect focuses on inferring complex mental states of others, based on eye regions alone. The participant is presented with a picture stimulus, a target word and three foil words. The foil words have the same emotional valence as the target word. The test is scored out of 36.
Judgement of Preference Task	Patients are presented with images of a cartoon face position in the centre of four coloured drawings (i.e., four different fruits). In the 'test' images the face looks at one item while smiling, and the subjects are asked to indicate which of the four items the cartoon face 'likes best'. In the control task, the face is looking at one image and the participants are asked to indicate which item that the face is 'looking at'. Errors were categorized as "favourite," in which participants chose their personal favourite object (as determined in the pre-experimental condition)

4.4.3.3 Mood and Functional Assessment

Participants were assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) to control for clinically relevant emotional disturbances. The HADS is a brief self-report measure of Anxiety and Depression, which is less reliant on motor symptoms of anxiety and depression over other commonly used screening tools. The revised

Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) (Cedarbaum et al., 1997) is a clinically validated screening tool used to document disease progression over time and was utilized in this study to compare disease severity within patient groups.

4.4.3.4 Statistical Analysis

Sequential rejection procedures were employed to correct for multiple comparisons, and this research applied statistical significance values at $p<0.05$. Analyses were conducted with independent t-tests using standardized scores based on matched healthy control data, categorical data were analysed using Chi-squared tests, and multiple comparison adjustments were applied. Statistical analyses were performed using SPSS© version 21.0 (IBM Corp., 2012).

4.4.4 Results

4.4.4.1 Clinical, Neuropsychiatric and Functional Data

59 patients with ALS (20 Bulbar; 39 Spinal) and 59 matched healthy controls (26 males and 33 females, age range 50.75-88.25, mean 64.65 ± 8.95 years, years of education 12.64 ± 3.07, pFSIQ 105.93 ± 8.18) were studied. Healthy controls were age-, gender-, education- and IQ-matched. Control performance was normally distributed, and provided comparative population based normative data, used when comparing patients groups [standardized formula: $z = \frac{\chi - \mu}{\sigma}$].

ALS patients were stratified into bulbar onset (7 males and 13 females, age range 44.58-82.83, mean 66.13 ± 8.77 years, years of education 12.40 ± 2.58, pFSIQ 99.71 ± 11.6), mean duration between diagnosis and assessment (10.80 months ± 9.2), and Spinal onset patients (30 males and 9 females, age range 43.58-77.17, mean 61.166 ± 9.13 years, years of education 13.46 years ± 3.49, pFSIQ 103.08 ± 9.24, mean month duration between diagnosis and assessment 14.41 ±12.67).

Spinal and Bulbar onset were matched for age (p= 0.07) years of education (p=0.23), and WTAR estimated pFSIQ (p= 0.40), current functioning/non-verbal IQ (p=0.078), HADS estimated Anxiety (p= 0.38) and Depression (p= 0.59). There was no significant difference between their times of diagnosis to the time of assessments (p= 0.26), patients' ALSFRS-R total scores (p = 0.37). Patients with spinal-onset ALS had significantly lower ALSFRS-R scores in the spinal sub-domain compared to bulbar-onset patients (p=.002). Furthermore,

patients with bulbar-onset ALS had significantly lower ALSFRS-R scores relative to the bulbar domain compared to spinal patients ($p<.001$). Neither group differed in their ALSFRS-R scores for respiratory function ($p= .829$). There was a significant difference in the distribution of gender between the groups ($p= .018$).

4.4.4.2 Neuropsychological Assessment

On neuropsychological assessment, controls scored significantly higher than patients on measures of working memory and lexical fluency, ($p= 0.01$; $p= 0.001$ respectively). This is congruent within the literature at the early stages of ALS, and reflects the executive and attention components of these tasks. Table 4.10 outlines ALS patient performance, stratified by disease onset.

On The Brixton Spatial Anticipation Test no differences were noted between patients and controls ($p=0.096$) and there were no significant differences between spinal and bulbar onset patients ($p= 0.12$). The Stroop Executive Factor yielded no differences between patients and controls ($p= 0.188$), and no differences were recorded between bulbar and spinal onset patients ($p= 0.362$). Working memory and attention were assessed using forward and backward digit-span. Patients and controls did not differ significantly on the forward digit-span ($p=0.091$), however patients performed significantly worse than controls on backward digit-span ($p=0.010$). There was no significant difference between bulbar and spinal onset patients on forward digit-span ($p= 0.09$) or backward ($p= 0.36$).

Patients were assessed on letter and categorical fluency. Patients' performance was significantly worse than controls on letter fluency ($p<0.000$), and categorical fluency ($p=0.001$). No significant differences on **letter** fluency ($p= 0.67$) or categorical fluency ($p= 0.16$) were noted between bulbar and spinal onset patients.

Table 4.10: ALS patient performance on cognitive testing, sub-stratified by disease onset

Cognitive Assessment	ALS Patients (N=59)	Spinal (n=39)	Bulbar (n=20)	*p*
Stroop Colour-Word Test	.285±1.04	.318 ±1.09	.022 ±.47	.36
Brixton Spatial Anticipation Test	-.258±1.33	.139 ±1.14	-.872 ±1.3	.12
Digit span	-.396±1.02	-.268 ±.98	-1.10 ±.96	.09
Backwards Digit Span	-.623±1.34	-.445 ±.383	-.608 ±.08	.36
Category fluency	1.41±1.71	-1.35 ±1.2	-1.29 ±89	.16
Letter Fluency	-.877±1.20	-.68 ±1.6	-1.57 ±1.8	.67
Reading The Mind in the Eyes Test	-1.57±2.05	-.945 ±1.59	-2.91 ±2.37	**.001**
Judgement of Preference Task	.498±1.56	.269 ±1.4	.892 ±1.7	.182

Mean z-score ±SD, significant within-group differences are highlighted in bold.

No significant difference was noted between ALS patients and controls on the Judgement of Preference Task (p=0.057). Differences were not observed between bulbar and spinal onset patients (p=0.182) using this test. However, using the Reading the Mind in the Eyes Test, a difference was noted between bulbar and spinal onset patients (p= 0.001; see Figure 1). Collectively, patients did not significantly differ to controls on this task (p=0.571).

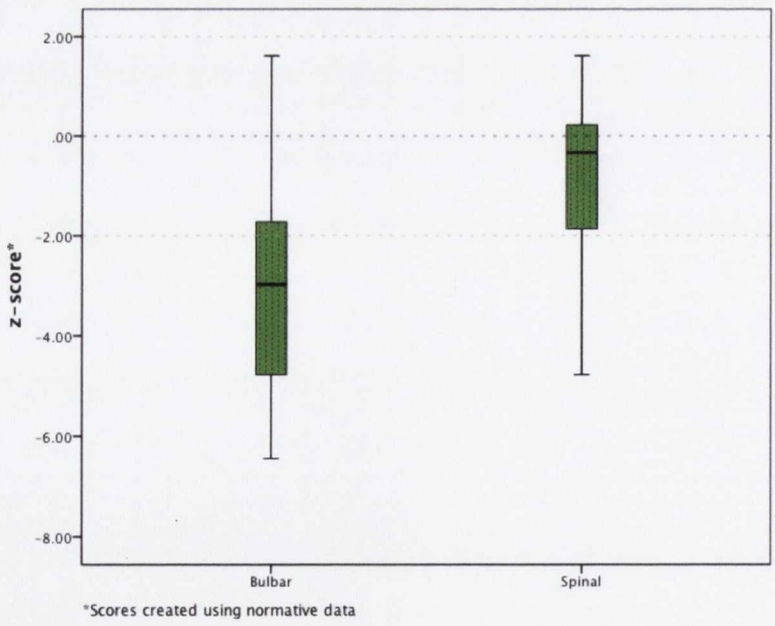


Figure 4.3: Reading the Mind in the Eyes Test Scores based on culturally specific normative data, stratified by Bulbar and Spinal Onset.

4.4.5 Discussion

The aim of this work was to investigate whether ALS patients, when stratified by disease-onset, differed on measures of executive function and social cognition. This exploratory work, which is part of our on-going study of the heterogeneous cognitive profiles of people with ALS, suggests that patients with bulbar onset are more likely to exhibit deficits of social cognition, when compared to spinal-onset patients, matched for age, education, disease duration, and executive impairment. Patients differed significantly in gender distribution, with more males present in the spinal-onset ALS group. However, considering that bulbar and spinal onset patients did not differ on their total functional measures of ALS, nor on non-verbal measures of current functioning, we would infer that these patients were well matched in the stages of their disease. Patients' significantly differed on the spinal and bulbar sub-scales of the ALSFRS-R, although this is to be expected given the sensitivity of measure, and that patients were stratified based on bulbar or spinal onset ALS.

Although measures of executive functioning were poorer in patients, compared to matched controls, there were no significant differences when comparing spinal and bulbar onset patient cohorts at the time of testing, consistent with previous findings. By contrast, scores in the measure of affective social cognition were severely impaired in the bulbar group. Considering there was no difference on measures of executive function when stratified by disease onset, these data indicate that it is possible for bulbar-onset patients to have greater social cognitive deficits, while matched on executive performance with spinal-onset ALS patients.

These data contribute further to the on-going theoretical debate regarding the structure and organisation of social cognitive processes, and whether or not they are subsumed by executive processes. Our data supports a network-based hypothesis that social cognitive processes may decline in the presence of executive dysfunction, but the severity of impairment is not necessarily congruent with executive impairment. Furthermore, these data suggest that subtle network-based cognitive syndromes may be explained by a model of disease progression incorporating cortical, bulbar, cervical, thoracic, and lumbosacral regions (Bak & Chandran, 2012). This model hypothesises that most MND patients with progressive cognitive decline will develop bulbar symptoms, and therefore dementia will be associated more often with bulbar, than with limb involvement. The model of caudal and adjacent disease progression proposes that this pattern of symptom progression is due to degeneration of the anatomically and functionally linked pre-motor regions, frontal lobes and the language-relevant perisylvian cortical regions (Bak & Chandran, 2012).

These findings are consistent with previous findings showing that bulbar onset patients were more impaired on measures of emotional processing when compared to controls. Moreover, bulbar onset ALS patients have a greater degree of frontal brain atrophy compared to spinal onset patients, and a disruption to frontotemporal and fronto-striatal networks, which could account for the findings (Kilani et al., 2004; Mioshi et al., 2013; O'Callaghan et al., 2014; Turner et al., 2012).

Our observations could be due to a number of confounding factors. Firstly, as Figure 4.3 illustrates, there is a wide variance in scoring patterns evidenced by both spinal and bulbar onset ALS patients and larger numbers are required to confirm our findings. Secondly, functional and structural imaging studies have reported involvement of fusiform regions in ALS, and the observed social cognitive deficit could also be due to secondary visual processing difficulties, specific to ocular regions. There are limitations to this study. These findings may apply only at particular stages of the illness, as this study was cross-sectional in design. Secondly there was an unequal distribution of gender within the patients groups when stratified by disease-onset.

Notwithstanding, our observations suggest that bulbar onset ALS patients are more likely to exhibit deficits in social cognition. These findings, if confirmed, suggest that deficits in social-affective processing may occur in ALS at differing intervals, and may have a trajectory that is separate to impairments of executive processing. This research further supports the view that multimodal testing, including tests of social cognition, should be incorporated in cognitive assessment batteries in ALS.

Future research could further focus on the difficulty, discriminability, and psycholinguistic properties of the RMET, as linguistic processing may be a confounding factor, specifically with bulbar-onset ALS patients (Abrahams et al., 1997). Secondly, given the trend toward significance reported here regarding the JoP task, and within the literature cited, it may be of interest to investigate case-by-case scoring patterns. Finally, ancillary methodologies such as electroencephalography could be employed alongside neuropsychological evaluation to further investigate network specific cognitive decline stratified by ALS-onset.

4.5 Functional Equivalence of Working Memory Tasks in ALS.

This study investigates whether visual working memory tasks (spatial span) are functionally equivalent with auditory working memory tasks (digit-span). As seen in the literature (see Chapter 2), there are discordant reports of working memory function in patients with ALS, and this is largely due to multi-modal testing. The question remains as to whether patients are experience executive deficits using these measures, or whether the tests are psychometrically congruous to detect the same effect. This study is outlined as follows:

4.5.1 Abstract

4.5.2 Introduction

4.5.3 Method

4.5.4 Results

4.5.5 Discussion

This work was presented at the Psychological Society of Ireland's Annual Conference in 2015, and was awarded *The Deirdre McMackin Memorial Medal* for Excellence in Neuropsychology Research in Ireland. This experiment is currently under second review at Cortex.

4.5.1 Abstract

Background: Amyotrophic Lateral Sclerosis (ALS) is a progressive neuromuscular degenerative disorder, and is known to implicate cognition. Executive dysfunction is the most common deficit reported in the heterogeneous cognitive profile of ALS. Language deficits, and difficulties with working memory have also been reported. Neuropsychological assessments must control for a degree of motor impairment with this patient group, possible by alternating auditory or spatial stimuli where possible. This study assesses the functional equivalence of working memory tasks utilising two retrospective cohorts of ALS patients.

Method: Patient cohorts were matched for age, years of education, current cognitive functioning, gender, and site of ALS onset. One patient cohort completed verbal working memory tasks i.e., Digit-Span Forward and Backward, and The Brixton Spatial Anticipation Task (n=50, 62% male; 68% spinal-onset), whereas the other cohort completed the visual analogue i.e., Spatial Span Forward and Backward, and the Intra-Extra Dimensional Set Shifting Task (n=50; 66% male; 78% spinal-onset).

Results: There was a large significant difference in the scoring profiles of patients on the forward span measures ($p<0.001$; $\eta^2 = 0.11$). No significant differences were found when comparing the backward working memory tasks ($p=0.212$; $\eta^2=0.01$) and the rule attainment/set-shifting tasks ($p=0.945$; $\eta^2=0.01$). Reliability statistics were conducted to confirm these results are indeed a reliable representation and not due to psychometric error.

Conclusions: While the measures employed in this research may show congruous methodological properties, the results of this study, together with the reviewed literature, suggest that not all measures are functionally equivalent. This study confirms previous findings within the literature, and has implications for both clinical practice and longitudinal research in ALS.

4.5.2 Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder with no effective disease modifying therapy and marked behavioural changes (Elamin, Phukan, Bede, Jordan, Byrne et al., 2011). Most studies of cognitive decline in ALS incorporate measures of working memory among a test battery, though few studies have specifically investigated the underlying cognitive components of working memory processes in ALS (Foxe, Irish, Hodges, & Pigeut, 2013). Forward versions of working memory tasks, where target stimuli of increasing length are reproduced in the order they were presented, evaluate modality-specific working memory systems (i.e., the phonological loop and the visuo-spatial sketchpad for verbal and visual/spatial data, respectively). The backward versions of both tasks, in which sequences of items have to be reproduced in the reverse order, have been shown to involve more central executive resources, as part of the same modality-specific systems (Bor, Duncan, Lee, Parr, & Owen, 2006; Monaco, Costa, Cltagirone, & Carlesimo, 2013).

Baddeley's model of working memory (Baddeley, 2003) suggests that the phonological loop retains speech-based material by means of articulatory and phonological rehearsal utilising the phonological buffer. The mechanism by which the visuo-spatial sketchpad retains spatial data is less well known, but may be related to attention processes operating over the contents of a representational buffer (Parmentier, Andres, Elford, & Jones, 2006). Spatial span performance in particular, depends not only on path length, but also on spatial location and temporal sequencing. These additional cognitive demands would suggest that this task is more than a spatial analogue of the auditory counterpart (Fischer, 2001). It may be for this reason that researchers have begun to investigate the functional equivalence of these measures (Wilde & Strauss, 2002).

To our knowledge, no study has compared the functional equivalence of working memory tasks in ALS. This research has both practical and theoretical implications within ALS and wider neurodegenerative research. As ALS is a rapidly progressive neurodegenerative condition, patients may be assessed in clinic, or for research purposes early in the disease. On follow-up assessment, they may be no longer able to engage with written tests due to impaired dexterity or with oral tests due to bulbar disability.

On a practical note for researchers in ALS and neuromuscular degenerative conditions, the findings may justify the creation of working memory composite scores in longitudinal large scale, multi-site research, if verbal-visual tasks are shown to be equivalent. This study

addresses the issue of utilising verbal/visual measures in a patient group where motor function is so rapidly compromised.

4.5.3 Method

Participants were recruited as part of an on-going longitudinal population-based investigation into the heterogeneous cognitive profile of people with ALS (Elamin, Bede, Byrne, Jordan, Gallagher, et al., 2013).

ALS patients recruited to this sub-study (N=100) were diagnosed with probable, or definite ALS, according to the revised El Escorial Criteria (Brooks, Miller, Swash, Munsat et al., 2000). Exclusion criteria included history of neurologic conditions that could affect cognition (such as major hemispheric stroke), alcohol dependence syndrome, and/or the use of high-dose psychoactive medications.

The study has been approved by the Ethics (Medical Research) Committee of Beaumont Hospital, Dublin, Ireland.

Retrospective cross-sectional neuropsychological data was ascertained from a randomised sample of 50 ALS patients who previously underwent detailed cognitive assessment to delineate the syndrome of cognitive impairment in ALS (Phukan et al., 2012). This cohort (62% male; 68% spinal-onset) underwent testing using the Digit-Span Forward (DSF) and Digit-Span Backward (DSB) tests (Wechsler, 1997) and The Brixton Spatial Anticipation Task (Burgess & Shallice, 1997). An additional 50 ALS patients were retrospectively randomised into a second cohort, who completed the analogous CANTAB tasks (Gallagher, Gray, Watson, Young, & Ferrier, 2014) Spatial Span Forward (SSF), Spatial Span Backward (SSB), and the Intra-Extra Dimensional (IED) Set Shifting Task (66% male; 78% spinal-onset). Considering the attention and visuo-spatial demands associated with verbal and spatial span tasks, measures of visuo-spatial function, sustained attention and inhibitory processes were compared (The Stroop Colour Word Interference Test; Trennery, Crosson, Deboe, & Leber, 1989) and visual memory (Rey Complex Figure Test: Meyers & Meyers, 1995). Disease severity was considered to ensure that motor involvement was not a confounding variable, and potential dysarthria secondary to ALS was controlled for using a previously outlined method (Phukan et al., 2012). In order to control for procedural effects, data from patient's initial assessment were used. Notwithstanding, serial assessment using many of these measures has been shown to have no effects (Burke, Wynne, O'Brien, Elamin, Bede, et al., 2015).

The neuropsychological performance of patients with ALS was standardized and compared utilizing a cohort of age-, sex- and education-matched healthy controls, as described previously (Elamin et al., 2013). Neuropsychological and CANTAB data were transformed into comparable z-scores using age, gender, and IQ matched controls. These measures of executive function were chosen as they have been shown to have good psychometric properties over time (Burke et al., 2015). Neuropsychological and clinical data were collected through hospital assessments and home visits.

In order to set an α error probability as $p<0.05$, an a priori analysis was conducted. This analysis confirmed that a minimum of 45 was required per group for power of 95.12%. Groups were compared using one-way analysis of variance (ANOVA). Statistical comparisons noted below were conducted using SPSS v22.0. These measures may have low inter-correlation properties i.e., one may expect to see discrepancies between these measures if they are measuring slightly different cognitive constructs, and so we sought to ensure our findings were not solely attributed to naturally occurring differences within the tests. In order to assess this, we examined the standardised psychometric difference between these tests, using the following formulae outlined in detail by Payne and Gwynne-Jones (1957):

$$Z = \frac{D_s}{\sqrt{(1 - rxx) + (1 - ryy)}}$$

whereby:

$$D_s = Z_x - Z_y;\ Z_x = \frac{X - \bar{X}}{\sigma};\ Z_y = \frac{Y - \bar{Y}}{\sigma}$$

$$r_{xx} = coefficient\ of\ reliability\ of\ 'test\ x'$$

$$r_{yy} = coefficient\ of\ reliability\ of\ 'test\ y'$$

4.5.4 Results

There were no significant differences in age, years of education, current cognitive functioning, gender, or site of onset between the patient groups, with further detail in Table 4.11.

There were no significant differences on measures of cognitive flexibility between patient groups on The Stroop CW task ($p=0.734$) or CWI task ($p=0.137$). Patents were also matched on visuo-spatial reproduction ($p=0.991$) and delayed recall of the visual stimulus ($p=0.556$). Contrary to expectation, differential patterns of performance were obtained on the auditory

and spatial span tasks, when stimuli were reproduced in a forward-span. There was a large significant difference in the scoring profiles of patients on these measures ($p<0.001$; $\eta^2 =0.11$), with performance on forward spatial span significantly lower as seen in Figure 1. No significant differences were found when comparing the backward working memory tasks ($p=0.212$; $\eta^2=0.01$) or the rule attainment/set-shifting tasks ($p=0.945$; $\eta^2=0.01$).

Table 4.11: Participant Characteristics

Demographic Variable	ALS Visual (n=50)	ALS Verbal (n=50)	p
Age at Testing	61.86±10.11	56.13±10.5	0.066
Disease Severity°	36.42±7.31	36.38±7.86	0.133
Current Cognitive Function§	26.76±4.44	31.04±4.49	0.158
Years of Education	13.42±3.45	14.60±3.05	0.083

°Amyotrophic Lateral Sclerosis Functional Rating Scale;

§Ravens Progressive Coloured Matrices

We further investigated the likelihood of finding the aforementioned discrepancy on the above tests within the general population using the Payne and Gwynne-Jones (1957). This method allows us to infer whether these findings are likely to occur due to the psychometric properties of comparing two tests, or whether our results are due to our independent variable. Comparing the IED and Brixton, the error of measurement would suggest that these scores would be seen by chance in <2% of the general population. Comparing the SSF and DSF, these scores could be seen in approximately 4.4% of the general population based on error measurement alone. Lastly, comparing the SSB and DSB, this discrepancy could be seen in 3.5% of the general population due to measurement error . Overall, we conclude that these results are indeed a reliable representation of the scores which reflect scores obtained by assessing in different modalities, and not a product of error measurement.

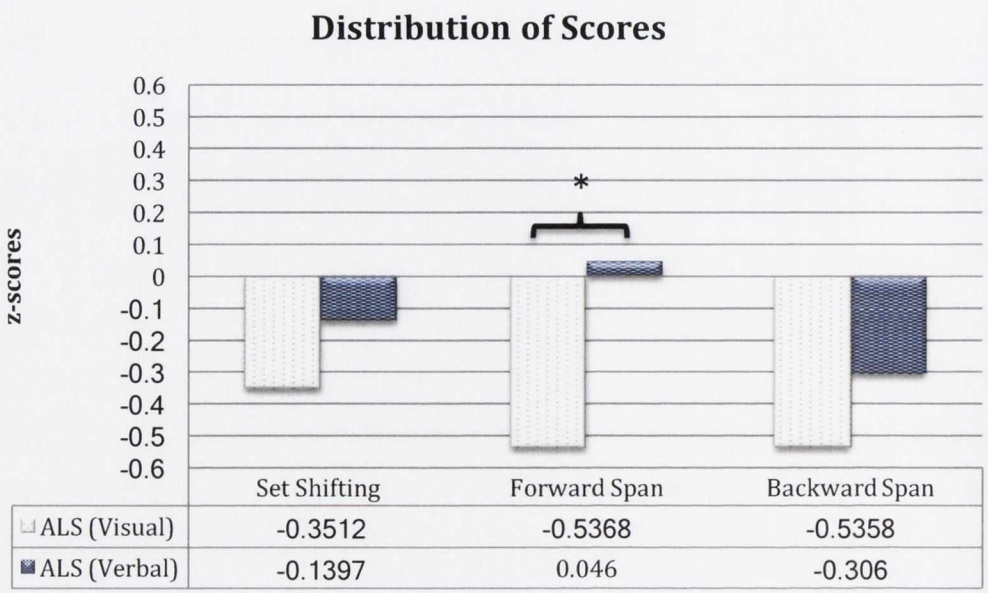


Figure 4.4: Distribution of scores. ALS Visual (n=50) refers to the cohort who completed the visually based measures of working memory i.e., spatial span. ALS Verbal (n=50) refers to the cohort who completed auditory tasks i.e., Digit-span. Data are represented as transformed z-scores based on control data, whereby the mean is 0. * $p<.0001$

4.5.5 Discussion

The aim of this study was to assess whether patients' performance were equivalent on measures of working memory, using bi-modal assessments in forward and reverse paradigms i.e., verbal (digit-span) or spatial (spatial span). This question has important pragmatic implications for neurodegenerative research, as ALS is a rapidly progressive neurodegenerative condition where motor disability is such a prominent feature, patients may no longer be able to engage with modality-specific stimuli, due to severe motor disability. The findings from this research suggest that in ALS, some tasks of working memory are functionally equivalent. For clinical practice, these data would suggest that patients could be assessed at baseline on a backward verbal/visual measure of working memory, and on follow-up could be reassessed using another modality.

In terms of population-based longitudinal research, this research would suggest that bi-modal backward working memory tasks could be collapsed into a single reverse working memory variable, and compared as equivalent measures of this cognitive construct.

Due to the integration of information from multiple modalities (visuo-spatial, temporal, motor), Spatial Span tasks are widely considered more difficult than Digit Span tasks (Parmentier et al., 2006). Our results, as illustrated in Figure 1, certainly confirm this finding. Both patient cohorts performed similarly on the IED and Brixton. By contrast, on the spatial tasks patients' scores reflected a higher task difficulty. Patients who completed the SSF task, performed significantly worse than the matched group who completed the DSF task. The additional executive component previously described may account for this, given that patient were required to not only remember the span length, but also temporal sequencing and span location. Variation of motor demands within each the tasks were accounted for, as patients were matched by disease severity.

Collectively, these findings suggest that in the early stages of the condition, participants are more sensitive to the executive requirement of the task, contingent with task modality. Our primary aim was to assess whether there was functional equivalence between the tasks, to address the needs of patients returning to clinic, or completing longitudinal research with a

specific battery of tests in place. These data would suggest that backward spans retain equivalence, as do set shifting tasks, however clinician-scientists should err on the side of caution if substituting a forward working memory task.

Our analyses further confirm that the results shown do not reflect measurement error. A limitation of this research is the cross-sectional design, with a neurodegenerative group. As such, our findings are restricted to cognitively intact ALS patients, at an early stage of the disease, and one should note the non-significant trend toward a younger patient group with more years of education completing the verbal tasks. Our results are also limited to the assumption that patients completed the tests using typical cognitive strategies i.e., phonological rehearsal strategies to assist encoding verbal stimuli, and spatial sequencing strategies for the visual stimuli. This limitation may also account for some of the discrepancy reported when comparing forward digit-span and spatial span, as one can easily adopt a phonological rehearsal strategy for the digit-span. By contrast, it may be more difficult for participants to encode and recall spatial stimuli, as there are no innate characteristics available to the participant such as categorical chunking, semantic associations or subjective linking. We hypothesis that this may be due to patients experiencing greater cognitive load caused by the additional executive demands of a spatial span task i.e., span location, which is inherently accounted for in the phonological rehearsal and span-length of digits. Future research could further delineate the equivalence of these tests by incorporating a longitudinal research design, and monitoring modality-specific encoding strategies. Furthermore, one could argue equivalence testing should occur simultaneously, however, the risk of cognitive strategy development i.e., chunking, phonological rehearsal etc., due to reduced novelty is far greater and this may influence performance (Burke et al., 2015).

While the Spatial and Digit Span tasks may show analogous properties methodologically, the results of this study, together with previous literature on spatial span performance (Fischer, 2001), cast doubt about whether these tasks in fact show similar operating characteristics. From a clinical perspective, our results demonstrate that short-term memory tasks have an important role to play in the cognitive assessment of neurodegenerative syndromes and that the combination of verbal and visuo-spatial span tasks prove a valuable combination when examining working memory in patients with ALS. In terms of clinical practice, these results illustrate the interchangeable qualities of some tasks, depending on a patient's physical presentation at repeat assessment. These data recommend caution when interchanging testing modalities on measures of working memory.

4.6 Executive dysfunction and visual memory in ALS

Considering the impact of executive dysfunction on social cognitive processes as outlined above, we sought to investigate whether other cognitive processes were significantly implicated by executive dysfunction. The focus of the following study was to use executive and demographic data to identify predictors of performance on a visual memory task. The following study is headed as follows:

4.6.1 Abstract

4.6.2 Introduction

4.6.3 Method

4.6.3.1 Participants

4.6.3.2 Neuropsychological Testing, and Procedure

4.6.3.3 Statistical Analyses

4.6.4 Results

4.6.4.1 ROCFT Copy Trial

4.6.4.2 ROCFT Immediate Trial

4.6.4.3 ROCFT Delay Trial

4.6.4.4 Predictors of ROCFT Performance

4.6.4.5 ROCFT Retention Percentage

4.6.5 Discussion

This paper was accepted for publication pending minor edits, and the time of this submission.

4.6.1 Abstract

This study aimed to illustrate the impact of executive dysfunction on non-executive cognitive processes i.e., visual memory, in Amyotrophic Lateral Sclerosis. Visual memory is thought to be unaffected by ALS, and is, therefore, termed "non-specific". Executive dysfunction is a core "ALS-specific" impairment yet the impact of executive dysfunction on cognitive domains such as visual memory remains unclear. Patients with ALS (n=203) were recruited through a population-based registry and national MND clinic. Participants with ALS completed a battery of neuropsychological tests. Sub-stratification was based on whether cognitive assessment detected no cognitive abnormalities (NCA: n=117), multiple executive cognitive deficits (ALS-Exec; n=56), or a comorbid frontotemporal dementia process (ALS-FTD; n=30). Matched healthy controls (n=117) also completed the battery. The Rey-Osterrieth Complex Figure Test (ROCFT) was the main dependent variable for visual memory in this study. At a group level, patients and controls significantly differed on the copy trial ($p<0.0001$: $\omega^2= .317$) immediate recall ($p<0.0001$: $\omega^2= .272$) and delayed recall ($p<0.0001$: $\omega^2= .308$) of the ROCFT. Post-hoc analyses were conducted in order to further delineate these differences, which revealed that greater executive dysfunction yielded lower ROCFT performance. Using regression analysis, we consider premorbid IQ, executive function, and demographics to predict performance on the ROCFT delayed recall trial ($R^2 =. 833$). Our cross-sectional findings illustrate that declining performance in visual memory tasks is related to increased executive dysfunction. This study suggests the use of a less executively demanding task in future ALS research, however, longitudinal analyses are required to confirm these findings.

4.6.2 Introduction

Amyotrophic Lateral Sclerosis (ALS) is a rapidly progressive and fatal heterogeneous neurodegenerative disorder. It is now well understood that ALS lies on a continuum with fronto-temporal dementia (FTD), with many overlapping clinical features (Lillo, Savage, Mioshi, Kiernan, & Hodges, 2012). Fronto-striatal deficits are currently the most commonly reported impairment in ALS patients and can present early in the disease course (Elamin, et al., 2015) resulting in a poorer patient prognosis (Elamin, et al., 2011), and higher caregiver burden (Burke, Elamin, Galvin, Hardiman, & Pender, 2015). Consistent with neurocognitive outcome data (Phukan, et al., 2012), fronto-striatal circuitry is pathologically implicated in ALS with compromised orbitofrontal (Bede, et al., 2013), anterior cingulate (Wilson, Grace, Munoz, He, & Strong, 2013) and dorsolateral prefrontal (Abrahams, et al., 1996) deficits and atrophy evident on structural and functional imaging (Tsermentseli, Leigh, & Goldstein, 2012). Executive dysfunction is a core predictor of impairment on auxiliary cognitive processes such as social cognition (Watermeyer, et al., 2015), and attentional deficits have been shown to implicate verbal encoding on list learning in ALS (Consonni, Rossi, Cerami et al., 2015). However, less is known about how it may impact on other cognitive processes such as visual memory in ALS (Machts, et al., 2014).

Visual memory is a more heterogeneous process involving both object perception and spatial perception. Some authors have suggested that verbal memory deficits in ALS reflect an encoding deficit mediated by executive dysfunction (Christidi, Zalonis, Smyrnis, & Evdokimidis, 2012), while others have attributed poor verbal memory performance to decreased left hippocampal volume in the absence of executive dysfunction (Abdulla, et al., 2014). Significant group level volume reduction for the right hippocampus has been reported in a cohort of ALS patients (n=10; 17%) compared to controls, yet many neurocognitive studies in ALS report visuo-spatial function and visual memory to be preserved (Byrne, et al., 2012). Research validating a clinic-based cognitive screen for ALS highlights that visuo-spatial dysfunction is "non-specific" to ALS (Abrahams, Newton, Niven, Foley, & Bak, 2014; Niven, et al., 2015) and a recent meta-analysis reports that visual performance yielded the lowest effect size in ALS research (Raaphorst, De Visser, Linssen, De Haan, & Schmand, 2010).

Executive function is accepted as an integral component of cognitive models of visual memory (Brewin, & Mersaditabari, 2013; Vingerhoets, Miatton, Vonck, Seurinck, & Boon, 2006), verbal memory (Eustache, & Desgranges, 2008), and working memory (Baddeley,

2000). The role of executive function in visual encoding is neatly explained by the extended hippocampal model (Gómez & Edgin, 2015), through the stratification of the corticostriatal system into four distinct, yet highly integrated loops (Seger, 2015). The visual corticostriatal loop is involved in aspects of visual stimulus processing; the motor corticostriatal loop is involved in response selection; and the executive and motivation corticostriatal loops are involved in processing feedback and reward. The visual corticostriatal loop links temporal and occipital cortices with the body and tail of the caudate (Middleton & Strick, 1996; Webster, Bachevalier, & Ungerleider, 1993).

In turn, visually related frontal lobe regions such as the ventro-lateral prefrontal cortex, which is implicated in visual working memory (Inoue & Mikami, 2007), also project to the body and tail of the caudate (Lau & Glimcher, 2007). Based on this model, the relationship between executive dysfunction and visual memory warrants further investigation within the context of a neurodegenerative condition with notable frontal lobe, hippocampal, and basal ganglia atrophy (Abdulla et al., 2014; Bede et al., 2013).

To investigate visual memory performance many studies in neurologic research have used the Rey Osterrieth Complex Figure Test (ROCFT). The ROCFT is a line-based stimulus assessing visuo-perceptual, visuo-constructional, and visual memory functions, with embedded features of executive functions such as planning and organization (Strauss, Sherman, & Spreen, 2006). The ROCFT is reliant on fine motor dexterity, gross motor movements, and adequate pen-grip; nevertheless it is widely used in ALS research (Bede et al., 2013; Elamin et al., 2011; Elamin et al., 2015; Phukan et al., 2012; Raaphorst et al., 2010; Wilson et al., 2001). There are many methods proposed for scoring the ROCFT, which makes the test versatile when considering multiple hypotheses (Bernstein, & Waber, 1996; Blysma, Bobbole, Schretlen, & Carren, 1995; Chiulli, Haaland, LaRue, & Garry, 1995; Hamby, Wilkins, & Barry, 1993; Rapport, Farchione, Dutra, Webster, & Charter, 1996; Savage, et al., 1999; Smith & Zahka, 2006; Stern, et al., 1999).

The objective of this study was to investigate ROCFT performance in relation to the presence, and severity of executive dysfunction in ALS.

4.6.3 Method

4.6.3.1 Participants

Participants with ALS (n=203) and healthy controls (n=117) were recruited as part of an on-going longitudinal population-based investigation into the cognitive profile of people associated with the condition. Using both published consensus criteria (Strong et al., 2009),

and specifically designed cognitive domain based criteria (Phukan et al., 2012), patients were stratified according to the following groups: No Cognitive Abnormalities (NCA; n=117, 57.6%), Multiple Executive Cognitive Deficits (ALS-Exec; n=56, 27.5%) or a comorbid Frontotemporal Dementia (ALS-FTD; n=30, 14.7%). Details of the test battery and cognitive categorisation method can be seen in Tables 4.12 & 4.13. None of the controls or ALS patients included in the NCA or ALS-Exec groups evidenced impairment on measures of memory, language, or visuospatial function. Inclusion criteria were a categorisation of probable or definite ALS based on the revised El Escorial Criteria (Brooks, Miller, Swash, & Munsat, 2000). Exclusion criteria included the presence of comorbid neurological and/or psychiatric condition such as stroke, psychosis, traumatic brain injury and substance abuse. Patients who tested positive for the C9orf72 expansion were excluded. Clinic and home-based assessments were used to gather clinical and neuropsychological data.

4.6.3.2 Neuropsychological Testing, and Procedure

Premorbid estimates of intelligence were created using the Wechsler Test of Adult Reading (Wechsler, 2001). Although the WTAR may be considered a predecessor of the more recent tests of premorbid function, it was current at the inception of this longitudinal research (Phukan., et al., 2012), and correlates well with current measures (Strauss et al., 2006). The revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R: Cedarbaum, et al., 1999) was also used to document symptomatology at the time of assessment. At the time of testing, the ALSFRS-R sub-score on fine motor skills was used to determine whether patients could engage with the ROCFT i.e., fine motor skills. Arterial oxygen and CO_2 levels were measured using a mobile transcutaneous sensor (TOSCA 500, Radiometer Ireland Ltd, Dublin).

The Rey-Osterrieth Complex Figure Test (ROCFT) was used to assess visuo-spatial and visual memory function (Taylor, 1979). The adopted, and most common scoring method scores the ROCFT out of 36 and involves scoring each of the 18 elements of the ROCFT between 0-2 points. Each element is evaluated for placement, degree of correctness, and level of distortion (Davies, Field, Andersen, & Pestell, 2011). To account for potential motor disability, 'time to copy figure' was not a variable considered for quantifying ROCFT performance on trials.

The study has been approved by the Medical Research Ethics Committee of Beaumont Hospital, Dublin, Ireland. Consent was obtained from all participants in this study.

4.6.3.3 Statistical Analyses

Group data were analysed using independent samples t-tests (age and years of education), with χ^2 used to test dichotomised variables. ANOVA were used to compare multiple cognitive outcome data. The threshold for statistical significance was set at $p<0.05$ with correction for multiple comparisons considered where relevant using Holm-Bonferroni. All statistical analyses were conducted using IBM SPSS Version 22.0. Regression modelling was employed to investigate the predictive value of cognitive and demographic variables on ROCFT performance. The distribution of data was homoscedastic for principal dependant variables.

Table 4.12: Details of the neuropsychological battery

Executive dysfunction	*Impairment that is two SD below the mean for healthy controls on at least two executive tasks*
Stroop Colour-Word Test	(a) Priming trial: patients presented with a multi-coloured list of colour names and asked to read as many words as they can in 2 minutes. (b) Inhibitory trial: a similar list is presented but colour names (e.g., 'blue') are printed in an ink colour not denoted by the name (e.g., red). Correct responses in two minutes are recorded. Non-executive factors (including bulbar disability) contribute equally to both trials. The difference in scores between the two trials represent the number of responses 'lost' due to the delay imposed by the extra executive demands in the inhibitory trial.
Brixton Spatial Anticipation Test	A rule attainment based task whereby the rule in operation, cannot be identified by any perceptually salient aspect of the stimuli. It consists of pages showing the same basic array of 10 circles set in two rows of five, with each circle numbered from one to 10. The changes in position are governed by a series of simple rules, which vary without warning.
Backward digit span	A measure of auditory attention and working memory. This test is composed of trials where examinees are read strings of digits and are asked to repeat them back aloud. The length of the digit strings is incrementally increased over successive trials.
Category fluency	Patients were asked to name as many animals as they could think of in 1 minute (spoken only).
Phonemic verbal fluency	Written/spoken, number of words starting with letter 'S' generated in 5 minutes and number of four letter words starting with letter 'C' generated in 4 minutes. Verbal Fluency Index used to adjust for disability.
Memory dysfunction	*Impairment that is two SD below the mean for healthy controls on at least four* of the parameters highlighted using +*
Logical Memory (LM)	+LM1 (immediate recall), +LM2 (delayed recall) and +LM retention (retention)
Verbal Paired Associate (VPA)	+VPA1 (immediate recall),+VPA2 (delayed recall) and +VPA retention (retention)
Auditory Delayed Recognition Task	+Sum of total recognition scores on Logical Memory and Verbal Paired Associates
California Verbal Learning Tests	+Total of five trials, +short delay free recall (immediate recall) +long delay free recall (delayed recall)
Rey-Osterrieth Complex Figure test	Non-verbal memory: parameters used: +immediate and +delayed recall trials
Language dysfunction	*Impairment that is two SD below the mean for healthy controls on this task.*
Boston Naming Test	
Visuo-spatial dysfunction	*Impairment that is two SD below the mean for healthy controls on copy trial of this task.*
Rey-*Osterrieth* Complex Figure Test	

Table 4.13: Categorisation method based on neuropsychological battery

Executive dysfunction	*Impairment that is two SD below the mean for healthy controls on at least two executive tasks*
Memory dysfunction	*Impairment that is two SD below the mean for healthy controls on at least four of the parameters highlighted using +*
Logical Memory (LM)	+LM1 (immediate recall), +LM2 (delayed recall) and +LM retention (retention)
Verbal Paired Associate (VPA)	+VPA1 (immediate recall),+VPA2 (delayed recall) and +VPA retention (retention)
Recognition Task	+Sum of total recognition scores on Logical Memory and Verbal Paired Associates
California Verbal Learning Task-II (CVLT-II)	+Total of five trials, +short delay free recall (immediate recall) +long delay free recall (delayed recall)
Rey-Osterrieth Complex Figure test	Non-verbal memory: parameters used: +immediate and +delayed recall trials
Language dysfunction	
Boston Naming Test	*Impairment that is two SD below the mean for healthy controls on this task.*
Visuo-spatial dysfunction	
Rey-*Osterrieth* Complex Figure Test	*Impairment that is two SD below the mean for healthy controls on copy trial of this task.*

There were no significant differences between patients (n= 203) and controls (n=117) on demographic factors such as age, gender, years of education or predicted IQ (see table 4.14 for details). At a group level, patients and controls significantly differed on the copy trial (p<0.0001: ω^2= .317), immediate recall (p<0.0001: ω^2= .272) and delayed recall (p<0.0001: ω^2= .308) of the ROCFT. Post-hoc analyses were conducted in order to examine these differences.

4.6.4.1 ROCFT Copy Trial

On the copy trial of the ROCFT, when healthy controls were compared to ALS patients with No Cognitive Abnormality (ALS-NCA), there was no statistically significant difference evident (p=0.996). Controls were compared to ALS patients with executive dysfunction (ALS-Exec) and ALS patients with comorbid frontotemporal dementia (ALS-FTD), with all analyses yielding statistically significant results (p< 0.0001; p< 0.0001 respectively).

Table 4.14: Participant Characteristics

Demographic Variable	Healthy Control (n=117)	ALS Patients (n=203)	*p*
Age at Testing	60.90 ±9.46	62.98±10.75	0.780
Years of Education	12.86±3.18	12.10±3.30	0.622
Gender (males)	59%	48%	0.395
Predicted IQ	104.38±8.77	99.95±12.55	0.185
ALSFRS-R* Total	-	35.74 ±7.97	-
ALSFRS-R Bulbar	-	9.11±3.24	-
ALSFRS-R Respiratory	-	10.81±1.87	-
ALSFRS-R Spinal	-	15.95±6.18	-
O^2% (Tosca 500)	-	97.07%±1.51%	-
pCo2 (kPa: Tosca 500)	-	5.27±.798	-
Spinal Onset (%)	-	65%	-

*Revised Amyotrophic Lateral Sclerosis Functional Rating Scale

ALS-NCA patients performed significantly better on the copy trial compared to ALS-Exec ($p< 0.0001$) and ALS-FTD ($p< 0.0001$). Performance on the copy trial was similar between ALS-Exec and ALS-FTD patients ($p= 0.779$), see Table 4.15, and illustrated in figure 4.5.

Table 4.15: Performance on the ROCFT

Cohort		Copy Figure	Immediate	Delay
Healthy Control	(n=117)	35.52 ± 2.85	17.73 ± 5.85	16.63 ± 5.58
ALS-NCA	(n=117)	33.04 ± 3.07	18.68 ± 6.94	18.30 ± 6.45
ALS-Exec	(n=56)	23.76 ± 9.92	9.10 ± 6.10	8.53 ± 5.87
ALS-FTD	(n=30)	21.78 ± 9.06	7.03 ± 5.28	5.61 ± 4.54

4.6.4.2 ROCFT Immediate Trial

ALS-NCA performance did not statistically differ from that of healthy controls on the immediate recall trial (p=0.833). Healthy controls performed better than ALS patients with single- and multiple-executive deficits, similar to the copy trial ($p< 0.0001$; $p< 0.0001$). ALS-NCA patients performed best on this trial, and were significantly better than patients with executive impairment (p<0.0001). Patients with ALS-FTD and ALS-Exec did not significantly differ (p=0.841).

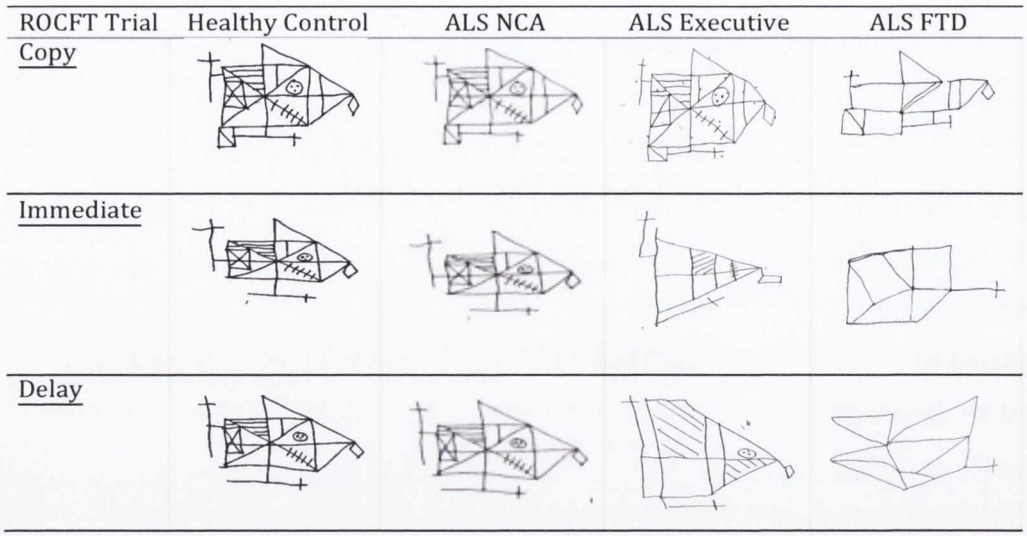


Figure 4.5: Examples of performance by trial and cohort. ALS No Cognitive Abnormalities (ALS-NCA); ALS-Executive (ALS-Exec); ALS with comorbid Frontotemporal Dementia (ALS-FTD).

4.6.4.3 ROCFT Delayed Trial

On the delayed recall trial of the ROCFT, ALS-NCA and controls did not significantly differ in their performance on this trial (p=0.308). Control performance was significantly higher than patients with single- and multi-executive impairment (ALS-Exec: p<0.0001; ALS-FTD: p<0.0001), as were cognitively intact ALS patients (ALS-Exec: p<0.0001; ALS-FTD: p<0.0001). All cohorts demonstrated lower scores after a standardised delay, which is illustrated in figure 4.6.

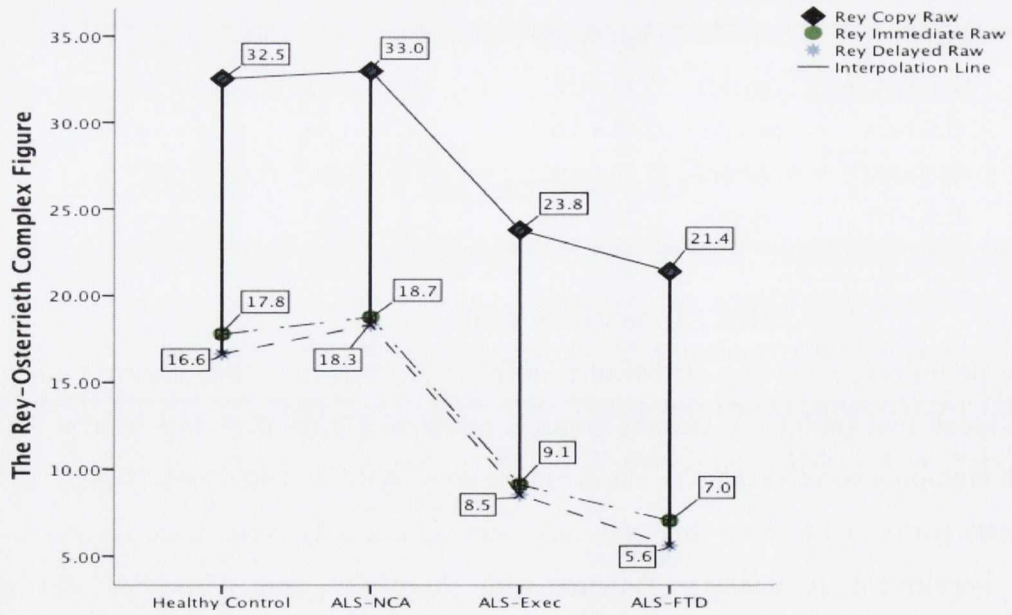


Figure 4.6: Mean score per cohort on the Copy, Immediate, and Delay Recall Trials

4.6.4.4 Predictors of ROCFT performance

To measure the degree to which the copy figure, measures of executive function, and demographic variables influenced immediate recall, and delayed recall of the ROCFT, we conducted multiple linear regression using a stepwise rejection method. To fully consider potential influences on performance across participant cohorts, the groups were stratified as above. Figures 4.7 and 4.8 illustrate the predictive properties of demographic data, and performance on measures of executive function

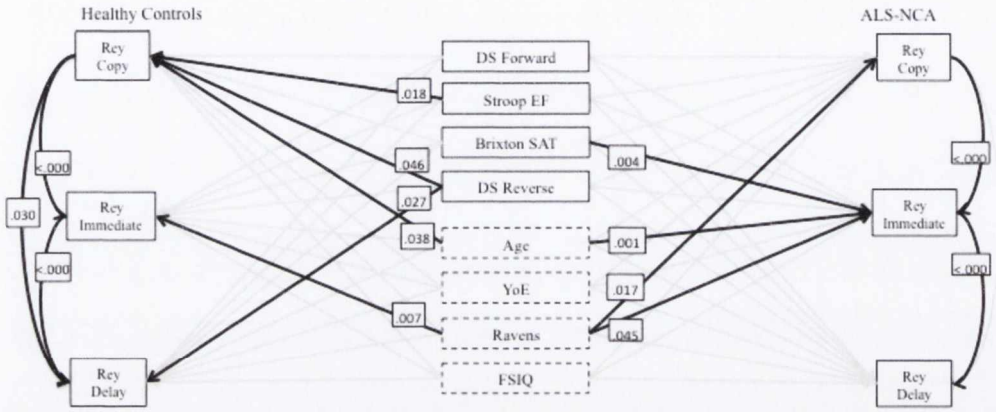


Figure 4.7: Healthy Controls and ALS patients with No Cognitive Abnormalities: Digit Span (DS); Stroop Executive Factor (EF); Brixton Spatial Anticipation Test (SAT); Years of Education (YoE); Full Scale Intelligence Quotient (FSIQ). Significant predictors are represented in bold (black), with significant values ($p<0.05$) detailed. Non-significant values ($p>0.05$) are not illustrated, and are represented by non-bold grey lines. Demographic variables are identifiable by a dashed variable boundary.

To clarify predictors of control and patient performance on the ROCFT, a stepwise model inclusive of premorbid estimates, performance on the preceding ROCFT (where appropriate), executive data, and demographic information were considered. The Full Scale IQ (FSIQ) metric, as measured by the WTAR, was rejected from the model. This model, which showed high significance, produced an R^2 =. 833, accounting for 83.3% of performance on the ROCFT delayed recall trial. This model was found to be significant for each trial of the ROCFT i.e., Copy (p=. 001), Immediate recall (p<. 001), and Delayed recall (p<. 001) with control data. Performance on the Rey Copy trial was predicted by The Stroop Executive Factor (see Table 4.12), Reverse Digit-Span, and participant age at assessment. The Rey Copy trial predicted subsequent performance on the Rey Immediate trial, with Ravens also reaching significance.

The Delay recall trial was predicted by the Rey Copy, and Immediate recall trial, as well as Digit-Span reverse, an auditory measure of working memory reported to be analogous with reverse spatial span.

An identical model was tested using patient data. ALS-NCA produced significant models for the Copy (p=. 020), Immediate recall (p<. 000), and Delayed recall (p<. 000) trials. Performance on the Ravens Progressive Coloured Matrices significantly predicted performance on the ROCFT Copy trail. The Copy trial was a significant predictor for the Rey Immediate recall trail, alongside performance on the Brixton SAT, participant age, and again the Ravens. Performance on the Rey delayed recall trial was only directly influenced by the performance on the Rey Immediate recall.

Figure 4.8 illustrates the predictive properties of the model with ALS-Exec, and ALS-FTD patients. For patients with multiple executive impairment (ALS-Exec), the Rey Copy figure predicted performance on the immediate recall trial, which was also predicted by years of education. The Immediate recall trial significantly predicted performance on the Delay recall, as did Digit-Span reverse. Of note within the ALS-FTD cohort, age was a significant predictor of immediate recall performance, which in turn predicted Delay recall performance.

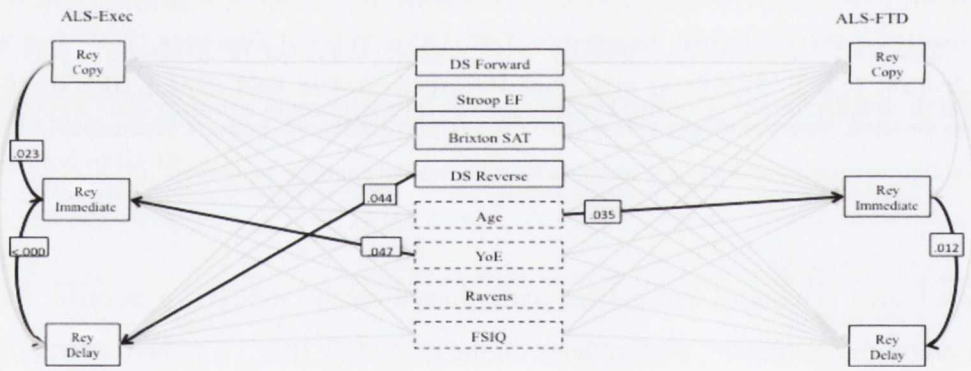


Figure 4.8: ALS-Exec, and ALS-FTD patients' predictive outcome variables in relation to the ROCFT. Digit Span (DS); Stroop Executive Factor (EF); Brixton Spatial Anticipation Test (SAT); Years of Education (YoE); Full Scale Intelligence Quotient (FSIQ). Significant predictors are represented in bold (black), with significant values (p<0.05) detailed. Non-significant values (p>0.05) are not illustrated, and are represented by non-bold grey lines. Demographic variables are identifiable by a dashed variable boundary.

4.6.4.5 ROCFT Retention Percentage

Considering the most consistent predictor of performance on the ROCFT delay task was the ROCFT Immediate recall variable, the amount of visual information retained by patients and controls from the immediate to the delay trial was used to create a retention score for comparison. ALS patients with no cognitive abnormalities ALS-NCA retained the most

information (99.90%) from the immediate trial to the delay, with controls retaining slightly less at 95.05%. Patients with ALS-FTD retained the least amount of information (80.2%), with ALS patients with executive dysfunction retaining 94.51%. As seen in figure 4.9, patients without executive deficits often recalled greater detail on delayed recall over immediate.

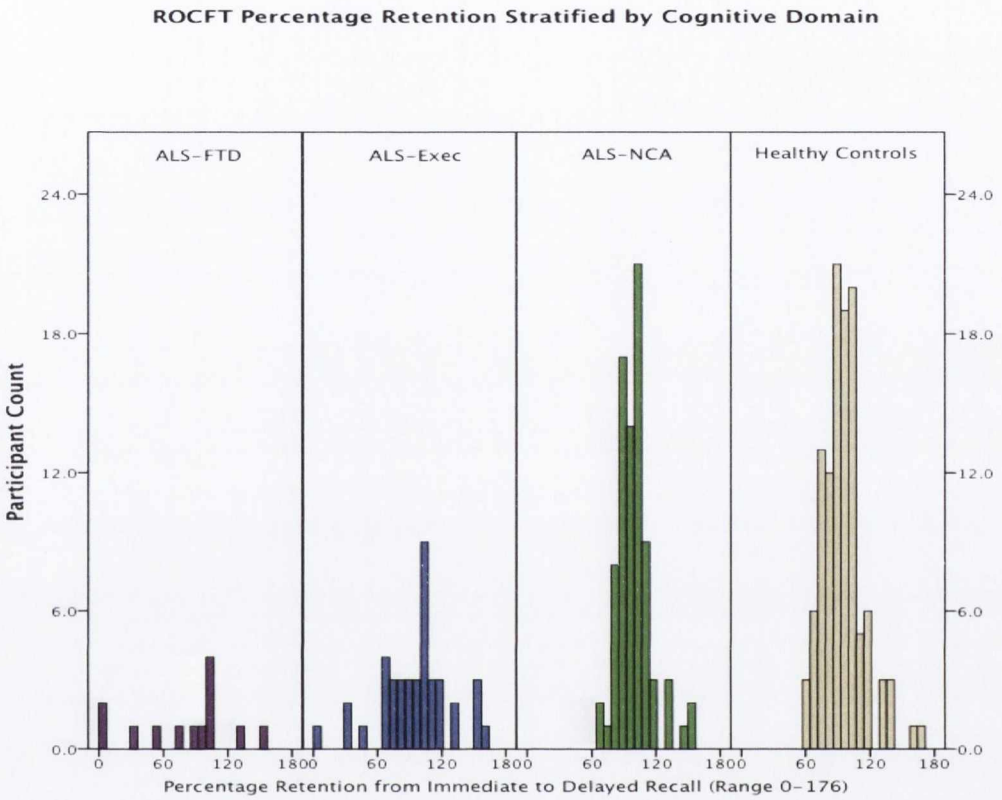


Figure 4.9: Percentage of stimuli retained from immediate to delay trial.

4.6.5 Discussion

The purpose of this study was to illustrate how varying severity of executive dysfunction in patients with ALS implicated visual memory encoding, retrieval, and recall performance. Previous studies have reported volumetric reduction in right lateralised hippocampal structures (Abdulla et al., 2014), in the absence of cognitive impairment evident on testing. Our findings are consistent with these findings, as patients without cognitive impairment performed as well as matched controls on the ROCFT, and are also consistent with other studies that broadly report that visual memory performance is relatively preserved in ALS (Raaphorst et al., 2010). However, this is the first study to specifically fractionate cognitive processes associated with visual memory encoding, immediate and delayed recall process, and information retention in a population based cohort of ALS patients stratified by severity of executive dysfunction.

Visual memory test performance has been used in ALS research to measure visuo-spatial deficits. Psychometrically the ROCFT is a well-validated tool (Davies et al., 2011), and widely used in ALS research - despite the onerous motor demands placed on patients. However, executive dysfunction does appear to influence performance on this task of visual memory.

These data would suggest that increase executive dysfunction contributes to low performance on the ROCFT. Although these data illustrate that patients experiencing greater executive dysfunction demonstrate greater difficultly on the Copy trial of the ROCFT, outcome on the immediate trial is most predictive of performance on the Rey Delay. This would suggest that encoded information is retained and retrieved over time, as further demonstrated through Figure 3. Through our statistical modelling within the control group, it can be seen that the Rey Copy trial may be influenced by executive dysfunction i.e., sustained attention, mental manipulation of stimuli, as identified through significant predictors (Stroop EF, Brixton SAT, and Digit-Span Reverse). These measures are particularly sensitive in measuring susceptibility to interference, inhibition, mental flexibility, schema shifting, and working memory. Patients with ALS are susceptible to executive dysfunction as measured by these tasks, and have been shown to implicate the basal ganglia on imaging, disrupting frontostriatal circuitry. These data further highlight functional disruption through the extended hippocampal model, implicating the visual corticostriatal loop. The Ravens Coloured Progressive Matrices were predictive of ROCFT performance. This is likely to a result of the Ravens assessing current function, and also that it is a visually based task.

Our data provide preliminary evidence to support that executive dysfunction is important in mediating performance on visual memory tasks, and may implicate the visual corticostriatal loop, as well as frontostriatal circuitry. Considering the rapidly progressive nature of cognitive decline in ALS, and the negative prognosis associated with executive deficits (Elamin et al., 2015), detailed assessments should aim to reduce the influence of executive dysfunction on visual performance tasks as newly developed and validated screening tools have done (Abrahams, et al., 2014; Niven et al., 2015). These data further demonstrate the intricacies of disrupted cognitive processes secondary to ALS, and support the view that ALS is a multisystem disorder with extrapyramidal features, which implicate cognitive functions and networks. A task requiring low motor dexterity, which does not involve disproportionate executive demands, may be more suited to an ALS cohort. There are numerous such tasks

(Strauss et al., 2006), although it should be noted that memory paradigms incorporate executive components.

This study has limitations. Firstly, while this study met a priori power requirements for sub-stratified groups i.e., ALS-FTD (n=30), there was insufficient power to include a subgroup of patients with heterogeneous non-executive cognitive impairments as reported within the literature (Phukan et al., 2012). Secondly, a recognition paradigm accompanies the ROCFT, which was not utilised within the research due to time constraints and the need to avoid undue test demands on patients.

These data have implications for interpreting cognitive impairment in ALS considering network-based impairment. It appears in the absence of executive impairment that patients performance is similar to controls, indicating that right lateralised function may be preserved in early stages of ALS, with left lateralised function previously shown to be implicated (Abdulla et al., 2014; Abrahams et al., 2014; Christidi et al., 2012). Future studies in ALS could investigate hemispheric encoding/retrieval asymmetry through left and right lateralised encoding paradigms of hemisphere specific stimuli accompanied by neuroimaging.

The implications of this study may clarify the confounding influence of executive processes on non-specific processes such as visual memory, and visuo-spatial processing. This study aimed to illustrate the negative implications that executive dysfunction presents on non-executive cognitive processes such as visual memory.

In summary, ALS patients exhibiting executive dysfunction may perform lower than expected on tests of cognitive function thought to be unaffected by ALS. Our findings illustrate the declining performance in visual memory tasks based on increased executive dysfunction. This study considers the use of a less executively demanding task of visual memory in future ALS research, however, longitudinal analyses are required to confirm these findings.

4.7 Do executive impairments mediate verbal memory difficulties in ALS?

The previous study demonstrates the role of executive dysfunction on visual memory, specific to executive dysfunction typically characterised in ALS. The following study investigates whether executive performance mediates memory performance in a group of ALS patients who were categorised as having "No Cognitive Abnormalities". The aim of this study is to investigate whether cognitively intact ALS patients, perform differently to controls on measures of executive function and list learning. These groups were not selected a priori. Participants for this study were selected post-hoc based on their performance on the cognitive battery, which determined their cognitive status i.e., No Cognitive Abnormalities etc. This method was chosen to specifically investigate test performance between groups, on those who were categorically unimpaired. The layout of this study is as follows:

4.7.1 Abstract

4.7.2 Introduction

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4.7.1 Abstract

Objective: Cognitive impairment presents in approximately 40-50% of patients with amyotrophic lateral sclerosis (ALS), where executive dysfunction has been consistently reported to be most prevalent. Although many patients do not meet criteria for impairment, cognitive deficits are evident on testing. Executive dysfunction has been shown to mediate auxiliary cognitive processes, and our objective was to investigate the role of poor executive performance on memory processes in a cognitively intact ALS.

Method: Data from ALS patients who met previously published criteria for "cognitively intact" were included this study (n=55). Patients were compared to healthy age-, gender-, education- and IQ-matched controls (n=103). Participants completed a full neuropsychological battery, with particular focus on executive function. The California Verbal Learning Test-II assessed verbal memory performance.

Results: Cognitively intact ALS patients' performance was significantly lower than controls on The Stroop Colour Word Interference Test (p= 0.036), Digit-Span forward (p= 0.008), The Brixton (p= 0.002) and Letter Fluency (p=0.001). On the California Verbal Learning Test-II, patients with ALS scored significantly lower than controls on the initial two free recall trials (p= 0.001; p= 0.039, respectively). On the short delay cued recall task, patients scored significantly lower than controls (p= 0.018).

Conclusion: ALS patients who do not fulfil the criteria for cognitive impairment nonetheless display subtle evidence of delayed processing and initial deficits in encoding secondary to mild executive impairment.

4.7.2 Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease, predominantly characterised by motor neuron degeneration with associated cognitive decline (Phukan, Elamin, Bede et al., 2011). Much is now known of the heterogeneous cognitive and behavioural impairments in ALS and their overlap with Frontotemporal Dementia (FTD: Byrne, Elamin, Bede et al., 2012; Trojsi, Corbo, Caiazzo et al., 2013). Executive dysfunction has been well reported and categorised as a cognitive syndrome, and a negative prognostic indicator in ALS (Elamin, Phukan, Bede et al., 2012). This executive impairment, elaborated through the executive hypothesis, is commonly associated with prefrontal dysfunction i.e., planning, behaviour change, social cognition, and set shifting, in other neurodegenerative conditions such as Huntington's disease (Crawford, Blackmore, Lamb et al., 2000). It is considered a main cognitive feature of ALS, and can be classified as a specific cognitive impairment (ALSci) in approximately 40-50% of ALS patients (Phukan et al., 2011; Abrahams, Leigh, Harvey et al., 2000; Abrahams, Leigh, & Goldstein, 2005; Elamin, Pender, Hardiman, & Abrahams, 2012).

Aspects of verbal memory have been showed to be impaired in ALS, although many studies include ALS patients that meet criteria for ALSci, and are often not very well matched to comparative samples or may have low statistical power (Giradi, MacPherson, & Abrahams, 2011; Machts, Bittern, Kasper et al., 2014). Furthermore, patient cohorts are often screened for cognitive impairment using non-ALS specific screening tools that do not take into account the motor deficits (Christidi, Zalonis, Smyrnis, & Evdokimidis, 2012; Mantovan, Baggio, Dalla-Barba et al., 2003). A recent investigation of the impact of executive dysfunction on memory performance in ALS and other neurodegenerative conditions, found that cognitively intact ALS patients' performance was similar to healthy controls using serial position effect analyses (Consonni, Rossi, Cerami et al., 2015). The authors report more impairment from cognitively impaired ALS, however both groups consisted of a small sample (<16).

This study aims to investigate the relationship between executive function and verbal memory performance in a population-based cohort of cognitively intact ALS patients, relative to a case matched control cohort.

4.7.3 Materials and Methods

4.7.3.1 Participants

Irish population-based studies have previously reported the cognitive profile of over 180 patients with ALS and identified 55 who were deemed to be cognitively intact (Phukan et al.,

2011; Elamin et al., 2012; Elamin et al 2013) using both published consensus criteria (Strong, Grace, Freedman et al., 2009), and specifically designed cognitive domain-based criteria as previously described in detail (Elamin et al., 2012). Inclusion criteria included a diagnosis of a probable or definite ALS based on the revised El Escorial Criteria (Brooks, Miller, Swash, & Munsat, 2000), with supported neurophysiology for diagnostic accuracy. Exclusion criteria included the presence of co-morbid neurological and/or psychiatric condition such as stroke, psychosis, traumatic brain injury and substance abuse. Clinic and home-based assessments were used to gather clinical and neuropsychological data. In addition, 110 healthy age-, gender-, IQ-, and education-matched controls were also recruited (see table 4.16). Within the healthy control group, those who evidenced impairment on the neuropsychological battery were excluded (n=7).

The study has been approved by the Ethics (Medical Research) Committee of Beaumont Hospital, Dublin, Ireland. Informed consent was obtained from all participants in this study.

Table 4.16: Demographic Data for patients and controls

Variable	ALS Mean (SD)	N	Healthy Control Mean (SD)	N
Age	60.43 (11.19)	55	60.90 (9.46)	103
Male %	63.65	55	50.5	103
Education (Years)	13.25 (3.13)	55	12.86 (3.18)	103
Estimated IQ	105.11 (9.33)	55	104.38 (8.77)	103
HADS	4.96 (4.32)	55	6.38 (3.87)	103
ALSFRS-r	36.41 (7.90)	55	-	-
Spinal Onset %	85.5	55	-	-

4.7.3.2. Neuropsychological assessment

Participants were assessed using a comprehensive battery of standardized neuropsychological measures (see table 4.17 & table 4.18). The battery consisted of measures known to be sensitive to cognitive changes in ALS. Of particular interest for the present study, measures of executive function and a measure of verbal learning and memory using a multiple-trial list-learning task, namely The California Verbal Learning Test-II (CVLT-II: Delis, Kaplan, Kramer, & Ober, 2000) were included.

Premorbid estimates of intelligence were created using the Wechsler Test of Adult Reading (WTAR: Holdnack 2001) and mood was assessed using The Hospital Anxiety and Depression Scale (HADS: Moorey, Greer, Watson et al., 1991). Although the WTAR may be considered a predecessor of more recent tests of premorbid function, it was most current at the inception of this research (Phukan et al., 2011). Patients also completed the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R: Cedarbaum, Stambler, Malta et al., 1999) at the time of assessment.

4.7.3.3 Statistical Methods

Demographic characteristics between this cohort of 55 ALS patients and matched controls were analysed using independent samples t-tests (age and years of education), with χ^2 used to test dichotomised variables. ANOVA were used to compare multiple dependent variables. The threshold for statistical significance was set at $p<0.05$. Cohen's classifications of effect size were employed (.01 as a small effect; .06 as a medium effect; .14 as a large effect). All statistical analyses were conducted using SPSS, Version 22.0 (IBM Corp, 2012). Holm-Bonferonni corrections for multiple comparisons were employed where relevant.

In order to study executive function as a predictor of memory performance, the scores for each participant on measures of executive function were converted to *z*-scores using normally distributed control data, and standardised formula. These standardised scores were then combined into a single, equally weighted composite score. The weighted importance of this executive composite on verbal encoding was tested using hierarchical multiple regression models, with data distribution homoscedastic for principal dependent variables.

Table 4.17: Details of the Neuropsychological Measures

Stroop Colour-Word Test (Trenerry, Crosson, Deboe et al., 1989)	(a) Priming trial: patients presented with a multi-coloured list of colour names and asked to read as many words as they can in 2 minutes. (b) Inhibitory trial: a similar list is presented but colour names (e.g., 'blue') are printed in an ink colour not denoted by the name (e.g., red). Correct responses in two minutes are recorded. Non-executive factors (including bulbar disability) contribute equally to both trials. The difference in scores between the two trials represent the number of responses 'lost' due to the delay imposed by the extra executive demands in the inhibitory trial.
Brixton Spatial Anticipation Test (Burgess & Shallice, 1996)	A rule attainment based task whereby the rule in operation, cannot be identified by any perceptually salient aspect of the stimuli. It consists of pages showing the same basic array of 10 circles set in two rows of five, with each circle numbered from one to 10. The changes in position are governed by a series of simple rules, which vary without warning.
Digit span (Wechsler, 2000)	A measure of auditory attention and working memory. This test is composed of trials where examinees are read strings of digits and are asked to repeat them back aloud. The length of the digit strings is incrementally increased over successive trials.
Phonemic Verbal Fluency (Abrahams et al 2000)	Written/spoken, number of words starting with letter 'S' generated in 5 minutes. Verbal Fluency Index used to adjust for disability.
CVLT-II (Delis et al., 2000)	Examines both recall and recognition over immediate and delayed memory trials. List A is composed of 16 words, four from each of four semantic categories (furniture, vegetables, ways of traveling, and animals). Words from the same semantic category are never presented consecutively. A 16-word interference list (List B) is then presented for one trial, followed by short-delay free-recall and short-delay cued-recall trials of List A. After a 20-minute delay, free-recall, cued-recall, and yes/no recognition trials of 'List A' are administered.

Table 4.18: Categorisation method based on neuropsychological battery

Executive dysfunction	*Impairment that is two SD below the mean for healthy controls on at least two executive tasks*
Memory dysfunction	*Impairment that is two SD below the mean for healthy controls on at least four of the parameters highlighted using +*
Logical Memory (LM)	+LM1 (immediate recall), +LM2 (delayed recall) and +LM retention (retention)
Verbal Paired Associate (VPA)	+VPA1 (immediate recall),+VPA2 (delayed recall) and +VPA retention (retention)
Recognition Task	+Sum of total recognition scores on Logical Memory and Verbal Paired Associates
California Verbal Learning Task-II (CVLT-II)	+Total of five trials, +short delay free recall (immediate recall) +long delay free recall (delayed recall)
Rey-Osterrieth Complex Figure test	Non-verbal memory: parameters used: +immediate and +delayed recall trials
Language dysfunction	
Boston Naming Test	*Impairment that is two SD below the mean for healthy controls on this task.*
Visuo-spatial dysfunction	
Rey-*Osterrieth* Complex Figure Test	*Impairment that is two SD below the mean for healthy controls on copy trial of this task.*

4.7.4 Results

4.7.4.1 Clinico-demographic Characteristics

Detailed demographic data are summarised in Table 4.16 for patients and controls. There were no significant differences recorded for estimated premorbid IQ (p= 0.561), age (p= 0.729), neuropsychiatric features (p= 0.402), years of education (p= 0.314) or gender (p= 0.360) between patients and controls.

4.7.4.2 Neuropsychological Data

Patient scores were statically lower than controls on all measures of executive function. The largest difference was noted on phonemic fluency, a measure considered to be most sensitive to cognitive changes in ALS (p= 0.001). Patients performed significantly lower than controls on The Stroop Colour Word Interference Test 'Executive Factor' (p= 0.036), Digit-Span forward (p= 0.008), and The Brixton Spatial Anticipation Test (p= 0.002), although still within an unimpaired range. Table 4.19 outlines the subtests of the California Verbal Learning Test-II, summarises the scoring profile, and Figures 4.10 and 4.11 visually represent the data.

Table 4.19: California Verbal Learning Test –II: Mean (SD)

CVLT-II	ALS	HC	*p*
Free Recall 1	-.423 (1.28)	.267 (1.33)	**.001**
Free Recall 2	.009 (1.12)	.354 (1.20)	**.039**
Free Recall 3	.278 (1.16)	.446 (1.10)	.306
Free Recall 4	.221 (1.12)	.383 (.990)	.247
Free Recall 5	.394 (1.08)	.271 (.920)	.617
Total Free Recall	53.66 (11.2)	55.13 (11.1)	.274
List B	-.086 (1.37)	.233 (1.05)	.066
Short Delay Free Recall	.153 (.926)	.364 (.931)	.103
Short Delay Cued Recall	.019 (1.15)	.383 (.891)	**.018**
Long Delay Free Recall	.144 (1.14)	.388 (.969)	.117
Long Delay Cued Recall	.076 (1.14)	.301 (.945)	.163
Free Recall Intrusions	-.279 (.666)	.048 (.956)	.169
Cued Recall Intrusions	-.372 (.588)	-.087 (.832)	.193
Total Intrusions	-.418 (.680)	-.048 (.945)	.152
Total Repetitions	-.407 (.825)	-.024 (.900)	**.018**
Recognition (Hits)	-.255 (1.21)	-.140 (1.73)	.775
Recognition (False Positives)	-.250 (1.19)	-.310 (.934)	.150

Conversely, patients did not significantly differ from controls on total immediate free recall (p= 0.274), short delay free recall (p= 0.103), long delay free recall (p= 0.117) or recognition (p= 0.775).

Subtle differences were noted when process based analyses were conducted, on the CVLT-II. Patients with ALS scored significantly lower than controls on the initial two free recall trials (p= 0.001; p= 0.039, respectively), with large effect size noted (η^2=0.16; η^2=0.14, respectively). On the short delay cued recall task, patients scored significantly lower than controls (p= 0.018; η^2=0.14).

Patients also evidenced more repetition errors than controls, with small effect (p= 0.018; η^2=0.04), as seen in Table 4.

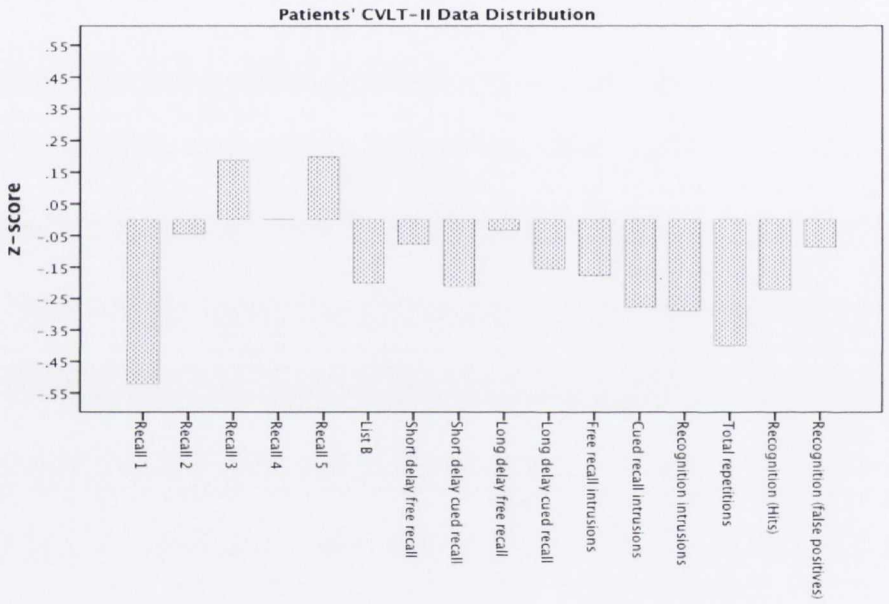


Figure 4.10. Distribution of Patients' California Verbal Learning Task Data

Using a hierarchical regression model, the executive composite was entered first followed by age at assessment, followed by predicted IQ. This allowed us to determine whether executive performance was a significant predictor of CVLT performance on Total Free Recall, while also investigating the variance attributed to age and premorbid IQ. The executive composite predicted a significant proportion of the overall variance in CVLT-II encoding (26.4%; p<0.0000). This variance represents the difference reported on initial encoding trials represented in Table 4.19. Entry of age at assessment into the model did not produce a significant increase in the percentage variance (0.004%; p=0.69) and premorbid IQ was rejected from the model.

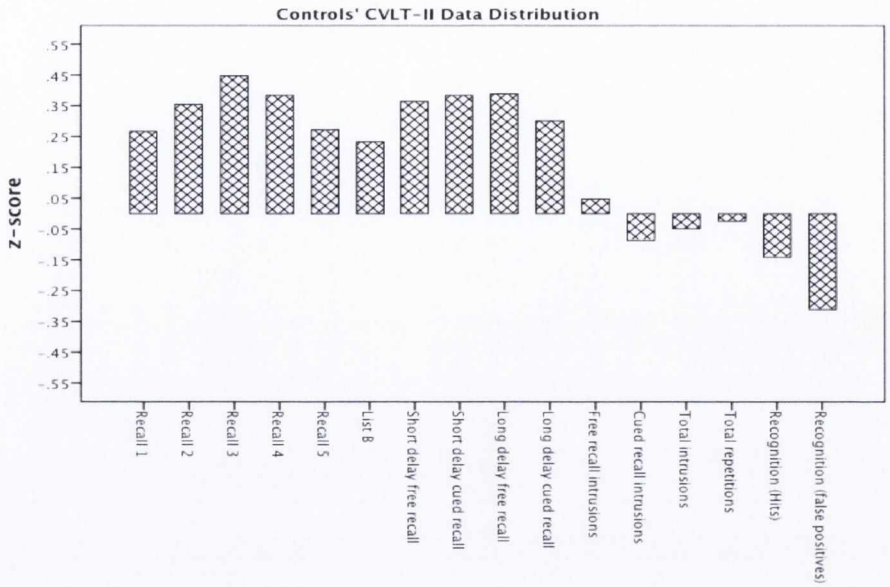


Figure 4.11 Distribution of Controls' California Verbal Learning Task Data

4.7.5 Discussion

Memory deficits in ALS have not been well categorised (Christidi et al., 2012). In this study, we investigated the neuropsychological profiles of 55 patients with ALS and previously categorized as cognitively intact to identify specific patterns of memory difficulties (Elamin et al., 2013).

When performance on cognitive measures was compared to age- gender- IQ- and education–matched controls, cognitively intact ALS patients demonstrated significantly lower scores albeit within a normal range. There were no significant differences between the groups as measured using the memory trials of the CVLT-II, which measure total free recall, short delay recall, long delay free recall, and recognition hits. Conversely, patients showed significantly lower scores when goal-orientated selective attention was required, such as the initial trials of encoding (Trial 1; Trial 2). Moreover, lower scores were evident when retrieving specific information (short delay cued-recall) and a greater number of repetition errors were noted compared to controls (recognition trial). These patterns of memory deficits are consistent with subtle deficits in executive function such as error monitoring, selective attention, response inhibition and initiation (See Table 4.19).

Empirical learning and rehearsal strategies of patients did not appear to differ greatly between patients and controls during testing i.e., semantic/serial clustering, as primacy and recency effects were observable on recall. Considering the latter encoding trials were non-significant,

our data suggests that ALS patients had an increased rate of new learning across the trials.

Retention of information over time was non-significant between the groups, although ALS patients did not appear to benefit from categorical cueing. As the presentation rate of words is consistent throughout testing, it may be possible that patients employed a cognitive strategy later than controls i.e., phonological rehearsal, or a suboptimal strategy.

Based on these findings, patients who present as cognitively intact should be assisted with enhanced encoding methods. These findings may also have implications for family caregivers, who may have observe these subtle deficits in cognitive intact patients during activities of daily living and compliance with supportive treatments.

This study has limitations. Its cross-sectional design makes the categorisation of cognitively intact ALS based on a single neuropsychological evaluation. Considering this, patients within the unimpaired cohort may have had a slowly progressive cognitive decline, which was not evident at the time of testing. Further studies of larger cohorts of cognitively intact ALS patients, with a detailed review of the neuropsychological profile over time, are required to determine the clinical accuracy and reliability of the term cognitively intact, with specific focus on executive function.

4.8 Reliable Change Index (RCI) in ALS: A Short Report.

This study sought to investigate whether a sub-group of patients who where classified with 'No Cognitive Abnormalities' were declining at a more progressive rate than other patients within the same category. We utilised the Boston Naming Test (BNT) in order to investigate whether some patients with ALS experienced lower than expected scores on re-test, controlling for the expected variance on the test, using control data. This study is outlined as follows:

4.8.1 Abstract

4.8.2 Introduction

4.8.3 Methodology

4.8.3.1 Participants

4.8.3.2 Measures

4.8.3.3 Statistical Analyses

4.8.4 Results

4.8.5 Discussion

This paper has been submitted to The European Journal of Neurology

4.8.1 Abstract

Introduction: Cognitive impairment is a frequent feature of Amyotrophic Lateral Sclerosis (ALS). Impairment in the executive domain occurs in up to 50% of incident patients with ALS, with deficits in language, emotional processing and social cognition documented. There has been limited reporting of the longitudinal cognitive profile of those who are normal on initial testing, although some patients may present self-reporting cognitive change.

Methods: Cognitively intact ALS patients who completed longitudinal assessment were studied. Using the Boston Naming Test (BNT), a Reliable Change Index (RCI) was calculated to assess whether clinically significant change was occurring between assessments on language for these cognitively intact patients (n=25), using control data for reliability statistics (n=30).

Results: Considering the standard error (*SE*=.514), Standard Difference (*SDiff*=.728), and reliability (*rxx*=.811) of the BNT, patient data from T2 was compared to their baseline performance. 32% of patients (n=8) exhibited performances that were above the 95% cut-off for significance.

Discussion: In this study, 32% of cognitively intact patients exhibited a change in their language profile, while remaining within the remit of an intact cognitive profile. This finding suggests the presence of subtle extra-motor involvement in some ALS patients who do not fulfil the formal criteria for cognitive impairment.

4.8.2 Introduction

Amyotrophic Lateral Sclerosis (ALS) is associated with impairment in social cognition, and executive dysfunction in up to 50% of cases (Phukan et al., 2011; Watermeyer et al., 2015). Few longitudinal studies investigate cognitive change longitudinally in those patients categorised as cognitively intact on initial testing using a "gold standard" neuropsychological battery (Elamin et al., 2013). We employ a Reliable Change Index (RCI; Maassen, 2004) to investigate whether clinically significant change occurs in individual patients within a cohort of cognitively intact ALS patients. RCI is a commonly used psychometric technique that measures change over time, controlling for performance variance expected on repeat assessments.

4.8.3 Methodology

4.8.3.1 Participants

Protocols for recruitment of patients and controls through our population-based register have been reported previously, with adjustments accounting for physical disability on assessment (Phukan et al., 2011). Inclusion criteria included a diagnosis of a possible, probable or definite ALS based on the revised El Escorial Criteria (Brooks et al., 2000) and no cognitive abnormalities on testing (Elamin et al., 2012). Exclusion criteria included the presence of comorbid neurological and/or psychiatric condition. Clinic- and home-based assessments were used to gather clinical and neuropsychological data.

4.8.3.2 Measures

The revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R; Cedarbaum et al., 1997) was used to document disease progression over time. Participants were assessed using a 30-item version of the Boston Naming Test (BNT; Graves, Bezeau, Fogarty et al., 2004), a commonly used visual confrontation naming task using black and white pencil drawings of objects. This study has ethical approval from Beaumont Hospital Medical Research Ethics Committee. Informed written consent was obtained from all participants in this study

4.8.3.3 Statistical Analyses

Subtracting a patient's BNT second assessment score from the baseline score, then dividing it by the standard difference created a Reliable Change Index (RCI). The Standard Difference (*Sdiff*), Standard Error (*SE*), Standard deviation (*Sx*), and test-retest reliability coefficient (*rxx*) were calculated using longitudinal age, gender, and education matched control data (n=30).

The raw score from the patient's Time 2 assessment on the BNT (X2) was then subtracted from their baseline assessment (X1), and divided by the *Sdiff* obtained from the control cohort, represented as:

$$RCI = \frac{X2-X1}{Sdiff}\text{; Whereby } Sdiff = \sqrt{2(SE)^2}\text{; considering } SE = Sx\sqrt{(1-rxx)}$$

Parametric analyses were conducted to identify whether there was a significant statistical difference over time, considering homogeneity of variance. Clinically significant deterioration on the RCI was determined by a cut-off z-score ≤-1.96, consistent with an alpha of .05

4.8.4 Results

25 patients with ALS were recruited, with demographic information in Table 4.20. Healthy controls were aged 63.36±9.00, with an estimated IQ of 107.93±7.30. Control performance on the BNT was 26.40±2.27 at baseline, rising to 27.30±2.21 on repeat.

Table 4.20: Clinical and Demographic Comparisons within ALS, stratified by RCI significance

Variable		ALS: Non-Significant RCI (n =17)	ALS: Significant RCI (n =8)	*p*
Age at Assessment	*M±SD*	59.47±11.46	59.70±8.99	.957
Age at Symptom Onset	*M±SD*	56.89±12.70	57.43±9.16	.926
Gender	Male *(%)*	86%	70%	.468
Disease Onset	*Spinal (%)*	80%	80%	.441
Years of Education	*M±SD*	14.67±3.284	13.33±3.04	.354
ALSFRS-R	*M±SD*	38.93±5.61	38.60±5.98	.889
ALSFRS-R Decline[o]	*M±SD*	-4.73±3.12	-6.10±5.95	.460
Full Scale IQ[§]	*M±SD*	108.24±12.45	100.92±12.28	.175
Verbal Comprehension Index[§]	*M±SD*	107.10±12.40	99.27±12.40	.144
Performance Reasoning Index[§]	*M±SD*	108.52±9.42	103.48±9.76	.224
Working Memory Index[§]	*M±SD*	107.68±10.67	101.88±10.44	.208
Processing Speed Index[§]	*M±SD*	102.64±6.85	98.67±6.43	.171
Current Non-Verbal Function [b]	*M±SD*	31.00±3.92	29.40±4.94	.378

[o] Calculated by subtracting ALSFRS-R Time 2 total score from Time 1; [§]Estimated values measured by the Test of Premorbid Function, UK edition; [b] as measured by Raven Progressive Coloured Matrices.

ALS patient performance on the BNT was 27.64±1.52. On repeat performance the mean was 26.88±3.00. There was no significant difference between the baseline and repeat assessment (p= .169). Using the control BNT data the *rxx* (.811), *Sx* (2.51), *SE* (.514), and *Sdiff* (.728) were calculated to adjust for the expected rate of change in a healthy population.

Controlling for the expected variance in repeat assessment, 32% of the ALS patients were identified as having clinically significant change on the BNT (n=8). Remaining patients had non-significant change.

4.8.5 Discussion

These data indicate that cognitively intact ALS patients do not experience decline in language function on a group level. Notwithstanding, the RCI suggests that clinically relevant decline may occur relative to the patient's baseline, suggesting the need for a person-centred, and individualised approach to cognitive deficits in ALS.

Patients with an RCI below cut-off appear to be declining, albeit at a slower rate than other cognitively intact patients with whom they are demographically matched. This work should be considered exploratory. Verification in an independent population is recommended. The sample is limited and over-represents males with spinal-onset ALS. Nonetheless, the data provide evidence for the utility of RCI to track subtle decline in patients whom otherwise be classified as cognitively intact.

4.9 Caregiver Burden in ALS: Cross-sectional Investigation of Predictors.

To this point, the focus of the results have considered patients' cognitive impairment. As detailed in the literature review (See Chapter 2), cognitive and behavioural change can be difficult for caregivers to identify, and manage new onset cognitive decline and behaviour change. We sought to further quantify this impairment in patients, and to investigate the predictors of caregiver burden. This study is outlined under the following sections:

4.9.1 Abstract

4.9.2 Introduction

4.9.3 Methods

4.9.3.1 Statistical Analysis

4.9.4 Results

4.9.4.1 Behaviour and Burden

4.9.4.2 Predictors of Caregiver Burden and Distress

4.9.4.3 Does Caregiver Burden Affect Patient Survival

4.9.5 Discussion

This paper has been published in The Journal of Neurology:

Burke, T., Elamin, M., Galvin, M., Hardiman, O. & Pender, N. (2015) Caregiver Burden in Amyotrophic Lateral Sclerosis: A Cross-sectional Investigation of Predictors. Journal of Neurology. Early Online

4.9.1 Abstract

Objective: To investigate whether cognitive and behavioural impairment in Amyotrophic Lateral Sclerosis (ALS) contributes to caregiver burden, and whether carer burden affects patient outcome.

Methods: Thirty-three dyads of incident patients with ALS and their primary caregivers (n=33) completed a series of measures to determine cognitive and behavioural profiles, (patients) and carer burden (carers) to investigate the psychological impact of ALS, and the impact of behavioural change since the onset of ALS.

Results: Caregivers were divided into high and low burden groups using previously established norms. High burden in carers was associated with significantly higher apathy (p=.009), disinhibition (p=.005), and executive dysfunction (p=.015) in patients. Regression analyses for burden confirmed significant predictors such as change in apathy (r= .390, F= 5.19, p=.03), disinhibition (r=.530, F= 11.32, p=.002), and executive dysfunction (r=.372, F=4.66, p=.039), with total behaviour change contributing to 31% of caregiver burden (r =.563, F= 4.17, p=.015). Total distress as measured by the Hospital Anxiety and Depression Scale was also a significant predictor of caregiver burden, contributing to 38.5% of variance (r=.621, F =18.79, p<.001). Caregiver burden did not affect survival (p= .496).

Conclusions: Caregiver burden in ALS is modulated by patient's cognitive and behavioural status, but does not significantly impact patient survival.

4.9.2 Introduction

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder of an unknown aetiology, limited treatment, with a rapidly progressive and fatal trajectory. ALS leads to progressive neurodegeneration and paralysis with death from respiratory failure within 3 years of symptom onset in the majority of patients (Elamin et al., 2011).

Caregiver burden has been reported to be a consequence of physical impairment worsening congruently with disease trajectory (Chio et al., 2005), although recent reports also implicate cognitive, behavioural and neuropsychiatric symptoms as significant factors contributing to caregiver burden (Bruletti et al., 2014; Gauhier et al., 2007; Mioshi et al., 2013). It has been suggested that caregivers' psychological status may influence the mental and physical outcome of patients (Bruletti et al., 2014; Chio et al., 2004; Rabkin et al., 2000; Thommessen et al., 2002). However, few studies have collectively considered the triad of impairments known to occur in ALS i.e., behavioural impairment, cognitive impairment and deteriorating physical condition.

Up to 50% of ALS patients exhibit cognitive and behavioural impairment (Mioshi et al., 2014). Behavioural symptoms preceding motor features are of clinical relevance, with the most commonly reported change in ALS patients being apathy, present in up to 60% of ALS patients (Grossman et al., 2007), followed by disinhibition (Lillo et al., 2011). Behavioural impairment increases carer burden, however, the impact of highly burdened caregivers on patient survival has not yet been established.

Through detailed neurocognitive assessment of patients with ALS, cross-sectional clinical interviews and assessment with their primary caregiver, we sought to further characterize factors contributing to caregiver burden, including behaviour, cognitive status, and physical condition and to determine whether high levels of burden influenced patient survival.

4.9.3 Methods

Participants were recruited as part of an on-going longitudinal population based investigation into the heterogeneous cognitive profile of people with ALS, previously described in detail (Eamin et al., 2011; Elamin et al., 2013; Phukan et al., 2012). ALS patients recruited to this sub-study (n=33) of carer burden were diagnosed with probable, or definite ALS, according to the revised El Escorial Criteria (Brooks et al., 2000). In all patient cases, their primary caregivers were interviewed once during recruitment (n=33), over a 3-month recruitment period. Exclusion criteria included history of neurologic conditions that could affect cognition

(such as major hemispheric stroke), alcohol dependence syndrome, and/or the use of high-dose psychoactive medications. Neuropsychological and clinical data were collected through hospital assessments and home visits.

Information on cognitive status, behavioural status, and physical progression were obtained through direct evaluation of ALS patients, and semi-structured interviews with their primary caregiver. The neuropsychological performance of patients with ALS was compared with a cohort of age-, sex- and education-matched healthy controls, as described previously. Abnormal performance on any task was defined as a score that is two standard deviations below the control mean. Extensive details of the neuropsychological battery, clinical data, and method for categorizing cognitive impairment have been described in detail previously, and supplementary information relating to the neuropsychological tests can be seen in Table 4.21. Measurements of caregiver burden were undertaken with the patients and caregiver dyads (n=33).

The Zarit Burden Interview (ZBI; Zarit, Reever, & Bach-Peterson, 1980) was used to assess subjective caregiver burden, where a score ≥24 indicates burden (Schreiner, Morimoto, Arai, & Zarit, 2006). For the purpose of this study, caregivers with a score of ≥24 were categorically defined as being in the 'burdened' group, with more psychometric information regarding the scale available (Ankri, Andrieu, Beaufils, Grand, & Henrard, 2005).

The McGill Quality of Life Questionnaire Single-Item Scale (MQOL-SIS: Cohen, Mount, Strobel, & Bui, 1995) specified the patient's perceived quality of life over the past two days, scoring 0-10, with higher scores being indicative of greater quality of life.

Table 4.21: Supplementary details of the neuropsychological battery

Executive dysfunction	*Impairment that is two SD below the mean for healthy controls on at least two executive tasks*
Stroop Colour-Word Test	(a) Priming trial: patients presented with a multicoloured list of colour names and asked to read as many words as they can in 2 minutes. (b) Inhibitory trial: a similar list is presented but colour names (eg, 'blue') are printed in an ink colour not denoted by the name (eg, red). Correct responses in two minutes are recorded. Non-executive factors (including bulbar disability) contribute equally to both trials. The difference in scores between the two trials represent the number of responses 'lost' due to the delay imposed by the extra executive demands in the inhibitory trial.
Brixton Spatial Anticipation Test	A rule attainment based task whereby the rule in operation, cannot be identified by any perceptually salient aspect of the stimuli. It consists of pages showing the same basic array of 10 circles set in two rows of five, with each circle numbered from one to 10. The changes in position are governed by a series of simple rules, which vary without warning.
Backward digit span	A measure of auditory attention and working memory. This test is composed of trials where examinees are read strings of digits and are asked to repeat them back aloud. The length of the digit strings is incrementally increased over successive trials.
Category fluency	Patients were asked to name as many animals as they could think of in 1 minute (spoken only).
Phonemic verbal fluency	Written/spoken, number of words starting with letter 'S' generated in 5 minutes and number of four letter words starting with letter 'C' generated in 4 minutes. Verbal Fluency Index used to adjust for disability.
Memory dysfunction	*Impairment that is two SD below the mean for healthy controls on at least four* of the parameters highlighted using +*
Logical Memory (LM)	+LM1 (immediate recall), +LM2 (delayed recall) and +LM retention (retention)
Verbal Paired Associate (VPA)	+VPA1 (immediate recall),+VPA2 (delayed recall) and +VPA retention (retention)
Auditory Delayed Recognition Task	+Sum of total recognition scores on Logical Memory and Verbal Paired Associates
California Verbal Learning Tests	+Total of five trials, +short delay free recall (immediate recall) +long delay free recall (delayed recall)
Rey-Osterrieth Complex Figure test	Non-verbal memory: parameters used: +immediate and +delayed recall trials
Language dysfunction	
Boston Naming Test	*Impairment that is two SD below the mean for healthy controls on this task.*
Visuo-spatial dysfunction	
Rey-*Osterrieth* Complex Figure Test	*Impairment that is two SD below the mean for healthy controls on copy trial of this task.*

Behaviour was assessed using the Frontal Systems Behaviour Scale (FrSBe: Grace & Malloy, 2001), a self- and proxy-report behaviour questionnaire associated with fronto-striatal circuitry, which measures Apathy, Disinhibition and Executive Dysfunction. The Hospital Anxiety and Depression Scale (HADS: Moorey, Greer, Watson et al., 1991) was administered, as a statistically reliable measure comprised of two subscales measuring Depression (HADS-D) and Anxiety (HADS-A).

Patients' survival data was captured by the Irish ALS register, as previously described.

This study was granted ethical approval from Beaumont Hospital Medical Research Ethics Committee. Informed written consent was obtained from all participants in this study (N=66)

4.9.3.1 Statistical Analysis

Comparisons of descriptive variables were made using independent sample t-test, and simple linear regressions were employed to investigate significant predictors of caregiver burden. According to power calculations, our sample per group met requirements to detect robust significance, with Bonferonni analyses used to correct for multiple comparisons. The distribution of the data was homoscedastic for principal dependent variables. All tests were set to an alpha value of .05.

4.9.4 Results

Information relating to caregiver–patient dyads is summarized cumulatively and subcategorized based on whether the patient's caregiver was experiencing high or low burden. The patients (19 men, 59.4%) had a mean age of 63.99 years (SD± 9.2 years; range 39-77), a mean duration of symptoms of 30.13 months (SD± 18.22 months), and a mean Amyotrophic Lateral Sclerosis Functional Rating Scale (revised) score of 36.63 (SD± 7.79). Primary caregivers (11 men, 34.4%) had a mean age of 58.17 (SD± 11.1; range 35-83); 26 were cohabiting spouses (81.3%), 4 were children (12.4%), and 2 were other relatives (6.3%). Some patients received additional care other than from their primary caregiver, approximately 8.55 hours (±8.01 hours) per week. For additional demographic, clinical and stratified group data, please refer to tables 4.22 and 4.23.

Table 4.22: Demographic, Clinical and Interview Data

ALS Patients (N=33)		Total Patient	Low Burden n=22	High Burden n=11	*p*
Males	n(%)	19 (59.4)	13(61.9)	6(54.5)	.317
Age at assessment	y(±sd)	63.99 (9.2)	65.80 (6.71)	60.5(12.5)	.228
Years of Education	*x*(±sd)	11.5(3.11)	11.5(3.15)	11.45(3.1)	.777
Spinal Onset	n(%)	22 (66.6)	14(63.63)	8(72.7)	.803
ALSFRS-R	*x*(±sd)	36.63(7.79)	36.95(7.74)	36.0(8.24)	.749
Onset-Assessment	month(±sd)	30.13 (18.22)	26.5(13.95)	36.1(23.9)	.173
Primary Caregivers (N=33)		Total Caregiver	Low Burden n=22	High Burden n=11	
Males	n(%)	11 (32.35)	7 (31.81)	4(36.36)	.162
Mean age at interview	y(%)	58.17 (11.1)	66.05(6.79)	60.5(11.9)	.265
Families w/ children	n(%)	10 (31.2)	3(14.3)	7(63.6)	.072
External Assistance	*x*(±sd)	8.55 (8.01)	6.12(4.32)	10.16(9.8)	.094

The mean ZBI score for all caregivers, regardless of level of burden was 21.62 (SD ±14.0). Subgroup analysis into those scoring above and below 24 revealed 2 main groups. The 'Low Burden' group reported a mean burden score of 12.75 (SD ±7.35), whereas the 'High Burden' group reported a mean burden score of 37.6 (SD ±8.66). Considering burden as the grouping variable, a significant difference in subjective burden was observed ($p<.001$).

Caregivers had a mean anxiety score of 7.35 (SD ±4.02), as measured by the HADS-A. There was a significant difference noted between groups with mean anxiety scores of 5.86 (SD ±3.37) and 9.88 (SD ±2.84) for the low burdened caregivers and high burdened caregivers respectively (p=0.007). No significant differences were noted on the HADS-D subscale between the high burdened caregivers and low burdened caregivers, with scores of 2.20 (SD ±2.14) and 3.88 (SD± 2.84) respectively ($p=.133$). Combining the HADS-A and HADS-D subscales creates a reliable 'Total Distress score' (HADS-T), and in this cohort there were significant differences between the burdened groups ($p=.015$).

The relationship between the HADS and the ZBI was also investigated. Greater distress scores were positively correlated with subjective symptoms of burden, congruent with previous studies (ZBI*HADS-A: $r=.360$; ZBI*HADS-D, $r=.301$; ZBI*HADS-T, $r=.383$).

Table 4.23: Additional Participant Characteristics

Neuropsychiatric and Burden Measures	Total Caregiver	Low Burden n=22	High Burden n=11	*p*
HADS: Anxiety	7.35 (4.02)	5.86 (3.37)	9.88 (2.84)	**.007**
HADS: Depression	2.77 (2.37)	2.20 (2.14)	3.88 (2.84)	.133
HADS: Distress	10.06 (5.93)	8.06 (5.03)	13.7 (5.47)	**.015**
ZBI	21.62 (14.00)	12.75 (7.35)	37.6 (8.66)	N/A
McGill QoL-SIS	6.90 (1.77)	6.91 (1.67)	6.5(2.42)	.674

Hours of Care Provided Per Day	8.30 (7.45)	5.96 (7.27)	9.93(7.09)	.875
Supervision	7.63 (7.37)	5.2 (5)	7.89 (7.85)	.436
Dressing	.861 (.51)	.75 (.43)	1(.612)	.563
Feeding	1.33 (.750)	1.66 (1.15)	1.37(.47)	.661
Toileting	.625 (.541)	.125(.176)	1(.5)	.107
Other	2.58 (2.05)	1.5(1.32)	3 (2.82)	.463
Medical	1.50 (.70)	2.00	1.00	N/A
Housekeeping	2.12 (1.35)	2(.816)	1.00	N/A
Transportation	1.33 (.57)	1.00	1.5(.707)	N/A

4.9.4.1 Behaviour and Burden

Caregivers were dichotomized based on their ZBI score, and using the FrSBe relative change in apathy (p=.009), disinhibition (p=.005), executive dysfunction (p=.015) and total behaviour (p=.001) we noted. The higher burden patient group showed greater mean changes from baseline in apathy (25 vs 12), disinhibition (10 vs 2) and executive function (9 vs 2). The mean total behaviour change, according to caregivers, from before onset of ALS to the time of testing was increased due to the aforementioned subtests (15 vs 6).

The ZBI was itemized to identify variables associated with increased caregiver burden (see table 4.24). Caregivers who experienced higher burden, as indicated through their ZBI scores, stated that the patients with ALS asked for more help than they may need (p=.033), or that the caregiver's personal time was being consumed by caregiving (p=.014). Caregivers report that stress was significantly increased due to caring for the patient (p=.002). High burden caregivers further reported that they felt more frustrated and strained (p=.003), and angry around their family members (p=.013). Feelings of impaired social life (p=.013) and personal privacy (p=.020) were significantly more intense in high burdened caregivers, and they felt that their relative was dependent on them (p=.005), with an uncertain future (p<.001).

High burdened caregivers expressed concern that they were the only person on whom the patient could depend for support (p=.002), that they would not be able to care for the patient indefinitely, (p=.022), and that they wished they could leave the care of their relative to someone else (p=.029).

Overall, when the dichotomized groups were specifically asked about the severity of burden experienced, the high burden group reported that they had lost control of their lives

(p=.004).Caregiver burden was not influenced by the efficacy of the caregiving (p=.069), whether caregivers felt they were doing enough (p=.093), uncertainty about what to do for their relative (p=.191) or financial implications (p=.593). Furthermore, caregiver burden was not associated with concern relating to patient behaviour in terms of feeling embarrassed (p=.295), or being uncomfortable when socializing with friends (p=.414) or family (p=.254), and denied that their health had been adversely affected due to their involvement in caring for their relative (p=.088).

4.9.4.2 Predictors of caregiver burden and distress

Significant neuropsychological predictors of burden were associated with increased mean change of apathy (r= .390, F= 5.19, p=.03), disinhibition (r=.530,F= 11.32, p=.002), and executive dysfunction (r=.372, F=4.66, p=.039) , with the total change in behaviour contributing to 31% to caregiver burden (r =563, F= 4.17, p=.015). The HADS-T score is a further factor contributing to caregiver burden, contributing to 38.5% of variance(r=.621, F =18.799, p<.000). Caregiver Quality of life (QoL-SIS; r=382, F=3.76, p=.65), patient age (r=.235,F= 1.57, p=.220), total hours caring (r=311,F=3.21, p=.083), cognitive status (r=.016, F=.007, p=.933), and patients' level of functioning as defined by the ALSFRS-R (r=.183, F=1.034, p=.317) did not significantly contribute to caregiver burden. Lastly, the gender of patients was not found to be a significant contributory factor (r= .128, F= .497, p=.486).

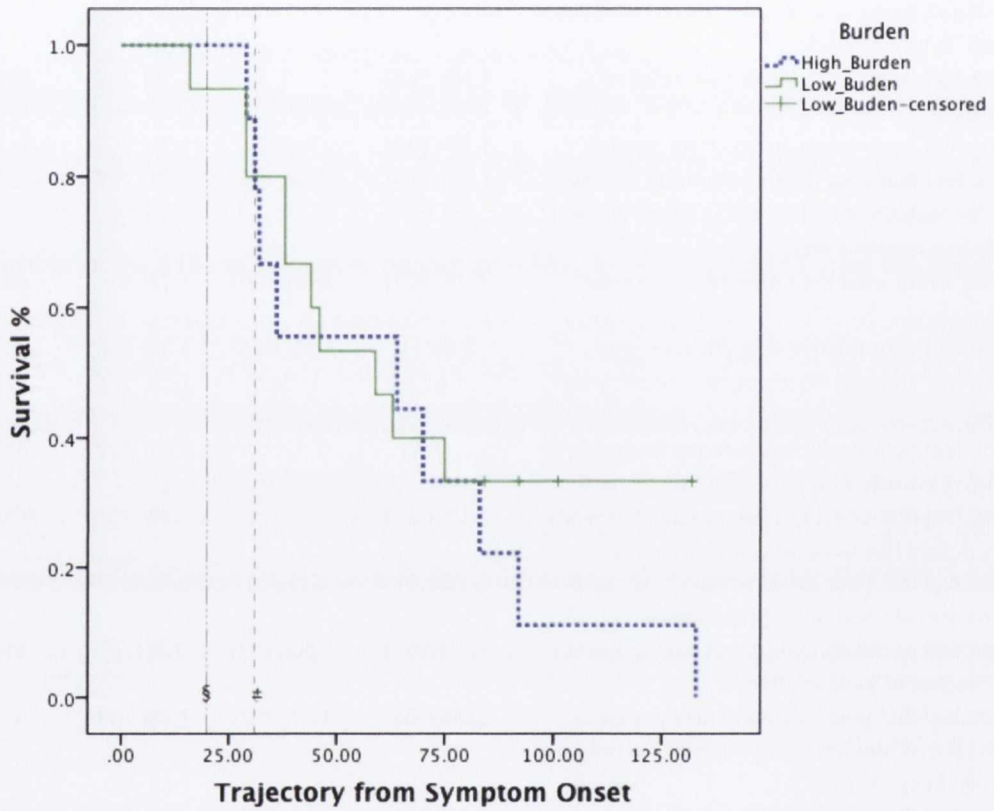
Table 4.24: ZBI Questions and Endorsement

ZBI Question	Total Caregiver N=33	Low Burden n=22	High Burden n=11	*p*
Do you feel that your relative asks for more help than he/she needs?	1.73 (.647)	1	1.86 (.690)	.033*
Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?	1.95 (.780)	1.78(.833)	2.50(.548)	.014*
Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?	2.37(1.11)	2.09(1.13)	2.78(1.09)	.002**
Do you feel embarrassed over your relative's behaviour?	1.40(.548)	1	1.50(.707)	.295
Do you feel angry when around your relative	1.82(.728)	2(.707)	1.71(.756)	.013*
Do you feel that your relative currently affects our relationship with other family members or friends in a negative way	1.80(.789)	2.50(.707)	1.75(.957)	.254
Are you afraid what the future holds for your relative	2.92(.977)	2.45(.820)	3.22(.833)	<.000**
Do you feel your relative dependent on you	2.80(1)	2.58(.996)	3.33(.866)	.005*
Do you feel strained when you are around your relative	2(.679)	1.75(.5)	2.29(.756)	.003*
Do you feel your health has suffered because of your involvement with your relative	2(.707)	-	2.33(.577)	.088
Do you feel that you don't have as much privacy as you would like because of your relative	2.10(1.19)	2	2.29(.756)	.020*
Do you feel that your social life has suffered because you are caring for you relative	2.19(1.07)	2(1.22)	2.33(.577)	.013*
Do you feel uncomfortable about having friends over because of your relative	1.75(.957)	1.50(.707)	2.5(1.37)	.414
Do you feel that your relative seems to expect you to take of him/her as if you were the only one s/he could depend on?	2.60(1.05)	1.75(957)	2.33(1.11)	.002**
Do you feel that you don't have enough money to take care of your relative in addition to the rest of your expenses	2.07(.829)	1.83(.753)	2(1.41)	.593
Do you feel that you will be unable to take care of your relative much longer	1.83(.937)	1.33(.577)	2.75(.886)	.022*
Do you feel you have lost control of your life since your relative's illness	2.40(1.13)	2.33(1.52)	2.50(.837)	.004*
Do you wish you could leave the care of your relative to someone else	2.09(1.22)	1.50(.707)	2.29(.951)	.029*
Do you feel uncertain about what to do about your relative	2.20(1.13)	2(1.41)	2.25(1.16)	.191
Do you feel you should be doing more for your relative	2.27(1.14)	1.67(.577)	2.60(1.51)	.093
Do you feel you could do a better job caring for your relative	2.36(1.02)	1.67(.577)	2.80(1.30)	.069
Overall, how burdened do you feel in caring for your relative?	1.86(.774)	1.56 (.527)	2.22(.833)	.006*

*p≤0.05; **adjusted sig. p≤.002

4.9.4.3 Does caregiver burden affect patient survival?

Dichotomized groupings based on the ZBI did not affect survival time (log rank test p=.496; see figure 4.12 for Kaplan-Meier Survival Plots). Considering a low participant cohort, linear contrast analytic modeling was conducted to determine whether an increased sample size would produce an alternate outcome of this analysis. Using this analysis we predict that higher burden in caregivers would not affect survival rates of patients (p=.138).



4.9.5 Discussion

The purpose of this study was to examine factors associated with caregiver burden in patients with ALS, and to determine whether high caregiver burden in the context of established disease influenced patient survival. Previous cross-sectional studies have found patients' level of disability, especially with spinal onset ALS, and depression were factors yielding the strongest correlation with caregivers' burden (Gauthier et al., 2007). Our findings are consistent with these findings for low mood, anxiety and total distress. Our findings are congruent with studies of caregiver burden in other chronic neurologic disorders.

Behavioural symptomatology is not routinely assessed in a systematic manner, and accurate profiling may enhance interventions specific to caregivers who experience higher levels of burden. Interestingly patients and caregivers reported similar levels of behavioural change

after the onset of ALS. The caregivers who experience higher burden report lower scores than caregivers within the low burden category, and this may reflect a difference in the manifestation of behavioural change. This could be investigated by future research, through qualitative means. The present study has demonstrated that patient behaviour is a major factor to be considered when investigating caregiver burden.

Our data suggest that behavioural change is of great importance as a mediator of caregiver burden. Considering the rapidly progressive and devastating physical features of ALS, comprehensive behavioural phenotyping, with detailed evaluation of social cognitive and executive processes, is required to further elucidate and understand the burden-behaviour relationship. Notwithstanding, survival analysis of impact of caregiver burden on patient survival suggests that a patient's disease trajectory, and ultimately survival is not negatively associated with higher levels of caregiver burden. However, considering models used with other patient cohorts, skills training and symptom management may be of considerable benefit in reducing caregiver burden.

Our study has several limitations. Due to the small sample, results from regression analyses should be considered exploratory, alongside the survival analysis. Secondly, these findings may apply only at particular states of the illness, as this study was cross-sectional in design, albeit in patients with established illness and moderate disability. A longitudinal follow-up of caregiver wellbeing, cognitive status of patients, detailed investigation of patient support, and intervention evaluation is required to determine whether caregiver burden shifts as the disease progresses.

In conclusion, our study has shown that caregiver burden is higher in dyads in which the patient has evidence of behavioural impairment.

4.10 Caregivers of Patients with ALS: QoL, Burden, and Service Engagement.

In the previous study we reported the utility of high/low burden categories using the Zarit Burden Interview (ZBI). In this study, we sought to further investigate whether service engagement, cognition, disease status, hospital admission, community based supports, financial income, or Quality of Life, statistically differed in caregivers based on the high/low stratification. This study is outlined as follows:

4.10.1 Abstract
4.10.2 Introduction
4.10.3 Method
- 4.10.3.1 Participants
- 4.10.3.2 Measures

4.10.4 Results
- 4.10.4.1 Patient Demographic and Clinical Variables
- 4.10.4.2 Health Service Engagement
- 4.10.4.3 Gender Differences in Caregiver Burden
- 4.10.4.4 Survival and Caregiver Burden
- 4.10.4.5 Burden and QoL in Caregivers

4.10.5 Discussion

This study has been published in the Journal of Neurology.

For further information on the impact of cognitive impairment and behavioural change on QoL see:

Burke, T., Galvin, M., Pender, N., & Hardiman, O. (2017). The Impact of Cognitive and Behavioural Change on QoL of Caregivers and Patients with ALS and other Neurological Conditions. In F. Pagnini, & Z. Simmons (Eds.) *Amyotrophic Lateral Sclerosis: Understanding and Optimizing Quality of Life and Psychological Well-Being.* UK: OUP

4.10.1 Abstract

Objective: Few studies in Amyotrophic Lateral Sclerosis (ALS) have profiled disease specific features of the condition in conjunction with assessment of caregivers' burden, distress, quality of life, and implication of patient survival. Here we report results from a population-based cohort of ALS patients and carer dyads.

Methods: Eighty-four ALS patients and their primary caregivers were enrolled to this study. Patients completed ALS-specific measures of physical and cognitive function, while caregivers completed measures of anxiety, depression, caregiver burden, and quality of life. Patient-caregiver dyads were interviewed about their health-service utilisation. Survival data was obtained through the national register for ALS.

Results: Participants were dichotomised into low/high groups based on the severity of caregiver burden. High burdened caregivers (n=43) did not significantly differ from low burdened carers (n=41) with respect to disease-specific characteristics i.e., ALSFRS-R, site of onset, disease duration and survival. However, significant differences were reported on subjective measures of anxiety (p=.001), depression (p<.001), distress (p<.001), and quality of life (p<.001).

Conclusions: These data confirm that caregivers of people with ALS experience significant burden. Considering a matched cohort of patients and caregivers, this study suggests that the subjective experience of individual caregivers is an important factor in the level of caregiver burden experienced.

4.10.2 Introduction

Amyotrophic Lateral Sclerosis (ALS) is a physically debilitating heterogeneous disease that incorporates extra-motor features of other neurodegenerative conditions, with a rapid disease trajectory (Burrell, Halliday, Kril et al., 2016). Cognitive and behavioural changes in ALS patients are known to increase caregiver burden (Trail, Nelson, Van et al., 2003), with new onset behaviour change i.e., apathy, disinhibition, and dysexecutive behaviours, being most predictive of high caregiver burden (Burke et al., 2015). High levels of distress, anxiety, and depression have also been reported in ALS caregivers (Rabkin et al., 2009), which are also predictive of burden. Sub-categorisations have been identified in common measures of burden, (Ankri et al., 2005), allowing for classification of burden specifically associated with the personal experience (subjective), or the role required (objective) in caregiving (Kamiya, Sakurai, Ogama et al., 2014). Subjective burden has further been defined as the negative experience resulting from the role-based demands related to caring for another person (del-Pino-Casado, Pérez-Cruz, & Frías-Osuna, 2014). Objective burden is defined as the emotional reaction, interpretation, and cognitive reasoning associated with caregiving (Hughes, Black, Albert et al., 2014).

Subjective and objective burden can have significant implications for Quality of Life (QoL) for both ALS patients (Gauthier et al., 2007) and their caregivers (Chio et al., 2005). QoL is a multidimensional concept (Haas, 1999), which can incorporate physical (Rejeski & Mihalko, 2001), emotional (Wehmeier, Schacht, & Barkley, 2010), social (Diener & Suh, 1997), spiritual (Holland, Kash, PAssik et al., 1998), and financial (De Judicibus & McCabe, 2007) components. Although reduced QoL and increased caregiver burden are features in a patient's journey from diagnosis to death (Foley, Timonen, & Hardiman, 2016), comprehensive profiles of caregivers' psychological wellbeing are infrequently reported. Moreover, few studies have sought to accurately profile the disease characteristics of ALS patients, the psychological profile of their caregivers, considering their overall health-service engagement. To this end, the current research investigates cognitive status, socioeconomic characteristics, health-service and specialist MDT engagement, financial factors, and disease specific variables on caregiver burden, QoL, and psychological distress.

4.10.3 Method

4.10.3.1 Participants

Protocols for the recruitment of patient-caregiver dyads through our population-based register have been reported previously. Patients fulfilling the El Escorial criteria for possible, probable or definite ALS were recruited (Brooks et al., 2000). Exclusion criteria included the presence of comorbid neurological and/or psychiatric condition such as stroke, psychosis, traumatic brain injury, chronically uncontrolled diabetes or an active or positive history of chronic substance abuse. Data were collected through home-based interviews and clinic-based assessments. The MITOS staging system was used to categorise patients' disease profile. According to standard operating procedures, stages are defined as: Stage 0, functional involvement but no loss of independence on any domain; Stages 1-4, number of domains in which independence was lost i.e., movement, swallowing, communicating, and/or breathing; and Stage 5, death. For the purpose of this study, stages 0-4 inclusive were utilised as grouping variables.

4.10.3.2 Measures

The Zarit Burden Interview (ZBI: Zarit et al., 1980) was used to assess caregiver burden, where a statistically derived score ≥24 indicates burden. For the purpose of this study, caregivers with a score of ≥24 were defined as being in a 'high burden' group. Psychometric information regarding the sub-stratification of the ZBI into personal strain, and role strain factors is available.

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS: Abrahams et al., 2014) is a brief multi-domain cognitive screening tool designed specifically to assess cognitive performance in patients with ALS. The ECAS investigates a range of cognitive domains to capture the heterogeneity of cognitive impairment known to occur in ALS. The ECAS is divided into two sections; one considering cognitive domains affected in ALS (Specific i.e., Language, Executive Function, & Verbal fluency) and another including relatively preserved cognitive function in ALS (Non-Specific i.e., Memory, and Visuospatial skills). The ECAS includes a structured carer interview investigating the presence of behavioural changes based on FTD diagnostic criteria (Strong et al., 2009).

The Hospital Anxiety and Depression Scale (HADS: Moorrey et al., 1991; Norton et al., 2013) was administered, as a statistically reliable measure of psychological distress comprised of two subscales measuring Depression (HADS-D) and Anxiety (HADS-A).

The McGill Quality of Life Questionnaire (MQOL: Cohen et al., 1995) measures subjective well-being i.e. the patient's experienced quality of life, over the past two days. Scores have a possible range from 0-10, where higher scores related to higher QoL.

Patients were interviewed on their engagement with health-services. Data on admission to Accident and Emergency, Outpatient appointments, and community-based services such as Occupational Therapists, Physiotherapists, Speech and Language Therapists, and a Dietician were captured. Alongside this, data regarding received aids and appliance such as communication aids and physical aids was captured i.e., motorised chair, eye-gaze etc.

The revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) (Cedarbaum et al., 1997) was used to document disease severity (range 0-46; a greater score indicates greater functionality). The ALSFRS-R was then used to categorise patients using the MITOS staging system. Patients' survival data was captured by the Irish ALS register, as previously described. The focus of the survival analyses was to determine whether caregiver burden was associated with disease trajectory.

This study has ethical approval from Beaumont Hospital Medical Research Ethics Committee. Informed written consent was obtained from all participants in this study (N=168).

4.10.3.3 Statistical Analyses

Comparisons of descriptive variables were made using independent sample t-test. According to power calculations, our sample per group met requirements to detect robust significance at a medium effect size, with Holm-Bonferroni analyses used to correct for multiple comparisons where relevant. ANOVA were used to assess for significance when homogeneity of variance was satisfied. All tests were set to an alpha value of .05. Statistical analyses were performed using SPSS version 21.

K-means clustering was employed to create statistically derived cut-off scores for Personal and Role Strain factors of the ZBI. This methodology was employed as caregiver burden, measured by the ZBI, has been shown to be a multidimensional concept, and this methodology is non-hierarchical. This method determined that a cut-off of $\geq$14 was suitable to detect high Personal Strain (Items 1, 4, 5, 6, 9, 13, 14, 16, 18, & 19), and $\geq$22 for was derived for high Role Strain (Items 2, 3, 7, 8, 10, 11, 12, 15, 17, & 22). A third factor has been

reported on the ZBI as Guilt (Items 20 & 21), with a cut-off of ≥2.5 categorising high endorsement.

4.10.4 Results

4.10.4.1 Patient Demographics and Clinical Variables

ALS patients (N=84) were grouped based on stratified in low burdened (n=41), and high burdened (n=43) groups based on their caregiver's experience (N=84). Demographic variables such as age at initial interview, number of children, and gender as well as disease specific variables such as site of ALS onset, patient age at symptom onset, ALSFRS-R sub-domains, cognitive performance on testing (ECAS), additional home care, and weight, we matched as seen in Table 4.25. MITOS staging criteria categorised 55% of patients at Stage 0 of the disease; 24% at Stage 1; 18% at Stage 2; 1% at Stage 3, as per standardised protocol. No patient met the criteria for Stage 4.

4.10.4.2 Health Service Engagement

Table 4.25: Clinical and Demographic Comparisons within ALS, stratified by Caregiver Burden

Variable		ALS Patient (Low Burdened Caregiver) (n =41)	ALS Patient (High Burdened Caregiver) (n =43)	*p*
Age at Assessment	*M±SD*	63.12±10.13	65.58±10.93	.289
Age at Symptom Onset	*M±SD*	60.46±10.65	62.95±10.83	.189
Gender	Male *(%)*	58.5%	60.5%	.349
Disease Onset	*Spinal (%)*	66%	72%	.138
Number of Children	*M±SD*	2.85±1.78	3.23±1.79	.335
Additional home care*	*Hours* M±SD	2.79±5.44	5.01±9.16	.184
ALSFRS-R	*M±SD*	33.63±8.35	32.14±8.27	.469
Bulbar	*M±SD*	9.37±2.62	8.94±2.96	.532
Spinal	*M±SD*	13.73±6.13	13.57±6.00	.918
Respiratory	*M±SD*	10.68±2.45	9.45±2.71	.057
Weight (KG)	*M±SD*	67.18±15.24	62.09±25.62	.573
ECAS Total§	*M±SD*	93.46±23.39	95.67±19.78	.673
Specific Score	*M±SD*	69.78±18.57	70.57±15.27	.848
Non-specific Score	*M±SD*	23.69±6.66	25.05±6.43	.388

*Hours per week; §Cognitive Assessment

There were no significant differences, between low or high burdened caregivers in engagement with health services. Figure 4.13 illustrates the distribution of community-based health-services accessed in the 6-month period prior to interview i.e., physiotherapy, occupational therapist etc. Neither were significant differences detected between low and high burden caregivers in the amount of government-funded state benefits or other illness benefits being received (p=.315); the amount of time spent engaging with palliative services per week (p=.347).

The number of hours patients spent weekly with counselling services (p=.475); the number of visits to the Emergency Department (p=.319); and the number of hospital admissions (p=.473).

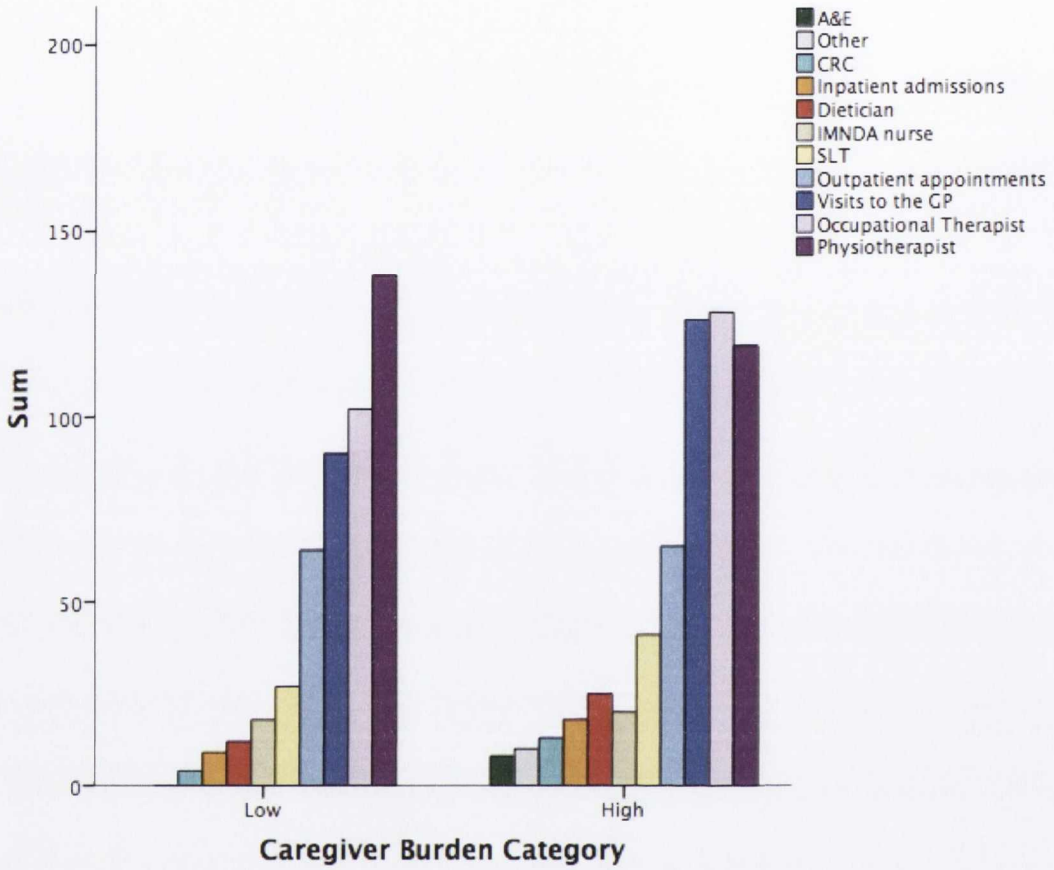


Figure 4.13: Total sum of patients' engagement with MDT community-based services stratified by level of caregiver burden

Community-based allied health professionals did not engage more with the patients of low burdened caregivers compared to highly burdened caregivers, considering physiotherapy (p=.619), dietetics (p=.504), occupational therapy (p=.611), speech and language therapist (p=.504), visits from the public health nurse (p=.538), home visits from the MND nurse specialist (p=.938), or visits by the central remedial clinic nurse specialist (p=.463).

There was no significant difference in the availability of aids and appliances received e.g., physical or communication aids (figure 4.14), between patients based on whether their caregiver was experiencing low or high levels of burden (p>.05).

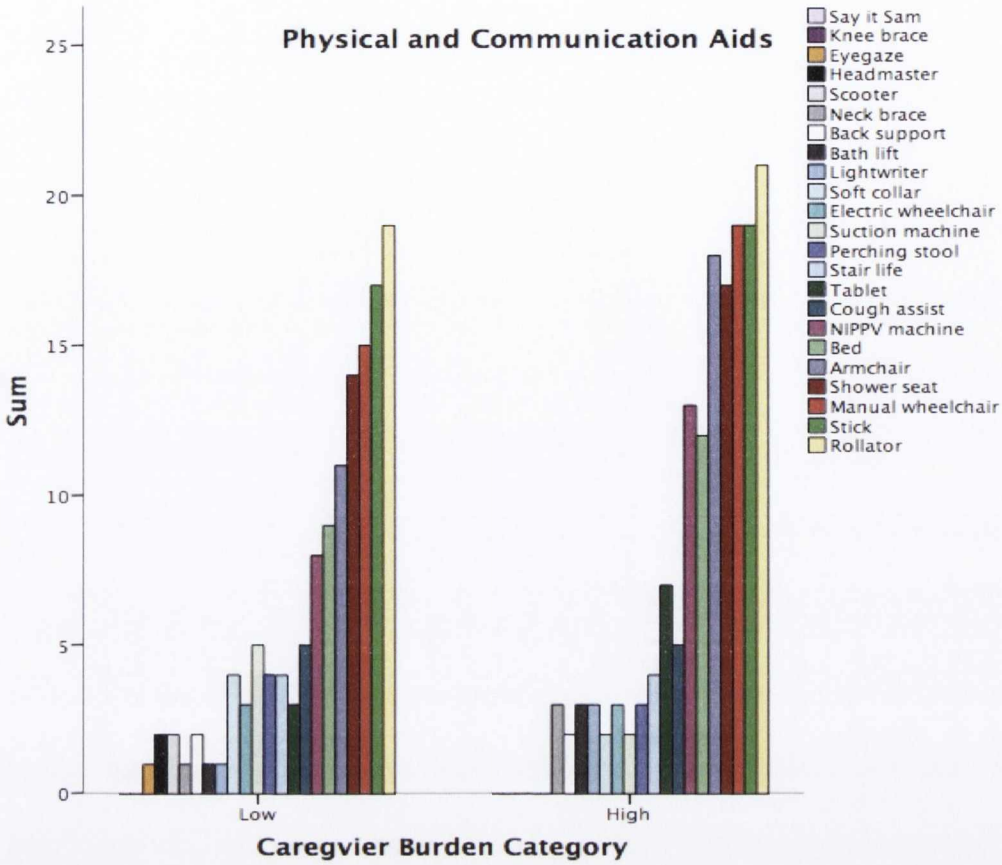


Figure 4.14: Total sum of patients' use of assistive technology (physical and communicative), stratified by level of caregiver burden

4.10.4.4 Gender Differences in Caregiver Burden

Considering the caregiver cohort as a total group, there was no significant difference in the total ZBI score when dichotomised by gender (p=.985). Males reported a mean of 26.76 (SD±14.66) and Females reported a mean ZBI of 26.70 (SD±14.11). Within the low burdened group, dichotomizing gender did not yield a significant difference on the ZBI (p=.865); in the high burdened group there was also no effect of caregiver gender (p=.644).

4.10.4.5 Survival and Caregiver Burden

Patients' disease trajectory, as measured by disease progression and outcome did not correlate with level of burden experienced by their caregiver. Equally, the disease trajectory from interview to death does not significantly impact caregiver burden. Log rank (Mantel-Cox), Breslow, and Tarone-Ware comparisons of the equality of survival distributions dichotomised by level of caregiver burden were non-significant (p=.373; p=.488; p=.446), as illustrated in figure 4.15.

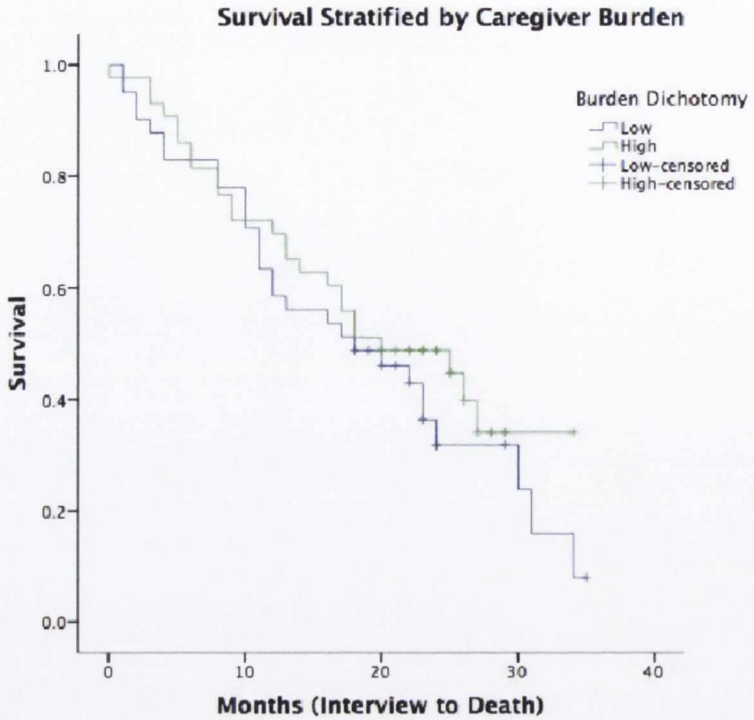


Figure 4.15: Kaplan-Meier survival analysis of patients with ALS from first interview to bereavement, dichotomised by level of caregiver burden.

4

.10.4.

5 Burden and QoL in Caregivers

The relationship between MQoL-SiS (Single-Item Scale) and caregiver burden can be seen in Figure 4.16. Caregivers were matched for age (low: 56.76±9.86, high: 57.44±11.32; p=.810) and gender (30% male; p=.06) when stratified by level of burden. As seen in Table 4.26, caregivers classified as having high caregiver burden had a significantly lower Quality of Life, and significantly higher anxiety, and depression.

Table 4.26: Caregiver self-report measures

Variable		Low Burden (N=41)	High Burden (N=43)	p
Zarit Burden Interview (ZBI)§	*M*±*SD*	14.70±5.53	38.13±10.43	**<.001**
HADS-Anxiety[1]	*M*±*SD*	7.80±4.04	10.88±4.13	**<.001**
HADS-Depression	*M*±*SD*	3.78±2.49	7.53±3.87	**<.001**
HADS-Distress/Total	*M*±*SD*	11.5±5.62	18.41±6.79	**<001**
McGill QoL-SIS	*M*±*SD*	6.93±1.66	4.74±1.90	**<.001**

§ ZBI variable used to dichotomised patients into high/low groups.

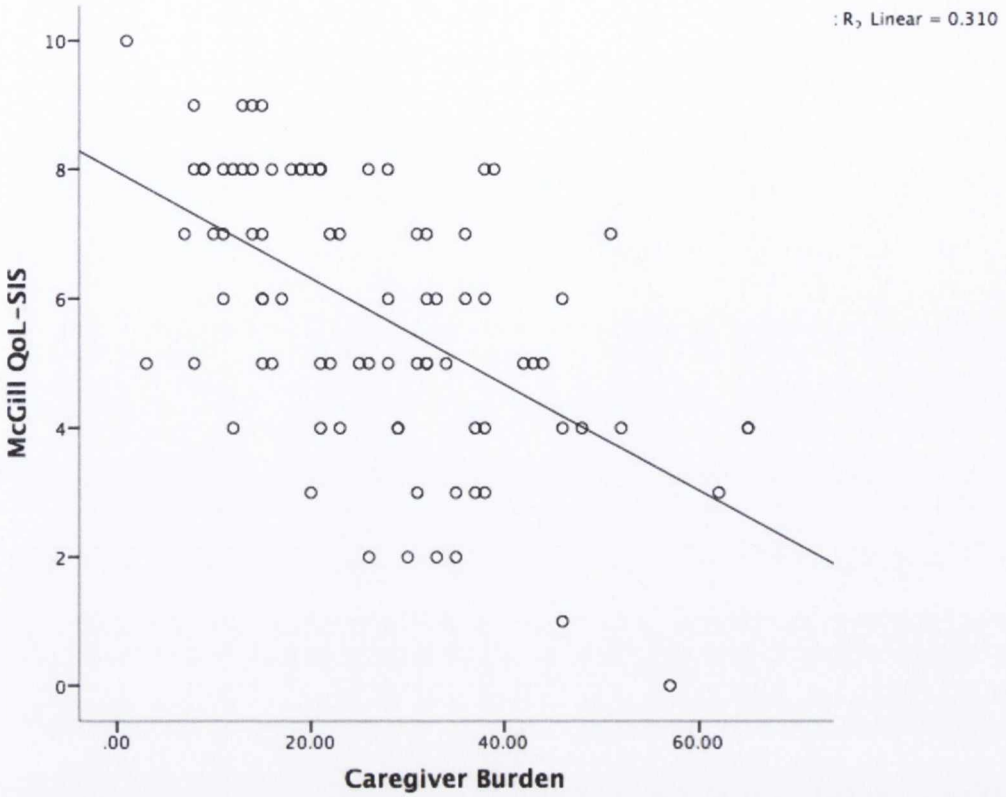


Figure 4.16: The relationship between quality of life and caregiver burden. This graph illustrates the linear relationship between low quality of life and high caregiver burden.

The ZBI was stratified into personal strain, role strain, and guilt factors, as noted above. Levels of personal strain and role strain were significantly higher in caregivers who were identified has having high burden according to their total ZBI endorsement ($p<.001$; $p<.001$). The items representing guilt were not significantly different between groups ($p=.391$).

All caregivers completed the McGill QoL questionnaire. All caregiver endorsements on this measure were initially stratified based on patient MITOS stage, in order to assess whether disease stage had an impact on QoL. There were no significant differences on QoL when stratified by patients' physical status alone. However, caregiver QoL was significantly lower in the high burden group when stratified by ZBI, compared to participants in the low burden group. Table 4.26 shows that QoL is significantly lower in the high burden group at an itemised level, using the McGill QoL questionnaire with multiple comparisons considered.

Table 4.27: Summary of caregiver QoL, dichotomized by burden *M±SD*.

McGill Quality of Life Item	Low Burden (n=41)	High Burden (n=43)	p
Considering all parts of my life- physical, emotional, social, spiritual and financial - the quality of my life has been: (0=bad; 10=excellent)	6.93±1.66	4.74±1.90	**<.001**
How big a problem was 'troublesome symptom 1'?	4.44±2.14	5.64±2.27	.069
How big a problem was 'troublesome symptom 2'?	6.00±3.31	5.58±1.77	.699
How big a problem was 'troublesome symptom 3'?	5.00±3.00	6.33±2.73	.524
Over the past 2 days, physically I have felt:	7.54±1.77	5.84±2.28	**<.001**
I have been depressed: (0=disagree 10=agree)	2.15±2.59	4.44±2.68	**<.001**
I have been nervous or worried:	3.07±2.59	4.81±2.51	**<.002**
How much of the time did you feel sad?	3.22±3.00	4.51±2.42	**.033**
When I think of the future I am constantly terrified	4.24±2.55	5.65±2.89	**.021**
My personal existence is utterly meaningless and without purpose	7.76±2.10	6.53±2.22	**.012**
When I thought about my whole life, I felt that in achieving life goals I have progressed to fulfilment	6.66±2.38	5.56±2.25	**.032**
When I thought about my life, I felt that my life to this point has been worthless/ worthwhile	8.46±1.41	7.09±2.23	**.001**
I have felt that I have no control over my life	6.76±2.40	4.42±2.40	**<.001**
I felt good about myself as a person	7.46±1.76	6.49±2.13	**.025**
To me, every day seems to be a gift	7.80±1.75	5.91±2.15	**<.001**
The world is a caring and responsive place to my needs	7.45±2.03	5.88±2.15	**.001**
I feel completely supported	8.34±1.65	5.58±2.57	**<.001**

Participants were prompted to consider their responses over the last 2 days as per instruction.

4.10.5 Discussion

The aim of this study was to investigate objective and subjective aspects of burden experienced when caring for a person with ALS. Burden was dichotomised into high burden and low burden groups, with personal, role, and guilt factors examined.

The findings suggest that in a cohort of matched patients and caregivers, caregivers' experience of burden is associated with high anxiety, high depression, and reduced quality of life to a greater extent than with disease-specific variables as manifest by the patient.

Demographics (including age of onset, site of onset, cognitive function, respiratory function, bulbar or spinal symptomatology, and weight,) of those patients cared for by high burden caregivers did not differ from those cared for by low burden caregivers. Neither did additional external factors such as additional formal homecare, finances, healthcare resources (occupational therapy, physiotherapy, speech and language therapy, and dietician), or emergency department, inpatient-, or outpatient-visits correlate with burden. This implies that although community-based health-services were equally utilised by both patient cohorts, a discrepancy remained in the severity of burden experienced by some caregivers. These data confirm that approximately 50% of caregivers of patients with ALS, who are clinically matched by age, onset, cognition, and ALSFRS-R, may experience clinically significant levels of burden requiring psychological intervention.

Survival data were captured using the Irish ALS register [48]. It has been previously been demonstrated that patient survival is not significantly implicated by caregiver burden [39], and we confirm this with our larger patient cohort in which we show that survival curve is not significantly different at the beginning (Tarone-Ware comparison p=.446), middle (Breslow comparison p=.488), or end (Mantel Cox comparison p=.373) when stratified by caregiver burden. These data demonstrate that caregiver burden is not a function of a more rapid disease trajectory.

Dichotomised by levels of burden, our data suggest that caregivers experience significantly lower quality of life in the high burden group, but not when stratified by MITOS stages. This implies that the experience of caregiving negatively impacts QoL in this cohort, rather than the characteristics or trajectory of the disease. Based on these findings, we speculate that resilience, coping style, premorbid personality, and informal support networks are important in the provision of protective factors safeguarding low burdened caregivers.

Future studies could further investigate whether low-burdened caregivers differ in their coping styles, resilience to stressful situations, or whether their interpretation of stressful events differs, and longitudinal analyses will be required to investigate whether role strain and personal strain differs over time, and indeed whether guilt becomes a significant factor. Future research could also consider the cognitive function of caregivers.

Limitations to this study include the cross-sectional profile reported, as well as a basic caregiver profile. These data are also specific to a cohort of patients who performed within an average range on cognitive testing. In conclusion, our study demonstrates that management of

caregiver burden will require targeted intervention aimed specifically at anxiety management, resilience-based strategies, and interventions known to improve QoL in caregivers and patients with neurodegenerative conditions.

4.11 Caregiver Burden in ALS: Elucidating the Trajectory of Psychological Distress

The final study contained within this thesis investigated the trajectory of caregiver burden longitudinally. Based on our previous findings contained within this thesis i.e., that anxiety and depression predict caregiver burden, we sought to examine the role of psychological distress (anxiety and depression) over the disease trajectory. This study is outlined as follows:

This study has been submitted to the Journal of Neurology

4.11.1 Abstract

Objective: Caregiver burden is a recognised consequence of caring for a patient with neurodegeneration. Amyotrophic Lateral Sclerosis (ALS) differs from other neurodegenerations by its rapid progression and impairment of motor, cognitive and behavioural function, which contribute to predictable levels of caregiver burden. However, factors that determine the extent of caregiver burden, and particular the impact of psychological distress among caregivers has not been established.

Methods: Patients with ALS (n=85) and their primary caregivers (n=85) completed three serial evaluations. The impact of providing care for ALS on caregivers was measured using the Zarit Burden Interview (ZBI). Anxiety and Depression were evaluated using the Hospital Anxiety and Depression Scale (HADS). The Edinburgh Cognitive-Behavioural ALS Screen (ECAS) was used to determine cognitive and behavioural function in patients. The ALS Functional Rating Scale (ALSFRS-R) measured disease progression.

Results: Using the ZBI, caregivers were categorised as high or low burden, based on statistically derived cut-off scores. In the low burden group the anxiety score from the HADS predicted caregiver burden (r= .410, F= 3.73, p= .033), whereas the depression sub-score from the HADS was predictive of caregiver burden in the high burden group (r=. 501, F=5.87, p=. 006). These findings were consistent among those who were followed longitudinally.

Conclusion: In a patient cohort with relatively preserved cognitive and behavioural function, anxiety was the best predictor of caregiver burden. This observation provides a mechanism by which caregiver burden can be identified by healthcare professionals and a programme of intervention initiated.

4.11.2 Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressive neuromuscular condition implicating cognitive function and resulting in behaviour change (Phukan et al., 2012). Cognitive impairment in ALS can occur in up to 40% of patients (Elamin et al,. 2013), with Frontotemporal Dementia (FTD) present in an additional 10-15% (Byrne et al., 2012). Moderate to severe behavioural impairment, in the absence of FTD, is known to occur in up to 40% of patients (Lillo et al., 2011). Cognitive impairment and behavioural dysfunction are independently associated with a more rapid disease trajectory, compared to those with an intact cognitive profile (Elamin et al., 2011).

The burden of care associated with ALS patients has received much attention in recent years, with investigations focusing on protective factors (Marconi, Gragnano, Lunetta, et al., 2015; Pagnini, Philips, Bosma, Reece, & Lange, 2016), predictors (Burke et al., 2015), and caregiver burden interventions (Mioshi et al., 2013). Neuropsychiatric and behavioural changes in patients are known predictors of increased caregiver burden (Caga, Turner, Hsieh, et al., 2016; Chio et al., 2005; Mioshi et al., 2014; Rabkin et al., 2000). However, less is known about the burden on caregivers when patients are cognitively and behaviourally intact (Thommessen et al., 2002). The presence of psychological distress in the caregiver i.e., anxiety and depression, may contribute to burden (Gauthier et al., 2007), although it is unclear as to whether psychological factors among caregivers results from, or are causative of caregiver burden (Lerum, Solbrække, & Frich, 2016), especially when considering the clinical heterogeneity of the disease trajectory (Foley, Timonen, & Hardiman, 2016). To date, investigations of caregiver burden have been limited by a cross-section research design (Burke et al., 2015; Chio et al., 2004), and few longitudinal ALS studies determine the progression and fluctuations of caregiver burden throughout the disease (Lerum et al., 2016).

4.11.3 Methods

4.11.3.1 Participants

Participants were recruited as part of an on-going longitudinal population-based investigation into caregiver burden. ALS patients recruited to this study (n=85) were diagnosed with probable, or definite ALS, according to the revised El Escorial Criteria (Brooks et al., 2000). The MITOS system was used to categorise stage of disease. According to this staging system, patients with ALS are categorised as Stage 0, functional involvement but no loss of independence on any domain; Stages 1-4, number of domains in which independence was lost

i.e., movement, swallowing, communicating, and/or breathing; and Stage 5, death. For the purpose of this study, stages 0-4 inclusive were utilised as grouping variables.
Assessments were conducted on 3 occasions at 4-month intervals. Information on patients' cognition, and the severity of physical impairment was obtained at baseline, and after two four-month intervals (n=58; n=42). Exclusion criteria included a history of other neurologic, psychiatric or medical conditions that can affect cognition, alcohol dependence syndrome, and/or the use of high-dose psychoactive medications. Neuropsychological and clinical data were collected through clinic-based assessments and home visits.

Primary caregivers were interviewed at the time of the patient's initial assessment (n=85), and on a further two occasions at four-month intervals (n=58; n=42). Measurements of caregiver burden were obtained from caregivers, as was proxy information on patient behavioural changes.

4.11.3.2 Measurement Tools

The Zarit Burden Interview (ZBI: Zarit et al., 1980) was used to assess subjective caregiver burden, where a score ≥24 indicates burden (Schreiner et al., 2006). For the purpose of this study, caregivers with a score of ≥24 were defined as being in a 'high burdened' group. This methodology has accurately predicted determinants of caregiver burden in ALS (Burke et al., 2015). Detailed psychometric information regarding the ZBI has been previously reported (Ankri et al., 2005).

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS: Abrahams et al., 2014) is a brief multi-domain cognitive screening tool designed specifically to assess patients with ALS. The ECAS investigates a range of cognitive domains to capture the heterogeneity of cognitive impairment in ALS. It is divided into two sections: one considering cognitive domains reported as affected in ALS (ALS Specific i.e., Language, Executive Function, & Verbal fluency) and another including cognitive domains reported to be relatively preserved in ALS (ALS Non-Specific i.e., Memory and Visuospatial skills). ALS specific components are scored out of 100, with a combined total score of 136. The ECAS is a unique screening tool in that it accommodates for both limb and bulbar related motor disability. It also includes a structured carer interview investigating the presence of behavioural changes based on FTD diagnostic criteria (Strong et al., 2009).

The Hospital Anxiety and Depression Scale (HADS: Moore et al., 1991; Norton et al., 2013)

was used as a statistically reliable measure comprising of two subscales measuring Depression (HADS-D) and Anxiety (HADS-A).

Progression of ALS was measured using the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R: Cedarbaum et al., 1999). This scale quantifies bulbar, spinal, and respiratory symptoms and summed to provide a total ALSFRS-R score (range 0-48). A higher score indicates better function.

This study was granted ethical approval from Beaumont Hospital Medical Research Ethics Committee. Informed written consent was obtained from all participants in this study (N=189).

4.11.3.3 Statistical Analysis

Comparisons of descriptive variables were made using independent sample t-test, and simple linear regressions were employed to investigate significant predictors of caregiver burden. According to power calculations, our sample per group met requirements to detect robust significance at a medium effect size (G*Power: n ≥26), with Holm-Bonferroni analyses used to correct for multiple comparisons, where relevant. The distribution of the data was homoscedastic for the principal dependent variables. All tests were performed with an alpha value at 0.05. Statistical analyses were performed using SPSS version 21 (IBM Corp, 2012).

4.11.4 Results

4.11.4.1 Clinico-demographics

Information relating to patient-caregiver dyads is summarised cumulatively, and sub-categorised based on the level of burden experienced by the caregiver i.e., high/low. ALS patients (n=85; 51 male, 60%; 59 spinal-onset, 69.4%) had a mean age of 63.88 (SD ± 11.23; range 35-87), 12.26 months (SD ± 11.71) from diagnosis to baseline assessment. A mean ALSFRS-R of 32.94 (SD ± 8.25) was recorded at baseline. Using the ALSFRS-R sub-score bulbar symptoms averaged 9.19 (SD ± 2.79), with mean spinal symptoms 13.67 (SD ± 5.96). Respiratory symptoms were reported at an average of 10.07 (SD ± 2.63). MITOS staging criteria categorised 57% of patients at Stage 0 of the disease, 25% at Stage 1, 16% at Stage 2, and 2% at Stage 3, as per standardised protocol. On a group level at baseline, MITOS staging categorisations did not significantly impact the ZBI endorsement as reported by caregivers when analysed using ANOVA (p=. 688).

Primary caregivers (n=85; 29% male) had a mean age of 54.77 (SD ± 13.16; range 25-76). At the initial assessment, 63 caregivers were spouses (74.1%), 16 were children (18.8%), and 6 were other relatives (7.1%). Additional care from external services was available on average for 3.6 hours ±7.12 (range 0-40) for ALS patients. Additional demographic, clinical, and stratified longitudinal group data are presented in Tables 4.28 and 4.29 (overleaf).

The mean ZBI score for all caregivers was 26.74 (SD ± 14.36). Participants were categorised with clinically significant burden if their ZBI score was ≥24. Caregivers who were categorised as 'Low-Burden' (a total ZBI score from 0-23 inclusive) reported a mean ZBI score of 14.70 (SD ± 5.53). The 'High-Burden' (51.7%; n=44) group reported a mean of 38.13 (SD ± 10.43). A significant difference in burden was observed ($p< .000$).

4.11.4.2 Baseline Anxiety, Burden, Cognition, and Depression

At baseline, the average time from symptom onset to assessment was 30.73 months (SD±4.45) for low burdened caregivers, and 30.39 (SD±3.39) for high burdened caregivers ($p=. 951$). Time of diagnosis to baseline assessment was also not significantly different between high and low burden groups ($p=. 840$).

Similarly, disease severity, as measured by the ALSFRS-R, was not significantly different when stratified by level of burden ($p=. 469$). The two groups of patients, stratified by level of caregiver burden, did not differ statistically on the sub-domains of the ALSFRS-R i.e., bulbar ($p=. 532$), spinal ($p=. 918$), or respiratory ($p=. 057$) function.

Table 4.28: Demographic, Clinical, and Interview Data for patients.

ALS Patients	Time 1				Time 2				Time 3			
	Total Patient n=85	Low Burden n=41*	High Burden n=44*	*p*	Total Patient n=58	Low Burden n=20*	High Burden n=38*	*p*	Total Patient n=42	Low Burden n=15*	High Burden n=27*	*p*
Males n(%)	51 (60%)	24 (58.5%)	27 (61.4%)	.222	38 (65.5%)	17 (85%)	21(55.3%)	.349	29 (69%)	12 (80%)	17 (63%)	.458
Age^	63.88±11.23	63.56±10.19	66.12±10.98	.272	63.82±10.74	63.68±9.98	65.55±10.43	.983	63.29±9.83	62.00±9.39	64.71±9.53	.306
Spinal Onset n(%)	59 (69.4%)	25(65.80%)	32(72.7%)	.138	45(77.5%)	14(70%)	31(81.6 %)	.327	33(64.7%)	12 (80%)	21(77.8%)	.913
ALSFRS-R Total^	32.94±8.25	33.63±8.35	32.14±8.27	.469	30.79±8.71	31.82±9.73	30.17±8.26	.629	30.11±8.86	27.63±9.88	31.91±8.04	.633
ALSFRS-R Bulbar^	9.19±2.79	9.37±2.62	9.02±2.97	.532	8.48±3.12	8.36±3.00	8.55±3.27	.876	8.00±3.84	8.40±4.39	7.77±3.76	.784
ALSFRS-R Spinal^	13.67±5.96	13.73±6.13	13.61±5.91	.918	11.96±6.48	11.90±8.31	12.00±5.43	.973	9.41±6.44	8.25±5.50	10.00±7.15	.679
ALSFRS-R Respiratory^	10.07±2.63	10.68±2.45	9.52±2.70	.057	9.96±2.32	10.45±2.38	9.66±2.30	.385	8.71±347	7.60±4.27	9.33±3.04	.392

*Patient information stratified by the level of caregiver burden at Time 1 as measured by the ZBI – low burden 0 to 23, high burden 24 or higher; ^Mean (SD).

Table 4.29: Demographic, Clinical, and Interview Data from Caregivers

Primary Caregivers	Time 1				Time 2				Time 3			
	Total Caregiver n=85	Low Burden n=41	High Burden n=44	*p*	Total Caregiver n=58	Low Burden n=20	High Burden n=38	*p*	Total Caregiver n=42	Low Burden n=15	High Burden n=27	*p*
Males n(%)	25(29%)	14(34.1%)	11(25%)	.820	18(31%)	5(25%)	13(34.2%)	.275	13(31%)	8(53.3%)	5(18.5%)	.504
Age	54.77±13.16	56.28±11.12	53.36±14.80	.304	57.91±10.51	57.95±9.77	58.05±11.11	.964	61.41±8.36	63.53±7.31	60.19±8.81	.222
Hours of Care ^	46.17±47.33	29.33±37.29	60.84±49.08	**.002**	57.54±51.03	49.28±53.91	58.99±47.13	.481	50.33±42.85	33.36±37.50	59.13±43.43	.067
HADS: Anxiety^	9.42±4.33	7.80±4.04	10.88±4.13	**.001**	9.48±4.62	7.52±4.53	10.52±4.43	**.020**	9.66±4.45	6.93±4.51	11.18±3.69	**.002**
HADS: Depression^	5.73±3.77	3.78±2.49	7.53±3.87	**<.000**	5.28±2.94	3.80±2.39	6.13±2.93	**.003**	5.90±3.46	4.13±2.61	6.88±3.52	**.012**
HADS: Distress^	15.10±7.08	11.5±5.62	18.41±6.79	**<.000**	14.74±6.79	11.15±6.05	16.65±6.51	**.003**	15.57±7.03	11.06±6.31	18.07±6.18	**.001**
ZBI^	26.74±14.36	14.70±5.53	38.13±10.43	**<.000**	30.12±13.57	15.65±4.95	37.73±9.92	**<.000**	30.59±13.62	18.06±5.35	37.55±11.67	**<.000**

Bolded text represents significance considering multiple comparisons. ^Mean (SD)

Caregivers had a mean anxiety score of 9.42 (SD ± 4.33) as measured by the HADS-A. There was a significant difference (p=. 001) observed between the high burden group (mean 10.88 SD ± 4.13), and the low burden group (mean 7.80 SD ± 4.04). Symptoms of depression, as measured by the HADS-D were reported (5.73 ± 3.77) for the total caregiver cohort. A significant difference (p<. 000) was observed when dichotomised between the high burden (7.53 ±3.87) and low burden (3.78 ±2.49) groups.

The difference in the total, ALS Specific and ALS-Non-Specific ECAS score of patients was not statistically different (p=. 673) between those who were highly burdened (95.67 ±19.78), or those experiencing low burden (93.46 ±23.39). The proxy behavioural component of the ECAS did not categorise patients as behaviourally impaired.

Patient gender was not found to be a significant contributory factor to caregiver burden (p=. 985), nor was the relationship type (p=. 399). Lower burden was reported when the caregiver was a patient's child (25.33 ±14.04), compared to a spouse (28.74 ±13.83).

4.11.4.4 Longitudinal Analyses

Patient attrition occurred from baseline to the first follow-up (average 5.2 months±1.2), with a retention rate of 68.2% (n=58). There was no significant difference between the patients who remained in the study for Time 2 repeat assessment with respect to ALSFRS-R total (p=. 956), ECAS (p=. 510), age at baseline assessment (p=. 248), time from diagnosis to assessment (p=. 511), or the ZBI endorsed by their caregivers (p=. 630). Neither were there significant differences in the time from diagnosis to Time 2 assessment at first follow-up, when stratified by level of burden (p=. 584) for those who remained in the study. At Time 2, 43.1% of patients were at Stage 0 using the MITOS criteria for ALS staging, 33.3% were Stage 1, 17.6% were Stage 2, and 5.9% were in Stage 3. Consistent baseline results, there was no significant difference at a group level on caregiver burden based on MITOS stratification (p=. 569).

At the third assessment, the retention rate was 49.4% of the original patient cohort (n=42). The time interval between testing was 4.6 months (SD±1.15) between Time 2 and Time 3. There were no significant differences between the patients who remained in the study for their Time 3 assessment on the ALSFRS-R total (p=. 997), ECAS (p=. 352), age at Time 2 assessment (p=. 092), time from diagnosis to assessment (p=. 423), or their caregivers' reported ZBI (p=. 620). Time from diagnosis to Time 3 assessment did not significantly differ

when stratified by burden (p=. 604). Caregiver burden was not significantly different when stratified by MITOS staging (p=. 696), with 25% at Stage 0, 50% at Stage 1, 19% at Stage 2, 3% at Stage 3, and 3% of ALS patients at Stage 4.

Caregiver attrition was closely linked to patient attrition with 68.2% retention (n=58) from baseline to the first follow-up, and 49.4% retention rate from the original cohort (n=42). At first follow-up 65% of caregiver participants experienced high levels of burden, and 64% at the third evaluation. Figure 4.17 illustrates the reported burden of caregivers across each time-point.

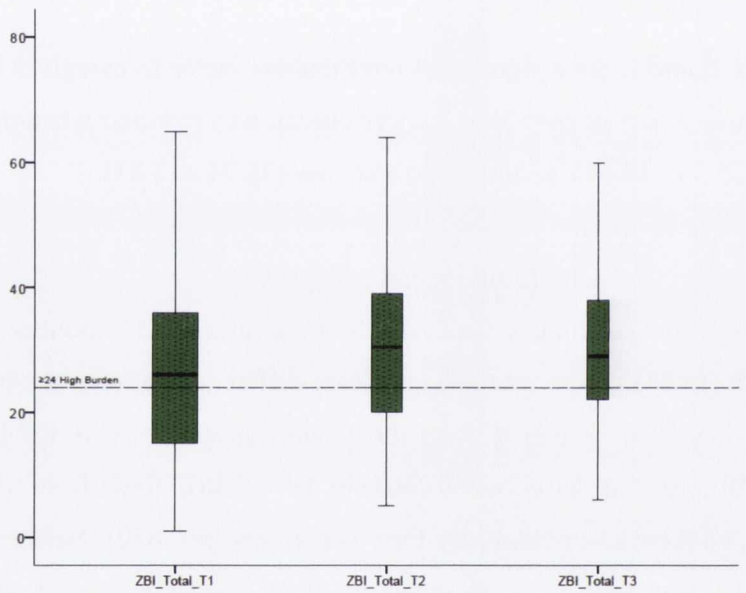


Figure 4.17: Longitudinal representation of caregiver burden. T1 n=85; T2 n=58; T3 n=42. The dashed line, and above, represents clinically significant burden.

At Time 2, the ZBI was significantly different (p<. 001) between those initially categorised as high burden (37.73 ±9.92) compared to low burden (15.65 ±4.95). Burden remained significantly different (p<. 001) between the high burden group, and those characterised as having low burden (37.55 ±11.67; 18.06 ±5.35, respectively) at Time 3. An itemised breakdown of the ZBI can be seen in Table 4.30 (overleaf). Similarly, follow-up performance on the ECAS by patients with high burden caregivers (101.66 ±16.78) did not significantly differ (p=. 480) from those with low level of burden (94.00 ±28.59).

4.11.4.4 Cross-Sectional and Serial Predictors of Burden

Among caregivers in the low burden group at baseline, patient performance on the ECAS was not predictive of burden, considering the ECAS specific total (p=. 624), and non-specific total (p=. 840). Neither the ALSFRS-R total score (p=. 804) nor the HADS-D was predictive of burden (p=. 574). By contrast, the HADS-A was predictive of burden (R^2=. 168; F=3.73; p= .041) for the low burdened group.

At the baseline assessment for the high burden group, the HADS-D was predictive of burden (R^2=. 263; F=7.12; p=. 002). By contrast, neither the ALSFRS-R, ECAS or the HADS–A was predictive, however, the HADS-D was predictive of burden (R^2=. 263; F=7.12; p=. 002). Figure 4.18 illustrates the relationship between caregiver burden, anxiety, and depression.

Table 4.30: The ZBI itemised, and stratified by both time-point and level of burden.

ZBI Question	Time 1				Time 2				Time 3			
	Total Caregiver n=85	Low Burden n=39	High Burden n=46	*p*	Total Caregiver n=58	Low Burden n=20	High Burden n=38	*p*	Total Caregiver n=42	Low Burden n=15	High Burden n=27	*p*
Do you feel that your relative asks for more help than he/she needs?	1.08±1.16	.59±.894	1.53±1.22	**<.000**	1.24±1.07	.50±.761	1.66±.994	**<.000**	1.36±1.16	.93±.799	1.59±1.27	.079
Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?	1.54±1.28	.63±1.04	2.37±.846	**<.000**	1.53±1.13	.45±.686	2.13±.844	**<.000**	1.86±1.09	1.20±.862	2.22±1.05	**.003**
Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?	1.86±1.21	.97±.959	2.67±.778	**<.000**	2.05±1.13	1.30±.923	2.45±1.05	**<.000**	1.88±1.06	1.13±.915	2.30±.912	**<.000**
Do you feel embarrassed over your relative's behaviour?	.36±0.769	.17±.495	.56±934	**.021**	.53±.878	.20±.523	.71±.984	**.035**	.50±.969	.00	.78±1.12	**.011**
Do you feel angry when around your relative?	.79±0.927	.41±.706	1.16±.934	**<.000**	.80±.846	.35±.671	1.03±.854	**.003**	.74±.857	.53±.743	.85±.907	.253
Do you feel that your relative currently affects our relationship with other family members or friends in a negative way?	.96±1.149	.32±.650	1.56±1.20	**<.000**	.78±9.66	.25±.639	1.08±.997	**.001**	.81±1.06	.20±.561	1.15±1.13	**.004**
Are you afraid what the future holds for your relative?	2.95±1.01	2.73±1.09	3.16±.898	.052	2.76±.885	2.85±.988	2.71±.835	.573	2.74±.964	2.27±.594	3.00±1.03	**.016**
Do you feel your relative dependent on you?	2.75±1.24	2.07±1.27	3.42±.794	**<.000**	2.98±.991	2.45±1.19	3.24±.751	**.003**	3.05±1.14	2.20±1.20	3.52±.802	**<.000**
Do you feel strained when you are around your relative?	1.15±1.04	.63±.829	1.65±.997	**<.000**	1.20±.979	.60±.754	1.50±.952	**.001**	1.33±.954	.73±.799	1.67±.877	**.002**
Do you feel your health has suffered because of your involvement with your relative?	.86±1.02	.24±.582	1.42±1.02	**<.000**	1.19±1.06	.40±.681	1.59±1.01	**<.000**	1.00±1.01	.40±.632	1.33±1.03	**.003**
Do you feel that you don't have as much privacy as you would like because of your relative?	.88±1.19	.27±.593	1.44±1.35	**<.000**	1.19±1.22	.30±.571	1.68±1.21	**<.000**	1.33±1.16	.67±.816	1.70±1.17	**.004**
Do you feel that your social life has suffered because you are caring for you relative?	1.53±1.30	.59±805	2.42±1.05	**<.000**	1.85±1.28	.75±.851	2.42±1.10	**<.000**	1.88±1.10	1.33±.900	2.19±1.11	**.015**
Do you feel uncomfortable about having friends over because of your relative?	.42±0.956	.15±.478	.70±1.20	**.008**	.55±.994	.00	.86±1.13	**.001**	.52±.994	.00	.81±1.14	**.009**
Do you feel that your relative seems to expect you to take of him/her as if you were the only one s/he could depend on?	1.56±1.53	.35±.622	2.67±1.26	**<.000**	1.71±1.48	.50±.889	2.29±1.33	**<.000**	1.83±1.44	1.13±1.24	2.22±1.42	**.017**
Do you feel that you don't have enough money to take care of your relative in addition to the rest of your expenses?	0.95±1.29	.56±896	1.35±1.49	**.005**	1.24±1.25	.65±.875	1.58±1.30	**.006**	1.26±1.28	.47±.743	1.70±1.32	**.002**
Do you feel that you will be unable to take care of your relative much longer?	.67±0.931	.20±.459	1.09±1.04	**<.000**	.95±1.00	.30±.657	1.32±.989	**<.000**	1.20±1.16	.50±.760	1.56±1.18	**.005**
Do you feel you have lost control of your life since your relative's illness?	1.36±1.28	.56±.923	2.09±1.10	**<.000**	1.75±1.26	.85±.988	2.21±1.16	**<.000**	1.67±1.18	.60±.737	2.26±.944	**<.000**
Do you wish you could leave the care of your relative to someone else?	.55±0.897	.07±.264	1.00±1.04	**<.000**	.56±.933	.00	.87±1.04	**<.000**	.71±.835	.53±.640	.81±.921	.301
Do you feel uncertain about what to do about your relative?	1.08±.996	.71±.901	1.44±.959	**.001**	1.27±1.01	.70±.801	1.61±.974	**.001**	1.31±1.07	.93±.799	1.52±1.15	**.090**
Do you feel you should be doing more for your relative?	1.12±1.02	1.05±.973	1.21±1.08	.477	1.32±1.10	1.10±1.16	1.42±1.08	.300	1.29±.891	.80±.775	1.56±.847	**.007**
Do you feel you could do a better job caring for your relative?	1.20±9.49	1.12±.842	1.30±1.03	.385	1.25±1.12	.85±1.04	1.50±1.13	**.037**	1.14±.899	.93±.799	1.26±.944	.265
Overall, how burdened do you feel in caring for your relative?	1.18±1.16	.37±.536	1.91±1.08	**<.000**	1.36±1.22	.30±.470	1.95±1.11	**<.000**	1.24±1.17	.64±.633	1.56±1.28	**.017**

Bolded text represents significance considering multiple comparisons.

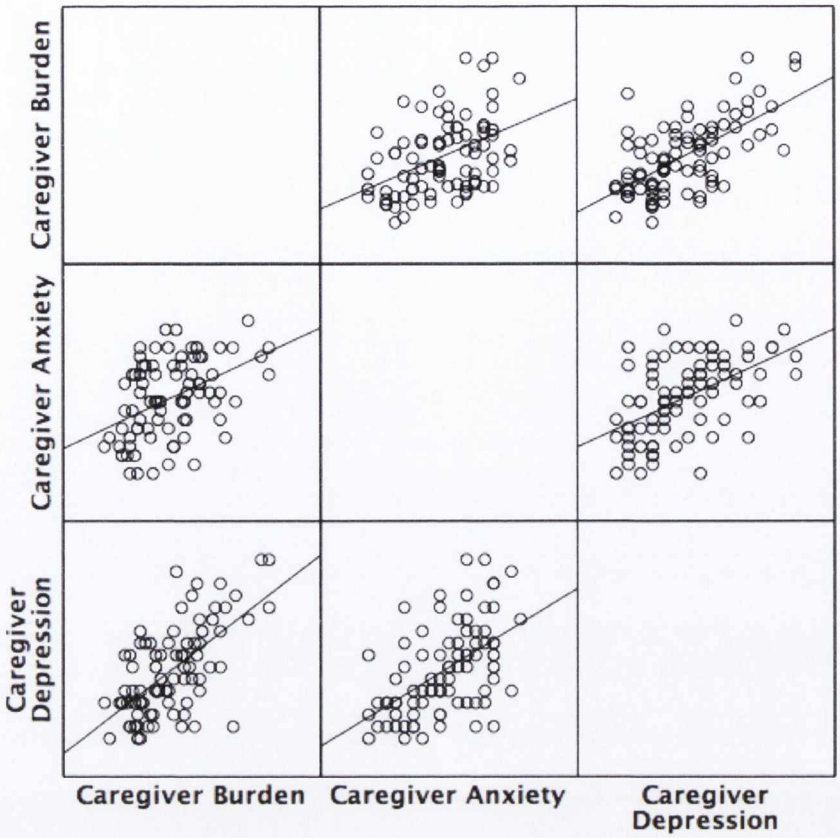


Figure 4.18: Correlation matrix of Burden, Anxiety, and Depression in caregivers at baseline.

Similarly, at the first 4-month follow-up assessment, he ECAS specific, ECAS non-specific, ALSFRS-R, and HADS-D remained non-significant predictors (p=506; p=. 949; p=. 199; p=874, respectively), and the HADS-A remained a significant predictor (R^2=. 513; F=8.43; p= .003) of caregiver burden. The predictive profile of high burden group remained constant, with the ECAS specific, ECAS non-specific, ALSFRS-R, and HADS-A yielding a non-significant predictive value (p=. 863; p=. 444; p=. 950; p=. 841 respectively). The HADS-D remained predictive of caregiver burden in the highly burdened group (R^2=. 251; F=5.83; p= .009). Figure 4.19 illustrates the relationship between caregiver burden, anxiety, and depression.

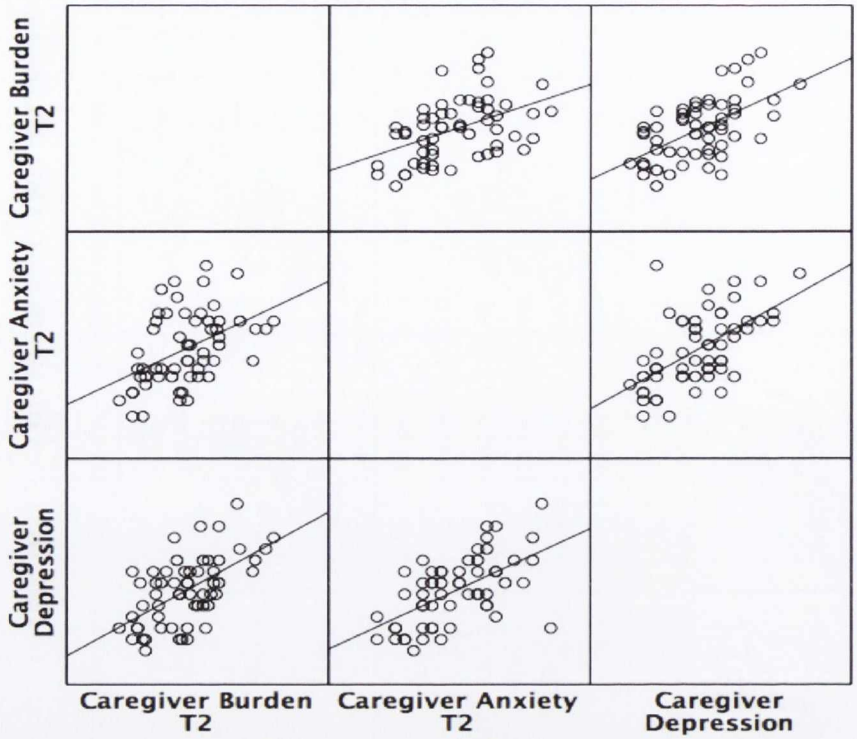


Figure 4.19: Correlation matrix of Burden, Anxiety, and Depression in caregivers at T2.

This pattern persisted at the third evaluation. For the low burden group, the HADS-A, but not the HAD-D was predictive of burden score (R^2=. 515; F=6.36; p= .006). Conversely, in the high burden group the HADS-A was also a significant predictor (R^2=. 343; F=6.27; p= .005) of burden, but not HADS-D (p=. 961). Figure 4.20 illustrates the relationship between caregiver burden, caregiver anxiety, and caregiver depression self-reports at T3. All remaining variables were non-significant predictors for both groups as documented above.

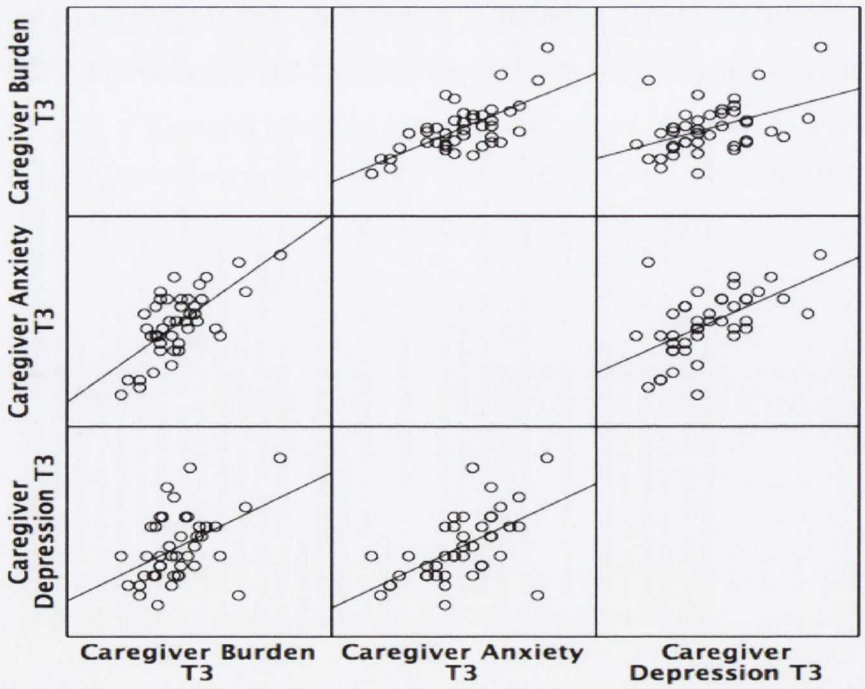


Figure 4.20: Correlation matrix of Burden, Anxiety, and Depression in caregivers at T3.

4.11.5 Discussion

This study investigated the role of psychological distress in relation to caregiver burden, considering the disease trajectory of ALS. These data suggest that burden remains constant throughout the disease, with little fluctuation, and confirms that anxiety and depression remain significant contributors to caregiver burden. This finding builds on previous cross-sectional methodologies (Burke et al., 2015; Choi et al., 2004), and those that have investigated the impact of severe behavioural impairment on caregiver burden (Chio et al., 2005; Mioshi et al., 2014).

Our findings are consistent with the literature, whereby anxiety and depression are significant predictors of caregiver burden in ALS (Gauthier et al., 2007). Novel findings include the role of anxiety as a significant predictor of caregiver burden early in the disease process, in a group who have clinically low burden i.e., before burden manifests into a clinically significant range. The prevalence of anxiety and psychological distress is persistent throughout the disease, and is predictive of burden at each time-point.

Neither cognitive performance, as measured by the ECAS, or the worsening disease profile as measured by ALSFRS-R sub-scores were predictive of caregiver burden. Caregiver burden did not change as the disease progressed, as demonstrated using the MITOS staging system These data suggest that the profile of caregiver burden relates more closely with subjective burden i.e., the caregiver's appraisal and perception of the caregiving role and tasks required. The observation that anxiety can be identified among caregivers who subsequently report high levels of caregiver burden implies that intervention strategies could be of benefit to this cohort early in the course of their caregiving experience (Marconi et al., 2015).

Skills training, psychoeducation, and anxiety management may be of considerable benefit in reducing caregiver burden, and consequently improving the Quality of Life of patient-caregiver dyads (Pagnini et al., 2016).

This study has limitations. These patients represent a cohort with high initial scores using the ECAS tool for cognitive and behavioural impairment. A more heterogeneous patient cohort experiencing cognitive and behavioural dysfunction would add to the clinical relevance of future studies, although many studies have reported the effects of cognitive/behavioural dysfunction (Caga et al., 2016; Mioshi et al., 2014). As with all longitudinal studies, there was a notable attrition between assessments. 32% of our baseline cohort did not engage at their scheduled follow-up appointment, due approximately 4-months later. Analyses of the patients' clinical and demographic data suggest that there were no significant differences

between those who dropped out of the study, with respect to ALSFRS-R, cognition, burden, or time since onset.

Our findings illustrate how caregivers for people with ALS experience significant anxiety, prior to clinically significant burden. In the absence of patient cognitive and behavioural dysfunction, this study confirms that psychological factors are cogent predictors of caregiver burden, requiring psychologically tailored interventions.

5.0 General Discussion

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5.2 Summary of Main Results

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- 5.2.2 Assessing Reliable Change
- 5.2.3 Atypical Social Cognition in HD
- 5.2.4 Discordance on Social Cognitive Performance in ALS
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- 5.5.1 Neuropsychological Assessment
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5.6 Conclusions

5.1 Introduction

The studies reported in this thesis have documented several findings relating to psychometric testing in neurodegenerative populations, the cognitive-behavioural profile of ALS patients, and the implication of patients' cognitive–behavioural change for the ALS caregiver. The hypothesis driven studies have focused on the interaction effect between executive dysfunction and social cognition. However, the data were gathered in a manner that facilitated the investigation of the reliability of the methodology being employed i.e., to question the reliability of executive assessment using a number of measures. These data allowed for a robust platform by which to test our hypotheses, study objectives, and research questions (for example, are commonly used assessment tools of social cognition applicable to an ALS cohort? or are the psychometrics of the tool reliable given the ALS-FTD spectrum?). The findings from these studies warranted further investigation. Cognitively impaired ALS patients showed greater social cognitive deficits, but it remained unclear as to the effects of executive functioning on the social cognitive tests. These data showed that bulbar-onset ALS patients demonstrate worse social cognitive performance, consistent with the executive dysfunction data. Considering this, this thesis sought to investigate the impact of executive dysfunction on other cognitive processes, such as visual/verbal memory, using the cognitive categorisation method to stratify patient groups. This final chapter will provide a summary of the main findings from this research and discuss the clinical and theoretical implications for the management of patients and their caregivers. The limitations of the current study are acknowledged and recommendations for future ALS research are considered.

5.2 Summary of Main Results

5.2.1 Repeating Neuropsychological Measures

This investigated the feasibility of serial testing, from a psychometric perspective, on commonly used measures of executive function. We investigated whether performance changed (2-tailed), at a statistically significant rate over a 12-month period in healthy controls. FSIQ was used as a covariate.

Our main effects for this sub-study showed that controls did not significantly improve or worsen, when their performance was assessed over time on commonly used measures of executive function. Controls completed a baseline assessment, and then two follow-up assessments, where executive performance was the main focus of the battery. The control cohort did not significantly improve over time. On a commonly used measure of working memory, controls performed with high consistency over time (Reverse Digit Span: p=.70).

Controls were also measured on a task of rule attainment and cognitive set-shifting, and were also found to be performing consistently over time (The Brixton Spatial Anticipation Test: p=.51). Letter fluency and cognitive flexibility were also assessed, and both were found to be consistent over time (VFI: p=.58; Stroop Colour Word Test: p=.55).

These data have important clinical implications for the results reported for ALS patients, and the tests examined are commonly used in ALS research. If a patient population with a neurodegenerative disease were to complete these assessments serially, and not decline over time, one could now reliably infer that their performance was due to a stable cognitive profile, rather than inflated performance as a result of practice effects. Burgess and Shalice (1996) posit that measures of executive function lose novelty over time, which compromises their utility in longitudinal research. This study challenges the views of Burgess and Shalice (1996).

When assessing practice effects Duff et al., (2005) argue that participants' performance may have been compromised due to age related cognitive decline on repeat assessment, and practice effects concealed this. This is a consideration that demands a cautious approach in any longitudinal research, however, this study only analysed data from participants at Time 3 (12-months after baseline), who completed all assessments. Therefore, if age related decline was occurring within the control cohort, it would be representative of the Irish populations aging profile. Secondly, the study objective being investigated was 2-tailed, and a significant drop in performance would have been identified. This study confirms and accepts that measures of executive function can be repeated over time without inducing negative implications.

5.2.2 Assessing Reliable Change

Considering an ALS cohort who are cognitively categorised as having "No Cognitive Abnormalities" (ALS-NCA), this sub-study sought to investigate whether statistically meaningful change was occurring, while remaining within the remit of ALS-NCA on repeat testing. This study used control data in order to standardise the expected variance between two testing time points. The overall aim was to assess whether sub-clinical cognitive changes could be reliably identified in ALS-NCA patients.

This study investigated baseline, and repeat performance on the Boston Naming Test (BNT), a commonly used measure of confrontational naming. This measure was chosen as there is an

increasing interest in language assessment in ALS, and this measure is widely employed within ALS research. Considering the Standard Error, Standard Difference, and test-retest reliability of the BNT, patient data from T2 was compared to their baseline performance. 32% of patients (n=8) exhibited performances that were above the 95% cut-off for significance. These data confirm that some patients with ALS-NCA are declining at a statically significant rate relative to their baseline performance on this measure of confrontational naming. Future research could build on the findings of this study through external validation on this commonly used measure, and by applying these formulae to other measures of cognitive function.

The results of this study do not support that ALS-NCA patients will have significantly lower performance on measures of cognitive function, specifically confrontational naming, when the Reliable Change Index formula is applied to patients in the present study. 32% of patients did experience a statistically significant decline, and therefore this research warrants further investigation with larger cohorts, and a greater range of cognitive assessments. Section 5.3 will discuss the theoretical and clinical implications of this study.

5.2.3 Atypical Social Cognition in HD: A Proof of Concept

An opportunity arose to examine these concepts, of executive function and social cognition, in a single case format. The patient was known to the service, and was known to have average executive function. This gentleman had a genetic diagnosis of Huntington's disease (HD), though did not meet the criteria for a clinical diagnosis at this time i.e., no overt motor features of HD. This case was of interest due to the similar underlying pathologies of ALS and HD, and similar cognitive profiles.

This man was undergoing psychological therapy, with intermittent neuropsychological evaluations, whereby his presenting complaint was social in nature. The patient was experiencing difficulty in maintaining relationships due to a new onset difficultly with inferring the intentions and emotional states of other people. Proxy reports confirmed his clinical presentation. It appeared, that this gentleman was experiencing difficulty with aspects of social cognition i.e., emotional processing, with an intact executive profile.

Social-affect deficits were found on facial, prosodic and cross-modal measures of emotional processing. Lower scores were noted on the more executively loaded subtests of the D-KEFS, which may be indicative of a progressive disease trajectory typically seen in HD. These data

illustrate how patients may present with deficits in emotional and social processing within the context of an otherwise cognitively intact profile. These data provide a rationale for investigating the role of executive dysfunction on social cognitive processes in other neurodegenerative diseases, namely ALS. These findings would suggest that one can process emotional prosody based on the language used, though may have difficulties with social cognitive processing if the semantic message and language are incongruent (e.g., a sad sentence said in an angry tone) or conflicting (e.g., a sad sentence said in a happy tone). Investigating these cognitive functions in this HD case allowed for an interesting feasibility assessment, and a proof of conceptual design. These data led to an interest in considering these processes in more detail in ALS patients, considering the cognitive and pathological profile of both ALS and HD, and investigating whether disease-specific features of ALS impact social cognitive performance.

5.2.4 Discordance on Social Cognitive Performance in ALS

A large cohort of ALS patients were recruited into this study to investigate whether performance on social cognition differed based on disease-onset. Considering the reading the mind in the eyes test accounts for motor disability during assessment, we examined aspects of the caudal degenerative model of ALS proposed by Bak and Chandran (2012), which hypothesised that bulbar-onset ALS patients may experience more severe cognitive deficits than spinal-onset ALS patients. In brief, the model proposed that ALS patients with bulbar-onset disease could present with greater cognitive impairment when compared to spinal-onset ALS patients, due to pathological onset and progression of bulbar-onset ALS.

This study found that bulbar-onset ALS patients may be more likely to experience social cognitive deficits compared with spinal onset patients, congruent with previous research on other tasks of executive function. These data suggest that Bak and Chandra's 2012 theory of caudal degeneration in ALS may implicate social cognition, and that these deficits are part of the disease process. Clinically, these findings confirm that disease-onset may be an important factor to consider when assessing cognitive function in ALS. The objective which was assessed in this study, stated that ALS patients would differ on measures of social cognitive performance based on disease characteristics, though further investigation is warranted to delineate the role of executive dysfunction on social cognition.

5.2.5 Measuring Social Cognition

From a theoretical perspective, the aim of this study was to investigate whether social cognitive processes decline alongside executive dysfunction. In order to generalise the findings of this thesis, this study also clarified a number of psychometric concerns surrounding the Reading the Mind in the Eyes Test (RMET). Our data suggests that this measure is of good psychometric standing, and a valid measure of social cognition in an Irish cohort. This was a priority to establish, as the RMET was initially developed for use with children with autism (Baron-Cohen et al., 2007).

This study also provides the first set of normative data available in Ireland for this measure, and internationally from a population-based control cohort. This study also shows that this measure is suitable for detecting impairment when used with ALS patients. Furthermore, this study documents that the RMET has an appropriate difficulty level, can discriminate between ALS patients who are cognitively intact, and those with ALS-FTD. On a group level, executive processes subsume social cognitive processes, and executive dysfunction predicts a decline in social cognitive processing. These data are particularly relevant given the on-going interest in social cognitive processes in ALS, and their potential utility as a marker for cognitive dysfunction. These findings may be integrated into a clinic based setting to assess whether a low score of the RMET is a sensitive and specific psychometric tool for detecting early stage ALS-FTD. Also, considering social cognition is impaired in ALS-FTD/FTD patients, it would be of value to investigate the relationship further between social cognition and behaviour change. The similarities and differences between executive dysfunction and a dysexecutive behavioural syndrome are discussed in Chapter 2, and the underlying concepts also apply to social cognition. Patients may perform well on cognitive assessments of social cognition, though their social behaviour may be impaired.

This study supports the primary hypothesis of this thesis. The Primary Hypothesis stated that executive function contributes to social cognitive processes in ALS. This data also show that individual items on the scale have excellent psychometric properties, which will be discussed further.

5.2.6 Multimodal Testing of Executive Function

There is a high importance placed on the assessment of executive function in ALS patients, throughout the natural history and progression of the disease. This study conceptualised the importance of assessment modality considering localised progression over time i.e., increased dysarthria/ reduced fine motor skill. Reflecting on this, a study objective was considered to

investigate the functional equivalence of measures of working memory, dichotomised based on whether they were presented verbally (requiring verbal responding), or visually (requiring tactile responding).

ALS patients were divided into groups of those who completed visual tasks (spatial span), and those who completed verbal tasks of working memory (digit-span). The main finding of this study was that reverse spans, from either visual or verbal modalities, appear to yield statistically equivalent results. Due to the integration of information from multiple modalities (visuospatial, temporal, motor), Spatial Span tasks are widely considered more difficult than Digit Span tasks, yet the literature is scarce around this in terms of an empirical justification. Our results, confirm this finding. Both patient cohorts performed similarly on the Intra-Extra Dimensional Set Shifting Task and The Brixton Spatial Anticipation Test ($p=.945$), and reverse tasks in both modalities ($p=.212$). By contrast, on the spatial tasks patients' scores reflected a higher task difficulty. Patients who completed the Spatial Span Forward (SSF) task, performed significantly worse than the matched group who completed the Digit-Span Forward (DSF) task ($p<.0001$). Variation of motor demands within each of the tasks were accounted for, as patients were matched by disease severity. These data suggest that the measures may be methodologically analogous, though the cognitive demands being placed on test-takers is significantly different. The additional executive component previously described in Chapter 2 may account for this, given that patients were required to not only remember the span length, but also temporal sequencing and span location. This study highlights the importance of considering the mediating role of executive (dys)function on many tests of cognitive performance. These data have both clinical and theoretical implications that are discussed in section 5.3.

This study examined whether working memory tasks through different modalities are functionally equivalent. This study found if a task invoked a high executive demand, then the performance was found to be functionally equivalent. However, if there was a discrepancy between the executive demands of the task, then modality was a confounding factor.

5.2.7 Executive Dysfunction Implicates Visual Memory

Having investigated the role of executive dysfunction on social cognition, the role of executive dysfunction on other cognitive processes was examined. Executive processes are an integral part of cognitive function, and a core feature investigated in ALS. Executive function is accepted as an integral component of cognitive models of visual memory (Brewin, &

Mersaditabari, 2013; Vingerhoets, Miatton, Vonck, Seurinck, & Boon, 2006), verbal memory (Eustache, & Desgranges, 2008), and working memory (Baddeley, 2000). The role of executive function in visual encoding is neatly explained by the extended hippocampal model (Gómez & Edgin, 2015), through the stratification of the corticostriatal system into four distinct, yet highly integrated loops (Seger, 2015). The extended hippocampal model states that the visual corticostriatal loop is involved in aspects of visual stimulus processing; the motor corticostriatal loop is involved in response selection; and the executive and motivation corticostriatal loops are involved in processing feedback and reward. The visual corticostriatal loop links temporal and occipital cortices with the body and tail of the caudate (Middleton & Strick, 1996; Webster, Bachevalier, & Ungerleider, 1993).

Visually related frontal lobe regions such as the ventro-lateral prefrontal cortex, which is implicated in visual working memory (Inoue & Mikami, 2007), also project to the body and tail of the caudate (Lau & Glimcher, 2007; for a detailed review of the role of corticostriatial degeneration in neurologic conditions, see Shepherd, 2013). Figure 4.21 illustrates recognised cortico-striatial loops within the literature, with the Caudate nucleus (Cn), Putamen (Put), Substantia Nigra (STN), Globus Pallidus externus (GPe), and Globus Pallidus internus (GPi) illustrated. Based on this model, the relationship between executive dysfunction and visual memory warrants further investigation within the context of a neurodegenerative condition with notable frontal lobe, hippocampal, and basal ganglia atrophy (Abdulla et al., 2014; Bede et al., 2013).

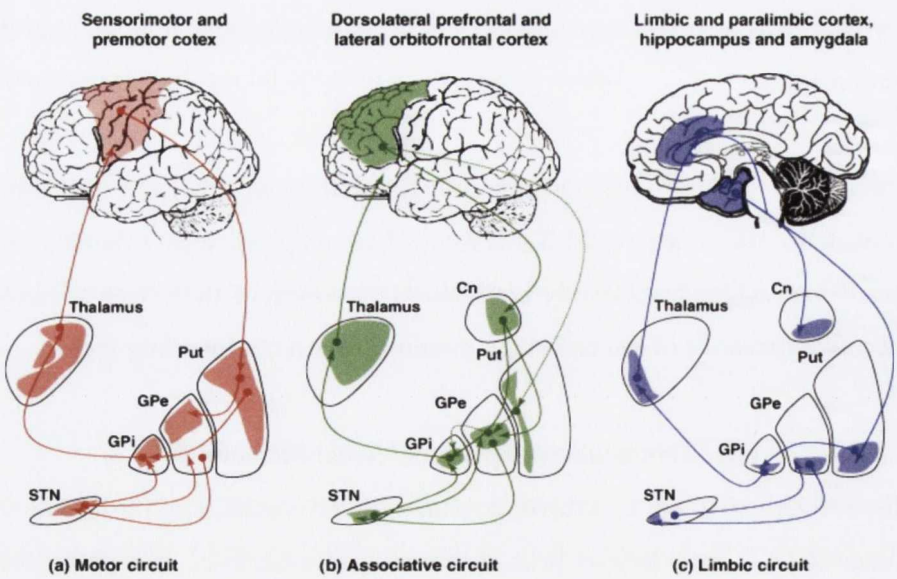

Figure 5.1: Cortico-striatial loops reported within the literature

Disrupted executive processes may impair encoding, consolidation, and retrieval on a memory-based task, the relative impact of executive dysfunction on memory was investigated. For this study, patients were categorised based on their cognitive performance on testing. Cognitive classifications were based on the severity of executive dysfunction as outlined by Phukan et al., (2011) i.e., no cognitive abnormalities, single executive deficit, and multiple executive deficits. Patients' performance on common measure of visual memory (ROCFT) was then investigated. The results of this study showed that greater executive dysfunction yielded more impairment on visual encoding, immediate recall, and delayed recall of the stimulus. This pattern of deficits was observed across all groups, with cognitively intact patients performance undistinguishable from controls. Patients and controls significantly differed on the copy trial, immediate recall, and delayed recall of the ROCFT. Post-hoc analyses were conducted in order to further delineate these differences, which revealed that greater executive dysfunction yielded lower ROCFT performance, which is consistent with the extended hippocampal model.

Another main finding from this study was the predictive nature of executive measures, and measures of current functioning on the ROCFT. Using regression analysis, we consider premorbid IQ, executive function, and demographics to predict performance on the ROCFT delayed recall trial (R^2 =. 833). These data question the suitability of the ROCFT in an executively compromised group, if the intention is to ascertain a metric of visual memory recall. Results from this study suggest that people with low years of education, lower than average current cognitive function, who are older, and perform poorly on measures of working memory, are predisposed to lower performance on the ROCFT. This study highlights the need to consider the role of executively demanding tasks in ALS research, when the desired outcome metric is not an executive function, but more broad areas of cognition. These findings support the anatomical model of the extended hippocampus. This research confirms that executive dysfunction contributes to performance on visual memory for ALS patients. This is most evident by the worsening performance on visual memory tasks, based on the severity of executive dysfunction, and highlights the need for executive function to be considered with every cognitive assessment.

5.2.8 Executive Dysfunction Influences Verbal Memory

The focus of many of the presented studies thus far has been to quantify the role of executive dysfunction across multiple cognitive domains, after stratifying by cognitive categorisation i.e., level of impairment. The negative consequence of severe executive impairment on non-

executive measures of cognitive function has been illustrated in the aforementioned study (see 5.2.7). This experiment stratified patients based on cognitive criteria, though then focused on patients classified as No Cognitive Abnormalities (ALS-NCA). Patients' scores were statistically lower on measures of executive function than those of healthy controls, at a significant level. Patient performance on a list-learning task was then profiled, and subtle findings were evident, reflective of those typically seen in executively impaired patients. Cognitively intact ALS patients' performance was significantly lower than controls on The Stroop Colour Word Interference Test, Digit-Span forward, The Brixton and Letter Fluency. On the California Verbal Learning Test-II, patients with ALS scored significantly lower than controls on the initial two free recall trials. On the short delay cued recall task, patients scored significantly lower than controls.

The main finding of this study illustrated that sub-clinical executive deficits could impact on other cognitive functions, such as verbal memory, while remaining within the remit of cognitively intact. This study confirms that cognitively intact ALS patients may perform slightly poorer on testing, using a cross-sectional analysis, evidenced by statistically lower performance when compared to matched healthy controls. This study considered whether cognitively intact patients perform significantly lower than controls on executive tasks, and aspects of memory tests, while remaining within the remit of ALS-NCA. This study confirms that patients with No Cognitive Abnormalities perform statistically lower than controls on executive measures, and that subtle changes are evident on other measures. This result is somewhat expected within the context of the current literature, as motor circuitry does not exist in isolation, but part of integrated networks (as illustrated above in figure 4.21). The relevance of executive function can be illustrated further in Figure 4.22.

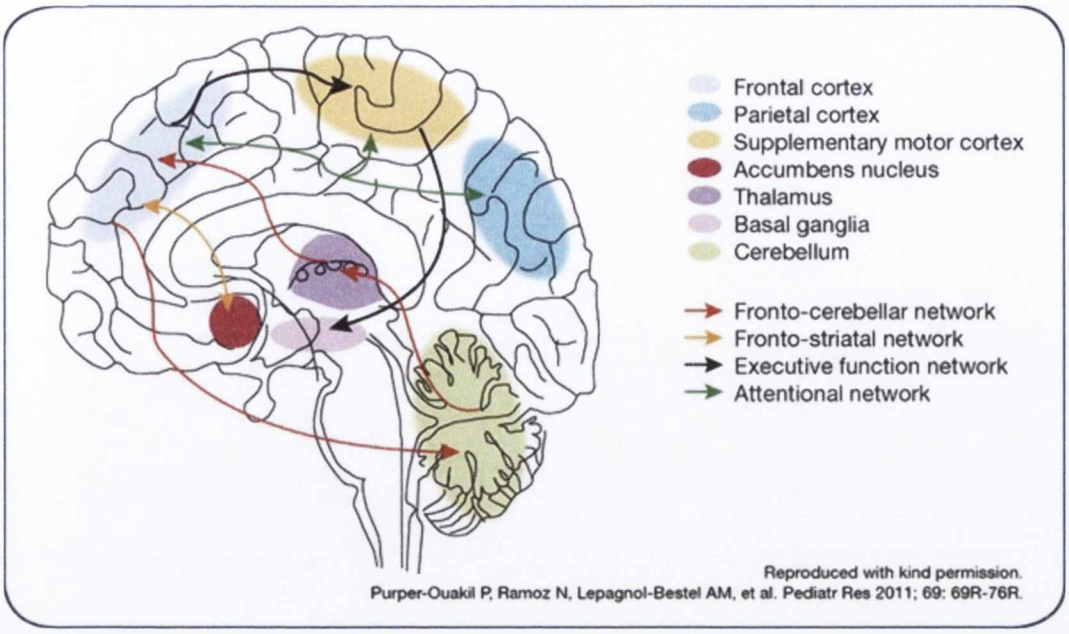

Figure 5.2: Functional and anatomical networks relating to frontal lobe function.

The studies, which have been reported on herein, detail the severity and range of cognitive impairment within the ALS patient cohort. ALS is a multi-systemic disease in terms of the degenerative process, but also when one considers the impact on the patient's family unit. Through clinic-based recruitment and home-based assessment, it was clear that more focus was needed to investigate the complex needs of caregivers.

5.2.9 Caregiver Burden and Predictors

The extent of executive dysfunction in ALS has been reported in this thesis, from single domain executive deficits, to global deficits presenting as a dementia like syndrome associated with bvFTD. The impact of executive dysfunction has also been reported on visual, and verbal memory. Cognitive dysfunction has not yet been considered in relation to ALS patient caregivers, nor has the contribution of behaviour change. The following study investigated whether patients with ALS, without bvFTD, will show increased behaviour change, related to frontal dysfunction. This research also tested if behavioural change predicts higher levels of burden in caregivers, consistent with the literature.

This study aimed to consolidate previous findings from this thesis, and investigate their impact on caregiver burden. More specifically, patients' cognitive dysfunction, disease characteristics, and behavioural change were investigated relative to caregiver burden. We proposed a statistically derived cut-off score for high burden, and used this metric to dichotomise caregivers (into low/high burden). This proved to be a useful metric for quantifying burden. Additionally, this study showed that behavioural change was a cogent

predictor of high caregiver burden, alongside total distress – an aggregate score derived from anxiety and depression subscales. This study also showed that patient survival was not negatively implicated by the level of caregiver burden. These findings would suggest that, although one may subjectively feel more burdened, it does not appear to affect their role as a caregiver.

Cognitive status and the disease characteristic of the patient i.e., ALSFRS-R, diagnosis metrics, or site of onset were not significant predictors of burden. Congruent with other neurodegenerative research, this would suggest that behavioural changes, and the caregiver's subjective experience, are more psychologically burdensome than areas of functional decline. Further replication in a larger cohort, and longitudinal analyses are recommended to enhance these findings. This experiment does not support one of our study objectives, which stated that a more rapid disease trajectory in ALS patients would increase their caregiver's burden. Alternatively, the most commonly reported behaviour changes reported by caregivers, were apathy, dysexecutive behaviour, and disinhibition, which predicted caregiver burden. These data promote the investigation of predictors of behaviour change in ALS patients, without comorbid bvFTD. This will be discussed further in section 5.5.

5.10 Caregivers' Quality of Life and Burden

This thesis has demonstrated the predictive nature of behavioural change on caregivers as a total group. The clinical utility of dichotomising caregivers based on their level of perceived caregiver burden into high/low categories has also been shown. This particular aspect of the thesis examined caregiver burden against patient engagement with local services, availability of assistive technology and communication aids, financial income and support, MITOS disease stage (See Appendix 7), and quality of life. The main 'negative findings' of this study were that patient disease stage did not affect caregiver quality of life. This finding is consistent with previous cross-section findings reported within this thesis. Caregivers were stratified based on their level of burden, which showed a highly significant difference in participants' quality of life. Participants, who reported greater caregiver burden, also reported significantly lower quality of life. There was no difference between the patients' disease profile, service utilisation, or household income between caregivers, once stratified by level of burden.

A study objective relating to the linearity between caregiver burden and caregiver QoL i.e., that QoL declines as caregiver burden increases, was generated based on the literature

outlined in Chapter 2. These data show that their level of burden directly impacts caregivers' QoL, though conversely AHP assistance and monetary factors may not alleviate burden. These data confirm the need for an investigation into psychologically tailored interventions for caregivers. This experiment investigated QoL and caregiver burden as two linear concepts, however, there is also a need to consider a multi-systemic approach to caregiver burden Based on these findings, we further investigated the relationship between anxiety, depression, and caregiver burden, through a longitudinal design, incorporating clinic-based assessments of cognition i.e., the ECAS (though see limitations of screening tools outlined in 5.4). This study sought to answer whether anxiety and/or depression predict caregiver burden, or whether caregiver burden leads to anxiety and/or depression. The main finding of this study suggests that anxiety is predictive of caregiver burden across the trajectory of ALS, before burden becomes clinically relevant i.e., in the low burden group. This experiment also showed that depression was a significant predictor of high burden in caregivers. These data confirm that anxiety, depression, and caregiver burden are consistent throughout the trajectory of ALS, warranting intervention and future studies on the functional impairment associated with high burden.

5.3 Clinical and Theoretical Implications

5.3.1 Implications for Healthcare Professionals

The results of these studies confirm the generally accepted position that cognitive–behavioural impairment in ALS is predominantly characterised by executive dysfunction, which can implicate other cognitive processes, and a range of behavioural change associated with frontal dysfunction. These deficits are consistent with many other neurodegenerative diseases, or condition which affect frontal lobe function. Anatomically, these deficits are linked to frontal-lobe regions, and the severity of cognitive dysfunction is associated with the compromised neuropathology. As reported in Chapter 1, patients presenting with anterior pathology, which progresses to superior-dorsal regions, often present with bvFTD, which then presents as FTD-ALS. Patients who present with ALS, may also present with pathology implicating the frontal lobes, associated with anterior-inferior-ventral degeneration, leading to cognitive and behavioural change, with prominent clinical feature of ALS. Cognitive dysfunction in this patient cohort is linked to this pathology, with negative implications observable on non-executive cognitive processes, due to the current view of distributed neural networks, implicated in ALS.

As outlined in Chapter 2, the Supervisory Attentional System is likely to be compromised in

ALS patients who experience executive dysfunction; this is evident within this cohort who perform worse on more executively demanding tasks, compared to controls. Patients' attentional resources are not as readily available under the time-trialled tasks, which can be seen once movement related deficits are controlled for. This is also reflected in poorer cognitive organisation, maintained by the SAS and executive function. The SAS then attends to the cognitive demands placed on the working memory system through the Central Executive, as described by Baddeley and Hitch (See Chapter 2), which is complemented by verbal and visual stores i.e., phonological loop and visuospatial sketchpad respectively.

It was a primary aim of this thesis, to investigate executive dysfunction within the context of these cognitive models, outlined in Chapter 2, and to investigate the impact of executive dysfunction on non-executive cognitive processes as outlined above. These data support current cognitive models of the SAS and working memory model, and have many clinical implications.

Compared to healthy controls, patients showed difficulties on tasks requiring abstract and flexible thinking, problem-solving and inhibitory control. For some patients, these deficits manifest in daily life, which can be inferred from behavioural data provided by caregivers. In addition to apathy, patients and their caregivers in the current sample endorsed increased dysexecutive behaviour and disinhibition since the onset of ALS using the FrSBe, which negatively implicated caregiver burden. Patients with this cognitive and behavioural profile may show problems in the following domains: (i) indifference towards others, (ii) indifference in managing financial affairs, (iii) difficulties in planning for future events, or (iv) difficulties in arriving at decisions regarding their clinical care. A recommendation from this thesis is to screen cognitive and behavioural status at the ALS specialist clinic, and to also screen for caregiver burden (See Appendix 7: pg425 for more information on the impact of cognitive and behavioural impairment on patients and caregivers).

Overall the current patient group performed worse on when interpreting the intentions and beliefs of others on executively challenging tasks. Clinicians should be mindful that ALS patients may respond appropriately to the emotions of others, they may have difficulty in anticipating or responding to the thoughts or intentions of others. Pragmatically speaking, these deficits can place strain on patient's interpersonal relationships, which become increasingly important as the disease progresses. In clinical consults with ALS patients and their families, psychologically tailored information should be integrated and discussed with

the caregiver.

Other cognitive functions such as language processes have been reported as impaired in ALS patients, with evidence indicating these deficits occur independently of executive dysfunction (see Chapter 2). Such findings have led to suggesting the need for revision of the Strong et al's (2009) cognitive consensus criteria (see Chapter 1) to reflect this heterogeneity. The fact that non–executive cognitive functions were relatively preserved in the current sample may merely reflect the recruitment of patients from a population showing single–domain executive impairment (e.g., Phukan et al., 2012). An absence of executive impairment should not be taken as an indication of intact cognitive function in other domains. Furthermore, we strongly propose that an impairment in social cognitive functioning being included as a core criterion for cognitive impairment.

In relation to longitudinal research and repeat assessment, these data show that measures of executive function can be repeated reliably. Furthermore, data relating to working memory tasks would suggest that backward-span tasks, regardless of task modality, can be interchanged and seen as functionally equivalent. These data have clinical implications for testing using a battery of neuropsychological tests, and also when administering screening tools. Due to the progressive disability caused by ALS, it may be necessary to tailor interventions to patients' physical status at the time of assessment. These data suggest that a bulbar-onset patient could reliably complete a reverse digit-span task at baseline assessment and then complete a reverse spatial-span task at follow-up, should their speech be compromised. These findings are transferrable to the ALS clinic also.

5.3.2 Implications for Caregivers

Caregivers have reported that clinical services place disproportionate focus on the practical rather than emotional adjustments to the disease (Brown, 2003; Oyebode et al., 2013). In the current study, patients' functional impairment, particularly behavioural dysfunction, was the main contributor to increased caregiver burden. This suggests that clinical communication with ALS families should emphasise the psychological challenges presented by the neurobehavioural features, as much as the physical manifestations of ALS. As a group, caregivers' depression and anxiety levels were significantly higher than in the patients themselves. Moreover, clinicians should be aware that the symptoms of ALS could pose differential effects on caregivers.

The current results revealed that caregiver depression, new onset behavioural dysfunction in patients, and caregiver anxiety together, predicted increased caregiver burden. Routine monitoring of the patient's functional, cognitive and behavioural functioning may prepare the clinical team to tailor their support for caregivers. It is important that caregivers are made aware of the possible interpersonal or behavioural changes accompanying ALS so that they do not misinterpret their partner's indifference or apathy as resulting from inherent problems within their relationship (Abrahams, 2011). Since some carers may be reluctant to discuss such concerns in front of the patient, caregivers should be interviewed separately either by clinicians themselves or affiliated psychological services. In clinics with limited resources, this could take the form of questionnaire packs for caregivers to return confidentially to the care team.

5.4 Limitations

As alluded to in the previous chapters' discussions, the current findings should be interpreted within the limitations of the study's design as these may affect the generalizability of the results to the wider population of ALS patients and their caregivers. Here, the general limitations of the current study are considered.

The exclusion criteria adopted by the study in the recruitment of the patients were extensive and somewhat restrictive. Whilst these criteria were in place to ensure that any cognitive or behavioural impairment found in the patients could not be attributed to comorbid conditions (e.g., diabetes, psychiatric illness, other neurological phenomena), the employment of these criteria may limit the representativeness of the current patient sample of the ALS population as a whole. While the exclusion of psychoactive use is preferable, and consistent within the literature, this may further reduce the representativeness of the patient sample to the wider ALS population.

Approximately 70% of eligible patients approached agreed to take part in the research. However, without detailed clinical data for the non–respondents, the influence of participation bias on the current study remains speculative. Potentially, patients with significant levels of cognitive–behavioural dysfunction, physical disability or mood symptoms might have refrained from taking part in the research, due to inertia or the expectation that testing would be too physically or mentally demanding. Alternatively, patients who do not have a high degree of disability and still able to maintain work commitments may have declined due to time constraints. In future research, an anonymous self-report questionnaire should be sent to

participants to return to the research team. Considering participants can withdraw from research without explicitly stating their reason, anonymous responding may allow for greater response, and remain ethically sound.

Patients in the current study were ethnically homogeneous (Caucasian Irish, with English as their first language), predominantly well–educated and, as a group were of average intelligence, as measured by the IQ estimates. This might limit the generalizability of the current patient results to the ALS population as a whole. There is limited evidence to suggest that lower educational attainment and premorbid IQ is positively associated with cognitive dysfunction in ALS (Massman et al., 1996; Phukan et al., 2012).

Caregivers were invited to take part in the study on the basis of the patient's participation and their agreement for their spouse to be contacted. The patient's participation was required as the study examined the relationship between objective measures of patients' neuropsychological performance and caregivers' outcomes. Nonetheless, these conditions might have excluded caregivers who were otherwise characteristic of the general ALS caregiver population. Caregivers who were experiencing low mood and/or high levels of strain and burden may potentially have been less motivated to take part. However, a large majority of caregivers in the study endorsed ZBI scores that met cut–off criteria for clinically significant burden. Conversely, caregivers experiencing high levels of strain and burden may have been more motivated to take part to communicate their distress. Control participants were matched to patients on demographic and mood variables. This was important to ensure that group differences could not be explained by differences on background variables. However, it does not eliminate bias associated with self–selection recruitment procedures. Certain personality traits, such as increased agreeableness, altruism and openness to experience have been positively associated with volunteering in research studies (Dollinger & Leong, 1993; Lönnqvist et al., 2007). Higher educational attainment and socioeconomic status are also suggested to predict research participation (Rosenthal & Rosnow, 2009); however, participants groups were matched on these variables.

Testing of patient participants was predominantly conducted in the patient's home, as opposed to a controlled laboratory setting. However, this was necessary to accommodate the patients' reduced mobility, or difficulty in attending the test centre. Stringent testing protocols were followed for both participant groups regardless of venue, reducing systematic bias introduced by disparate testing contexts. There is no suggestion within the literature to

suggest a difference in performance based on home- or hospital-based assessment. The testing battery was long raising the risk of fatigue. Where fatigue was suspected or expressed, breaks were encouraged or the testing session was terminated. Although distractors were more readily available within the patient home i.e., spouse/radio/unscheduled interruptions, home-visits appear to be the most effective way in hindsight to collect these data. Economically speaking, time may have been spent in patients' homes before and after the cognitive assessment, though this was a testament to the patients' interest and overall willingness to participate in the project, and engage with me, the researcher.

One way to control for fatigue, and minimise secondary influences on cognitive testing, is to conduct shorter batteries of tests, or implement screening assessments. One such assessment which has been discussed and implemented for this thesis is the Edinburgh Cognitive and Behavioural ALS Screen (ECAS; Abrahams et al., 2013). As previously noted, it is a brief (~15 – 20 min) multi–domain screening measure, assessing executive function, social cognition, language, memory and visuospatial functioning, which was employed in aspects of this study (Chapter 4). It is designed to minimise the confound resulting from patients' physical impairment on cognitive performance, with items adapted to account for ALS symptoms (i.e., dysarthria or motor impairment). Limitations of screening tools, such as the ECAS, include lower sensitivity and specificity, when compared to a full neuropsychological evaluation, and also a great propensity to identify false positives in terms of cognitive impairment i.e., the ECAS may falsely suggest someone is cognitively impaired. This has been recently shown when the ECAS was compared to a neuropsychological battery within an Irish cohort (Elamin, Pinto-Grau, Burke et al., In Press).

A further limitation associated with the use of cognitive screening tools, is the potential for over interpretation of the data (including sub-scores), an equal weight being given to a screening tool as to a full neuropsychological evaluation, and greater variation within scoring profiles depending on the administrators level of training in psychometrics (e.g occupational therapist, nurse, social work, medical doctor, neuropsychologist).

Missing data due to patient disability is a pervasive limitation in neuropsychological investigations in ALS. However, the selection of measures ensured that non–participation due to physical impairment was avoided. At times, this was difficult to judge given the rapid trajectory of this heterogeneous condition.

The utmost respect was given to patients and their families on the day of assessment, to complete as much of the assessment as they felt able. To capture this methodologically, the ALSFRS-R total, and sub-scales were reported in each of the aforementioned studies. As seen in the longitudinal and survival analyses within this thesis, the fatal trajectory of ALS is often a cause of attrition, which has been captured and illustrated within the survival graphs. Many of the patients and families who enrolled within this study are bereaved at the time of finalising this thesis, and as such, every effort was, and will continue to be made, to disseminate the body of this work. Alongside academic publications, these data will be used to form knowledge exchange and development seminars for families, caregivers, and patients currently living with this condition, and study days are planned to implement best practice guidelines for healthcare professionals.

As multiple between–group comparisons were undertaken, the current study conducted Bonferroni corrections to reduce the risk of Type I errors. Although this may reduce the number of false rejections of the null hypothesis, it might also increase the risk of Type II errors. In the current study, findings that were significant following this correction were classed as significant findings, while those that were significant only prior to the correction were considered as supportive findings or trends. Both were considered in discussion of the results.

While this may be a prudent approach, no consensus on the use of correction methods for multiple testing has been reached (Gelman et al., 2012) and thus the interpretation of these findings requires caution. Missing data further reduced the statistical power of certain tests. The selection and number of predictors for regression analyses was restricted by sample size, in particular for the cross-sectional caregiver study. Furthermore, the creation of composite scores could have been incorporated to reduce the inflation of Type I error. Moreover, a major methodological limitation of aspects of the current research is that the data are cross–sectional, and therefore precludes identification of causal relationships. The use of Structural Equation Modeling in this instance may have benefited this thesis, however, it was not prospectively planned during the development of this thesis.

Comparisons based on mean and median scores are useful for indicating overall differences between groups, however, they may mask the potential heterogeneity of impairment within ALS samples. Single–case analysis could reveal the prevalence of subtle impairments within a specific domain and is better positioned to identify subgroups within patient samples. For example, no between–group differences were found between the cognitively intact ALS

patients, controls, or patients with single-executive deficits on the RMET. Single–case analysis could reveal that more deficits in the patient groups, compared to the control group.

A qualitative component, such as Interpretative Phenomenological Analysis (IPA), could have been incorporated into a multi-method research design for this thesis. This is considered a limitation as it may have allowed for richer data to be extracted regarding the nature of, and intervention for, caregiver burden.

5.5 Future Directions

5.5.1 Neuropsychological Assessment

The assessment of neuropsychological status can be time consuming, and cumbersome for patients. One way to reduce the burden on patients is to develop ALS specific screening tools. Alternatively, short-forms of commonly used tests can be psychometrically validated. To this end, the data presented on the RMET could be used to develop a short form of the task. The psychometric properties of the measure indicate that the tool has excellent split-half reliability, and 18 of the 36-items have excellent discriminant properties. Future research could utilise these data and compile a short form of this tasks. Retrospective analysis could then be completed on the data to assess whether the RMET short form is a sensitive and specific as the full 36-item version.

Considering the finding associated with the working memory tasks i.e., that backward spatial span is equivalent to the backward digit span, future research could test this within one group, rather than two well matched ALS patient cohorts. This would allow for greater inferences to be made about the findings.

Another finding of this study was that patients could be categorised as cognitively intact, yet statistically differ from controls on measures of executive function. This was shown to then implicate aspects of memory function. Future research could compare patient and control data on a case-by-case basis, in order to quantify common deficits. This would provide greater clarity into the subclinical cognitive deficits being experienced by ALS patients, which may have clinical implications.

5.5.2 Ancillary Investigations

Many studies within the literature have reported the relationship between cognitive performance and ancillary methodologies such as electroencephalography and brain imaging

(Chapter 2). Data outlined in the presented studies could be complemented by the inclusion of such methodologies. Regarding the findings on social cognitive performance, this thesis has statistically shown the linear relationship between the poor performance on the reading the mind in the eyes task, and executive function. The findings of this study could be supported by neuroimaging, much like the work published within the HD literature (Mason et al., 2015). Furthermore, to assess the discordant profile of ALS patients on measures of social cognition, patients who are in the early stage of the disease should be assessed and dichotomised based on disease-onset. MR imaging could then investigate this.

Results from this thesis show that social cognitive performance on testing is a predictor of behaviour change. Functional or structural correlations could be employed to assess the relationship of this finding in order to understand the role of social cognitive dysfunction in greater detail. Considering the role of social cognition in frontotemporal dementia, a study such as this could have greater implications for the ALS-FTD continuum.

Electroencephalography (EEG) could also be employed to address these findings within the context of distributed neural networks. Such techniques could be useful in supporting the role of executive dysfunction on auxiliary cognitive processes, and identifying the neurophysiological correlates of cognitive dysfunction. Moreover, cognitive classifications could be used to stratify patients undergoing neurophysiological test paradigms, in order to ensure a homogenous sample is being tested. This may lead to more sensitive and specific inferences being made, otherwise heterogeneous cognitive function may be a confounder.

5.5.3 Longitudinal Research

These data show that practice effects are not a statistically significant confounding variable in longitudinal testing, on some measures of executive function. Future research could investigate whether this is consistent across multiple cognitive domains evaluated in ALS patients. This would allow for greater inferences to be made about the reliability of longitudinal data, in domains other than executive function. This has particular relevance given the emerging interest in language (Chapter 2). To this end, reliable change indices could be employed to also investigate whether ALS patients whom are cognitively intact are declining at a statistically significant, subclinical rate.

Longitudinal research could also investigate the relationship between social cognition and behaviour change in ALS patients. Data contained within this thesis has shown that poor

performance on social cognitive tasks can predict behavioural change in ALS, and a longitudinal investigation could confirm this.

5.5.4 Clinical Management of Caregivers

Future investigations of caregiver burden in ALS families could focus on the efficacy of intervention-based studies. Through the identification of predictors of burden, and the associated management strategies available, future research could profile patients and caregivers according to their cognitive and behavioural status, and implement strategies accordingly. By classifying the factors associated with burden in ALS, and the typical behaviours which present, clinical intervention programs could capitalise on effective management strategies used in similar cohorts i.e., frontotemporal dementia.

Future research should also qualitatively investigate the experience of caregivers of ALS patients to explore the lived experience of caregiving specifically in this cohort, rather than relying on generic measurement scales.

5.6 Conclusions

The current thesis has described the literature surrounding cognitive–behavioural change in ALS patients and sought to improve upon the methodology of previous studies investigating social cognition within ALS cohorts. Furthermore, this thesis has aimed to contribute to the psychometric knowledge regarding the testing being used in ALS research, methodologies employed, and the theoretical understanding of cognitive concepts in both ALS and healthy controls. This was achieved by using a range of tasks in a large ALS sample and by furthering the knowledgebase on the relationship between patients' executive functioning and performance on social cognitive tasks, including task difficulty and discrimination coefficients (Burke, Pinto-Grau, Lonergan, et al., 2016). These studies also suggest that executive tests can be repeated without practice effects on a control cohort, which would suggest that stability over time is a genuine effect and not a product of psychometric error (Burke, Wynne, O'Brien, et al., 2015). This thesis has also shown the negative implications of behaviour impairment in ALS patients on their caregivers, and typical behavioural features which may present in some ALS patients (Burke, Elamin, Galvin, Hardiman, & Pender, 2015). This thesis has also shown how social cognitive processes may plausibly decline in neurodegenerative conditions, while executive function remains intact (Burke, Healy, Casey, Hardiman, & Pender, 2015). Specific to ALS patients, this thesis has shown that bulbar-onset patients may be more susceptible to social cognitive decline, when compared to spinal-onset ALS patients (Burke, Elamin, Bede et al., 2016). The executive demands placed on ALS

patients to complete visual memory assessments was highlighted, and future research may incorporate these findings to reduce the impact of coexisting executive dysfunction.

The thesis also sought to expand understanding of caregiving perceptions in ALS, and to identify predictors of burden (Burke et al., 2015). The research is the first published work to include objective measures of patients' cognitive function, patients' disease status and behaviour, in examining the impact ALS poses upon caregivers in terms of their mood, perceived role strain, personal strain, and feelings of guilt. Instead of patients' cognitive status, the results of this study affirmed previous reports implicating the role of patients' behavioural dysfunction in caregivers' responses to ALS. Further analysis of these patients and caregivers revealed that caregiver quality of life was significantly implicated if one was highly burdened. This finding was highly significant, and prompts future research to investigate caregiver based interventions.

The thesis has outlined several limitations of the current research, which restrict the interpretation of results, but also provide a landscape for future development. These caveats, as well as those from the literature, have promoted recommendations for the design of future studies of ALS patients and their caregivers. It is hoped that this research will contribute to greater awareness and acceptance of the multisystem nature of ALS for the future development of interventions for patients and caregivers alike.

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7.0 Appendices

Appendix 1: Ethical Approval Letter

Appendix 2: Consent and Information Sheets

Appendix 3: Neuropsychological Test Battery

Appendix 4: Proxy Reports for Caregivers

Appendix 5: Edinburgh Cognitive ALS Screen (ECAS)

Appendix 6: El Escorial Criteria

Appendix 7: MITOS Staging Standard Operating Procedure (SOP)

Appendix 8: Classification of FTD variants

Appendix 9: Conference Proceedings

Appendix 10: Print Publications Arising from this Thesis

Appendix 1: Approval Letter Ethics

Ethics (Medical Research) Committee - Beaumont Hospital
Notification of ERC/IRB Approval

Principal Investigator: 13/102 – Dr. Niall Pender (Psychology)

Consultant co-investigator: Prof. Orla Hardiman

REC reference: 13/102

Protocol Title: Neuropsychological and Functional Correlates to Social Cognition if Neurodegenerative Diseases

Ethics Committee Meeting Date: 13th December 2013

Final Approval Date: 24th January 2014

From: Ethics (Medical Research) Committee - Beaumont Hospital, Beaumont, Dublin 9

Documents Reviewed

Document and Date	Date Reviewed	Approved
Application Form, signed N. Pender, 25/11/13	24/1/14	Yes
V3, 18/5/15	28/5/15*	Yes
Research Protocol, no version no.	24/1/14	Yes
Patient Information Leaflet (Motor Neurone Disease), V2, 6/1/14	24/1/14	Yes
V3	28/5/15*	Yes
Consent Form, (Motor Neurone Disease), no version no.	24/1/14	Yes
V2	28/5/15*	Yes
Patient Information Leaflet (Huntington's Disease), V2, 6/1/14	24/1/14	Yes
Consent Form, (Huntington's Disease) no version no.	24/1/14	Yes
Recruitment Poster (Healthy Controls), version X	24/1/14	Yes
Information Leaflet (Healthy Controls), V2, 6/1/14	24/1/14	Yes

Consent Form, (Healthy Controls) no version no.	**24/1/14**	**Yes**
Return Postcard, V2, 10/11	**24/1/14**	**Yes**
Letter after phonecall with details of appointment, xx/1/14	**24/1/14**	**Yes**
Letter prior to 6-month follow up phonecall, xx/6/14	**24/1/14**	**Yes**
GP Letter, xx/1/14	**24/1/14**	**Yes**
Amendment: - #1, 19/3/15 (change timing of patient assessments, limit amount of patient travel expenses, give patients options in consent form)	**28/5/15***	**Yes**
List of Neuropsychological Assessments, no version no.	**24/1/14**	**Noted**
CAMI Research Subject Scan Request Form, no version no.	**24/1/14**	**Noted**
Grant Agreement, TCD, and Irish Institute of Clinical Neuroscience	**24/1/14**	**Noted**

Dr. Peter Branagan
ERC/IRB Convenor's Signature
Approval # 2, dated 28th May 2015*

Appendix 2: Consent form and Information Sheet

MOTOR NEURON DISEASE CONSENT FORM

Protocol Title:

Neuropsychological and Functional Correlates of Social Cognition in Huntington's Disease and Motor Neuron Disease

Please tick the appropriate answer.

I confirm that **I have read and understood the Patient Information Leaflet** attached, and that I have had ample opportunity to ask questions all of which have been satisfactorily answered.

I understand that **my participation in this study is entirely voluntary** and that I may withdraw at any time, without giving reason, and without this decision affecting my future treatment or medical care.

I understand that **individuals may view my records and data** with specific delegated authority from Professor Hardiman, Dr. Pender and their research team.

I understand that my identity will remain confidential at all times.

I am aware of the potential discomforts of this research study i.e., fatigue.

I have been given a copy of the Patient Information Leaflet for my records.

FUTURE USE OF **CODED DATA**:

I agree that I will not restrict the use to which the results of this study may be put. I give my approval that unidentifiable data concerning my person may be stored or electronically processed for the purpose of scientific research and may be used in related or other studies in the future

Neuropsychology [ ] MRI Scanning [ ] EEG [ ]

Participant _____ _____

Signature Block capitals

To be completed by the Principal Investigator or nominee

I the undersigned, have taken the time to fully explained to the above patient the nature and purpose of this study in a manner that he/she could understand. I have explained the risks involved, as well as the possible benefits and have invited him/here to ask questions on any aspect of the study that concerned them.

_____ _____ _____

Signature **Block Capitals** **Date**

Website: www.beaumont.ie

Ospidéal Beaumont

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
Telephone: 809 3000 / 837 7755 Facsimile: 837 6982

Patient

Information Leaflet: Version 3

Motor Neuron Disease

Research Title:

Neuropsychological and Functional Correlates of Social Cognition in Huntington's Disease and Motor Neuron Disease

Principal Investigator's Name: Professor Orla Hardiman

Principal Investigator's Title: Clinical Professor Consultant Neurologist

Telephone No. of Principal Investigator:

(01) 8093000; Beeper XXX

You are being invited to take part in a clinical research study carried out at Beaumont, Trinity College Dublin and St. James's Hospital, Dublin. Before you decide whether or not you wish to take part, you should read the information provided below carefully and if you wish discuss it with your family, friends or GP. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you – this process is known as Informed Consent.

You are not obliged to take part in this study and failure to participate will have no effect on your future care. You may change your mind at any time (before the start of the study or even after you have commenced the study) for whatever reason without having to justify your decision and without any negative impact on the care you will receive from the medical staff.

PURPOSE OF RESEARCH

You have been asked to participate in a research study of thinking and behaviour in Motor Neuron Disease (MND) and Huntington's Disease (HD). Some people with MND/HD have difficulties with thinking, though not everyone.

We would like to assess how much thinking, memory and decision-making is affected in MND/HD and if we can see any evidence of that on a brain scan.

The overall aim of the study is to describe the features of this condition on Magnetic Resonance Imaging (MRI), which is a sophisticated brain scan. The description of these changes may help us to classify Motor Neuron Disease into different subtypes and could potentially be used to predict cognitive changes.
If you consent, you will also undergo a specialist EEG test (an EEG is a test that measures brainwaves in your brain). This process measures electrical activity in the brain when you hear and see things.

WHO IS DOING THIS STUDY?

This study is being conducted by Professor Hardiman, who is a Consultant Neurologist, and Dr. Niall Pender, Principal Clinical Neuropsychologist, and their team in Beaumont Hospital.

WHY AM I BEING ASKED TO TAKE PART?

You have been asked to take part in this study based on your diagnosis of Motor Neuron Disease. We are examining the changes in thinking caused by Motor Neuron Disease and would value your participation in this research.

HOW WILL IT BE CARRIED OUT?

This study will involve some neuropsychological tests, followed by an MRI scan and EEG in St. James' Hospital/Trinity College Dublin

WHAT WILL HAPPEN TO ME IF I AGREE TO TAKE PART?

If you agree to participate in this study we will first ask you to take part in a neuropsychological test. These tests are designed to test memory, language and attention. In total this lasts approximately 2 hours, and you may take breaks if you would like to.

The second part of the study is to perform an MRI that will take place in St James`s Hospital in Dublin. No harmful X-rays will be used. Before scanning we will ask you a series of questions to make sure you have no recent joint replacements in the past 6 months, or implanted metallic devices such as pace makers, or aneurysm clips. If you have any of these metallic medical devices we will not be able to perform the scans, but you can still complete the other tests if you wish. We will ask you to take off all jewellery, watches, earrings and dentures.

You will be asked to lie still for about 45 minutes while the pictures of the brain are being taken.
The scanner is a rather small, enclosed space and it might cause some discomfort to lie still for 45 minutes. Earplugs and protective headphones will be provided because the scanner produces a loud thumping noise.

Lastly we will conduct the EEG. This involves some electrodes being fitted to a cap, which fits quite like a swimming cap. These electrodes are fitted with gel to record electrical activity in your brain. The placement of the cap, inserting the gel, and adding the individual electrodes may take up to 60 minutes, and the testing process takes approximately 30 additional minutes. The time is variable on this task due to the set-up, and we would kindly ask participants to allow at least 2 hours from start to complete finish. Once the testing is complete the cap is removed without any delay, although you may wish to wash you hair after the removal of the electrodes to remove the gel. Wash facilities are available adjacent to the EEG lab. This task may be conducted in Trinity

College Dublin, or St. James's Hospital, this is dependent on equipment availability and the researcher will liaise with you regarding the time, place and date of the task.

We would like to repeat the neuropsychological tests, MRI brain scan and EEG after the first assessment, first 4 months later, then 8 months after the initial test etc. We plan to repeat the assessments in order to gain a better understanding of Motor Neuron Disease as the disease changes over time, but you can withdraw from the study at any stage or reduce your involvement, without reason, and this will not affect your medical care.

WHAT ALTERNATIVE TREATMENTS ARE AVAILABLE TO ME?

The proposed study does not involve any change to your existing treatment plan. You may decide to withdraw consent from the study at any time without justifying your decision and your future treatment will not be affected.

BENEFITS:

There is no immediate benefit to you in participating in this study, however the overall benefits of this study aim to increase diagnostic accuracy and treatment options for the future.

RISKS:

Many of the participants already had a brain scan, but for those who have not had one to date, it is also possible that the brain scan might identify an unexpected or previously unknown condition. If this occurs, the new findings will be followed-up and your GP will also be notified.

WHAT IF SOMETHING GOES WRONG AS A RESULT OF MY PARTICIPATION IN THIS STUDY?

We do not anticipate that anything will go wrong. However, if at any time you feel that your participation in this study has become unduly stressful, you are free to discontinue. This will not affect in any way the quality of care that you receive, or the access that you will have to specialist services.

WILL THERE BE ANY ADDITIONAL COSTS INVOLVED?

Due to a limited availability in funding, we are only able to reimburse costs associated with taking part in the research to the value to €40. We hope through conscious appointment scheduling the costs occurring from taking part are kept to a minimum.

YOUR RESPONSIBILITIES AS A PARTICIPANT

If you agree to participate in this study we request that you cooperate to the best of their ability. You can withdraw from the study at any stage without justifying your decision and your future treatment will not be affected.

OUR RESPONSIBILITIES TO YOU AS INVESTIGATORS

All data will be maintained in a strictly confidential manner. The information that you provide will be stored in a way that it cannot be accessed except by the named researchers. It will only be used for the research purposes to which you have explicitly agreed.

CONFIDENTIALITY ISSUES

Your GP will be notified of your participation in the study unless you request otherwise. The GP will not receive any of the details of the information that you provide unless you request that it be sent to him/her. Some hospital employees will be looking at your chart.

All the information obtained from participating individuals will be treated in a strictly confidential manner and your name will never be presented beside your data. We will transfer your data collected from the machines in TCD and St. James' Hospital using encrypted devices and they will be analysed and stored at Beaumont Hospital.

All of the information obtained will be stored on a password-protected computer database to which only the named researchers will have access. Each individual entered on the database will be assigned a unique number. The names of the individuals will be maintained in a separate password-protected encrypted database with access limited to the named researchers. Publications which arise from the collected data will not contain any personal information.

IF YOU REQUIRE FURTHER INFORMATION

If you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be affected.

You may choose to take part in any aspect of the study or none of the study.
If you have any further questions about the study now or any future time please contact:

Mr. Tom Burke

Website: www.beaumont.ie

Ospidéal Beaumont

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
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Tel: 01 809 3262 / 0851624668

Return Postcard to:

Mr. Tom Burke; Clinical Research Fellow, Department of Psychology, Beaumont Hospital, Dublin 9, Ireland.

RE: My participation in the research project titled:

Neuropsychological and Functional Correlates of Social Cognition in Neurodegenerative Diseases

DEAR PROFESSOR HARDIMAN AND TEAM,

THANK YOU FOR YOUR LETTER REGARDING THE PARTICIPATION IN THE RESEARCH PROJECT CONCERNING THINKING AND MEMORY IN PEOPLE WITH MOTOR NEURON DISEASE.

PLEASE TICK APPROPRIATE BOX:

☐ I CONFIRM THAT I **DO** WISH TO TAKE PART IN THIS STUDY. PLEASE CONTACT ME FOR FURTHER INFORMATION.

☐ I CONFIRM THAT I **DO NOT** WISH TO TAKE PART IN THIS STUDY.

YOURS SINCERELY,

NAME SIGNATURE

ADDRESS:

CONTACT PHONE NUMBER

PLEASE INDICATE IF YOU HAVE A PREFERRED TIME TO RECEIVE PHONE CALLS :

Website: www.beaumont.ie

Ospidéal Beaumont

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
Telephone: 809 3000 / 837 7755 Facsimile: 837 6982

Information Leaflet

Healthy Controls

Research Title:

Neuropsychological and Functional Correlates of Social Cognition in Neurodegenerative Diseases.

Principal Investigator's Name: **Professor Orla Hardiman**

Principal Investigator's Title: **Clinical Professor Consultant Neurologist**

Telephone No. of Principal Investigator:

(01) 8093000, Beeper 622

You are being invited to take part in a clinical research study carried out at Beaumont, Trinity College Dublin and St. James's Hospital, Dublin. Before you decide whether or not you wish to take part, you should read the information provided below carefully and if you wish discuss it with your family, friends or GP. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you – this process is known as Informed Consent.

You are not obliged to take part in this study and failure to participate will have no effect on your future care. You may change your mind at any time (before the start of the study or even after you have commenced the study) for whatever reason without having to justify your decision and without any negative impact on the care you will receive from the medical staff.

PURPOSE OF RESEARCH

You have been asked to participate in a research study of thinking and behaviour in Neurodegenerative disorders, although you do not have a neurodegenerative condition. We would like to assess how much thinking, memory and decision-making is affected in Motor Neuron Disease and Huntington's disease and if we can see any evidence of that on a brain scan. Your role in this research is to be the comparative healthy group. The overall aim of the study is to describe the features of this condition on Magnetic Resonance Imaging (MRI), which is a sophisticated brain scan. The description of these changes may help us to classify Motor Neuron Disease into different subtypes and could potentially be used to predict cognitive changes.

You will also undergo a specialist EEG test (an EEG is a test that measures brainwaves in your brain). This process will use an Evoked Potential test (An evoked potential measures the response in your brain to a sensory stimulus – such as a flashing light or sound. Evoked potentials give us information about circuits within the brain).

WHO IS DOING THIS STUDY?

This study is being conducted by Professor Hardiman, who is a Consultant Neurologist, and Dr. Niall Pender, Principal Clinical Neuropsychologist, and their team in Beaumont Hospital.

HOW WILL IT BE CARRIED OUT?

This study will involve some neuropsychological tests, followed by an MRI scan and EEG in St. James' Hospital/Trinity College Dublin

WHAT WILL HAPPEN TO ME IF I AGREE TO TAKE PART?

If you agree to participate in this study we will first ask you to take part in a neuropsychological test. These tests are designed to test memory, language and attention. In total this lasts approximately 2 hours, and you may take breaks if you would like to.

The second part of the study is to perform an MRI that will take place in St James`s Hospital in Dublin. No harmful X-rays will be used. Before scanning we will ask you a series of questions to make sure you have no recent joint replacements in the past 6 months, or implanted metallic devices such as pace makers, or aneurysm clips. If you have any of these metallic medical devices we will not be able to perform the scans, but you can still complete the other tests if you wish. We will ask you to take off all jewellery, watches, earrings and dentures.

You will be asked to lie still for about 45 minutes while the pictures of the brain are being taken. The scanner is a rather small, enclosed space and it might cause some discomfort to lie still for 45 minutes. Earplugs and protective headphones will be provided because the scanner produces a loud thumping noise.

Lastly we will conduct the EEG. This involves some electrodes being fitted to a cap, which fits quite like a swimming cap. These electrodes are fitted with gel to record electrical activity in your brain. The placement of the cap, inserting the gel, and adding the individual electrodes may take up to 60 minutes, and the testing process takes approximately 30 additional minutes. The time is variable on this task due to the set-up, and we would kindly ask participants to allow at least 2 hours from start to complete finish. Once the testing is complete the cap is removed without any delay, although you may wish to wash you hair after the removal of the electrodes to remove the gel. Wash facilities are available adjacent to the EEG lab. This task may be conducted in Trinity College Dublin, or St. James's Hospital, this is dependent on equipment availability and the researcher will liaise with you regarding the time, place and date of the task.

We would like to repeat the neuropsychological tests, MRI brain scan and EEG after the first assessment, first 4 months later, then 8 months after the initial test etc. We plan to repeat the assessments in order to gain a better understanding of neurodegenerative conditions as they change over time, but you can withdraw from the study at any stage or reduce your involvement, without reason, and this will not affect your medical care.

WHAT ALTERNATIVE TREATMENTS ARE AVAILABLE TO ME?

The proposed study does not involve any change to any treatment plan you may be on. You may decide to withdraw consent from the study at any time without justifying your decision and your future treatment will not be affected.

BENEFITS:

There is no immediate benefit to you in participating in this study, however the overall benefits of this study aim to increase diagnostic accuracy and treatment options for the future for neurodegenerative disorders.

RISKS:

Many of the participants already had a brain scan, but for those who have not had one to date, it is also possible that the brain scan might identify an unexpected or previously unknown condition. If this occurs, the new findings will be followed-up and your GP will also be notified.

WHAT IF SOMETHING GOES WRONG AS A RESULT OF MY PARTICIPATION IN THIS STUDY?

We do not anticipate that anything will go wrong. However, if at any time you feel that your participation in this study has become unduly stressful, you are free to discontinue. This will not affect in any way the quality of care that you receive, or the access that you will have to specialist services in the future.

WILL THERE BE ANY ADDITIONAL COSTS INVOLVED?

Due to a limited availability in funding, we are only able to reimburse costs associated with taking part in the research to the value to €40. We hope through conscious appointment scheduling the costs occurring from taking part are kept to a minimum.

YOUR RESPONSIBILITIES AS A PARTICIPANT

If you agree to participate in this study we request that you cooperate to the best of their ability. You can withdraw from the study at any stage without justifying your decision and your future treatment will not be affected.

OUR RESPONSIBILITIES TO YOU AS INVESTIGATORS

All data will be maintained in a strictly confidential manner. The information that you provide will be stored in a way that it cannot be accessed except by the named researchers. It will only be used for the research purposes to which you have explicitly agreed.

CONFIDENTIALITY ISSUES

Your GP will be notified of your participation in the study unless you request otherwise. The GP will not receive any of the details of the information that you provide unless you request that it be sent to him/her. Some hospital employees will be looking at your chart.

All the information obtained from participating individuals will be treated in a strictly confidential manner and your name will never be presented beside your data.

All of the information obtained will be stored on a password-protected computer database to which only the named researchers will have access. Each individual entered on the database will be assigned a unique number. The names of the individuals will be maintained in a separate password-protected encrypted database with access limited to the named researchers. Publications which arise from the collected data will not contain any personal information.

IF YOU REQUIRE FURTHER INFORMATION

You may choose to take part in any aspect of the study or none of the study.

If you have any further questions about the study now or any future time please contact:

Mr. Tom Burke

Clinical Research Fellow

Department of Psychology

Beaumont Hospital
Dublin 9
Tel: 01 809 2963 / 0851624668

CONTROL PARTICIPANT CONSENT FORM

Protocol Title:

Neuropsychological and Functional Correlates of Social Cognition in Huntington's Disease and Motor Neuron Disease

Please tick the appropriate answer.

I confirm that **I have read and understood the Patient Information Leaflet** attached, and that I have had ample opportunity to ask questions all of which have been satisfactorily answered.

I understand that **my participation in this study is entirely voluntary** and that I may withdraw at any time, without giving reason, and without this decision affecting my future treatment or medical care.

I understand that **individuals may view my records and data** with specific delegated authority from Professor Hardiman, Dr. Pender and their research team.

I understand that my identity will remain confidential at all times.

I am aware of the potential discomforts of this research study i.e., fatigue.

I have been given a copy of the Patient Information Leaflet for my records.

FUTURE USE OF **CODED DATA**:

I agree that I will not restrict the use to which the results of this study may be put. I give my approval that unidentifiable data concerning my person may be stored or electronically processed for the purpose of scientific research and may be used in related or other studies in the future

Neuropsychology [ ]	MRI Scanning [ ]	EEG [ ]

Participant _____ _____

Signature Block capitals

To be completed by the Principal Investigator or nominee

I the undersigned, have taken the time to fully explained to the above patient the nature and purpose of this study in a manner that he/she could understand. I have explained the risks involved, as well as the possible benefits and have invited him/here to ask questions on any aspect of the study that concerned them.

Signature	**Block Capitals**	**Date**

Appendix 3: El Escorial Criteria

The Revised El Escorial (or Airlie-House) criteria for diagnosis of Amyotrophic Lateral Sclerosis(Brooks et al., 2000)

- *Definite ALS*: Upper and lower motor neurone signs in at least three body regions (upper limb, lower limb, bulbar, thoracic).

- *Clinically probable* ALS: Upper and lower motor neurone signs in at least two regions, with some upper motor neurone signs necessarily rostral to the lower motor neurone signs.

- *Clinically probable* laboratory-supported ALS: Clinical signs of upper and lower motor neurone dysfunction in only one region, or when upper motor neurone signs alone are present in one region and lower motor neurone signs defined by electromyographic criteria are present in at least two limbs, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.

- *Clinically possible* ALS: Clinical signs of upper and lower motor neurone dysfunction are found together in only one region, or upper motor neurone signs are found alone in two or more regions, or lower motor neurone signs are found rostral to upper motor neurone signs and the diagnosis of clinically probable: laboratory supported

Appendix 4: MITOS Staging SOP V1.0 (July, 2014)

Definition of MITOS Staging System

Critical milestones in ALS progression were defined by loss of independent function in four key domains that are included in both the ALSFRS-R and that involve loss of autonomy: walking/self-care, swallowing, communicating and breathing (Table). Impairment in each domain is determined by thresholds that reflected loss of autonomy in the specific ALSFRS-R scores. Values of 0 (below threshold) or 1 (above threshold) are assigned, and the stages are determined as the sum of those values across the four domains.

Stages are defined as: stage 0, functional involvement but no loss of independence on any domain; stages 1 to 4, number of domains in which independence was lost; and stage 5, death.

Table

Functional domains and stages

MITOS Domain	ALSFRS-R Item	ALSFRS-R Score		MITOS Score
Movement (Walking/Self-care)	**8 Walking**	4 Normal 3 Early ambulation difficulties 2 Walks with assistance		**0**
		1 Non-ambulatory functional movement only 0 No purposeful leg movement		**1**
	6 Dressing and hygiene	4 Normal function 3 Independent and complete self-care with effort or decreased efficiency 2 Intermittent assistance or substitute methods	***OR*** *	**0**
		1 Needs attendant for self-care 0 Total dependence		**1**

* The MITOS score 1 for Movement should be recorded if either Walking or Dressing and hygiene are scored 1.

MITOS Domain	ALSFRS-R Item	ALSFRS-R Score	MITOS Score

		4 Normal eating habits 3 Early eating problems; occasional choking 2 Dietary consistency changes		**0**
Swallowing	**3** **Swallowing**			
		1 Needs supplemental tube feeding 0 NPO (exclusively parenteral or enteral feeding)		**1**

MITOS Domain	**ALSFRS-R item**	**ALSFRS-R score**		**MITOS Score**
		4 Normal speech processes 3 Detectable speech with disturbances 2 Intelligible with repeating		**0**
	1 Speech	1 Speech combined with non-vocal communication 0 Total dependence		**1**
Communicating		4 Normal 3 Slow or sloppy; all words are legible 2 Not all words are legible	*AND**	**0**
	4 Handwriting	1 Able to grip pen but unable to write 0 Unable to grip pen		**1**

*The MITOS score 1 for *Communicating* should be recorded when both Speech and Handwriting scores are 1. Otherwise, the score is 0.

MITOS Domain	**ALSFRS-R item**	**ALSFRS-R score**	**MITOS Score**

		4 None 3 Occurs when walking 2 Occurs with one or more of: eating, bathing, dressing		0
	10 Dyspnoea	1 Occurs at rest, difficulty breathing when either sitting or lying 0 Loss of useful speech		1
Breathing		4 None 3 Intermittent use of NIPPV	***OR***	0
	12 Respiratory insufficiency	2 Continuous use of NIPPV during the night 1 Continuous use of NIPPV during the night and day 0 Invasive mechanical ventilation by intubation or tracheostomy		1

* The MITOS score 1 for *Breathing* should be recorded if either Dyspnoea or Respiratory Insufficiency are scored 1.

MITOS Score

ALS-MITOS	Stage	Functional domains lost
	0	None
	1	1 domain
	2	2 domains
	3	3 domains
	4	4 domains
	5	Death

The final staging is determined by the sum of functional score of 1 for each domain.

Appendix 5: Classification of FTD variants

Possible bvFTD

Three of the following behavioral/cognitive symptoms must be present to meet criteria. These symptoms should occur repeatedly, not just as a single instance.

1 Early behavioral disinhibition (one of the following must be present)
    1 Socially inappropriate behavior: touching or kissing strangers, inappropriate sexual acts, public urination, criminal behavior, etc.
    2 Loss of manners or decorum: examples include
        1 crude or sexually explicit remarks, jokes or opinions which may be offensive to others;
        2 lack of response to social cues (e.g., will continue talking despite other's attempts to end a conversation);
        3 physical behaviors such as flatulence, touching private body parts, belching or spitting;
        4 poor hygiene or grooming (malodorous, stained, torn or inappropriate clothing),
        5 loss of respect for interpersonal space
    3 Impulsive, rash or careless actions: impulsive behaviors which may or may not be performed in a social context (e.g., new- onset gambling, taking things, stealing (usually food or visually stimulating objects), buying or selling property without regard for consequences)
2 Early apathy or inertia (one of the following must be present)
    1 Apathy: loss of interest, drive or motivation (e.g., passivity, lack of spontaneity, does not engage in previously rewarding activities)
    2 Inertia: decreased initiation of behavior (e.g., needs prompting to initiate or continue routine activities, less likely to initiate or sustain conversations)
3 Early loss of sympathy or empathy (one of the following must be present)
    1 Diminished response to other people's needs and feelings: positive rating of 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 other's pain or distress, making inappropriate jokes
    2 Diminished social interest, interrelatedness or personal warmth: general decrease in social engagement (coldness, lack of eye contact, etc.)
4 Early perseverative, stereotyped or compulsive/ritualistic behavior (one of the following must be present)
    1 Simple repetitive movements: tapping, clapping, rubbing, scratching, picking at skin or clothing, pursing lips, lip smacking, etc.
    2 Complex, compulsive or ritualistic behaviors: counting and cleaning rituals, collecting, checking, repetitive trips to the bathroom, ordering objects, walking fixed routes, etc.
    3 Stereotypy of speech: repeating words or phrases that have no communicative value
5 Hyperorality and dietary changes (one of the following must be present)
    1 Altered food preferences: carbohydrate craving (particularly sweets) or food fads
    2 Binge eating, increased consumption of alcohol or cigarettes: patient continues to eat despite satiety (weight gain ____ lb); compulsive smoking, chewing tobacco or gum; or alcohol ingestion

3 Oral exploration or consumption of inedible objects

6 Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions (all of the following must be present)

1 Deficits in executive tasks: Trails-B, generation tasks (letter fluency/design fluency) or presence of errors (e.g., perseverations or rule violations)

2 Relative sparing of episodic memory

3 Relative sparing of visuospatial skills e.g., ability to copy simple line drawings

Probable bvFTD

1. Meets criteria for possible bvFTD
2. Exhibits significant functional decline (by caregiver report or as evidenced by CDR or FAQ scores)
3. Imaging results consistent with bvFTD (one of the following must be present)
    1. Frontal and/or temporal atrophy on CT or MRI (Disproportionate atrophy in frontal and/or anterior temporal regions)
    2. Frontal hypoperfusion or hypometabolism on SPECT or PET (Disproportionate frontal or frontotemporal hypometabolism or hypoperfusion)

bvFTD with Definite FTLD Pathology

1. Meets criteria for possible or probable bvFTD
2. Meets one of the following
    1. Histopathological evidence of FTLD on biopsy or at post-mortem e.g., FTLD-tau, FTLD-TDP, FTLD-UPS, FTLD-IF, FTLD-ni, BIBD
    2. Presence of a known pathogenic mutation e.g., MAPT, PGRN, CHMP2B, VCP

Exclusion Criteria for bvFTD

Criteria 1 and 2 must both be answered negatively for any bvFTD diagnosis. Criterion 3 can be positive for possible bvFTD but must be negative for probable bvFTD.

1. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders (excludes all bvFTD diagnoses) e.g., delirium, cerebrovascular disease, cerebellar disorder, systemic disorders (e.g., hypothyroidism) or substance-induced conditions
2. Behavioral disturbance is better accounted for by a psychiatric diagnosis (excludes all bvFTD diagnoses) e.g., depression, bipolar disorder, schizophrenia, pre-existing personality disorder
3. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process (excludes diagnosis of probable bvFTD) e.g., genetic mutations, extensive PIB binding, CSF markers

Semantic Variant PPA (SV-PPA)

The diagnostic criteria for semantic variant PPA (SV-PPA) developed by an international group of PPA investigators use two diagnostic categories: clinical diagnosis and imaging-supported diagnosis. The criteria must be met as defined without meeting any of the exclusion criteria for primary progressive aphasia (PPA)

Primary Progressive Aphasia (PPA)

Criteria 1-3 must be answered positively for a PPA diagnosis.

1 Most prominent clinical feature is difficulty with language: e.g., word-finding deficits, paraphasias, effortful speech, grammatical and/or comprehension deficits
2 These deficits are the principal cause of impaired daily living activities: e.g., problems with communication activity related to speech and language, such as using the telephone; or performing routine job responsibilities that require verbal communication
3 Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease.

Exclusion Criteria

Criteria 1-4 must be answered negatively for a PPA diagnosis.

1 Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders: e.g., neoplasm, cerebrovascular disease, hypothyroidism
2 Cognitive disturbance is better accounted for by a psychiatric diagnosis: e.g., depression, bipolar disorder, schizophrenia, pre-existing personality disorder
3 Prominent initial episodic memory, visual memory and visuo-perceptual impairments: e.g., inability to copy simple line drawings
4 Prominent initial behavioral disturbance: e.g., marked disinhibition, emotional detachment, hyperorality or repetitive/compulsive behaviors

Diagnostic Criteria for Semantic Variant PPA (SV-PPA)

Also known as semantic dementia (SD) or PPA-S

Clinical Diagnosis of SV-PPA

Both of the core features (1 and 2) must be present, and at least three of the following other features (3-6) must be present.

1 Poor confrontation naming (of pictures or objects), particularly for low familiarity or low frequency items
2 Impaired single-word comprehension
3 Poor object knowledge, particularly for low frequency or low familiarity items
4 Surface dyslexia and/or dysgraphia
5 Spared repetition
6 Spared motor speech (no distortions) and grammar

Imaging-Supported SV-PPA Diagnosis

Both of the following criteria must be present.

1 Clinical diagnosis of SV-PPA
2 Imaging must show one or more of the following results:
    1 Predominant anterior temporal lobe atrophy on MRI
    2 Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET

Nonfluent/Agrammatic Variant PPA (NFAV-PPA)

The diagnostic criteria for nonfluent/agrammatic variant PPA (NFAV-PPA) developed by an international group of PPA investigators use two diagnostic categories: clinical diagnosis and imaging-supported diagnosis. The criteria must be met as defined without meeting any of the exclusion criteria for primary progressive aphasia (PPA)

Primary Progressive Aphasia (PPA)

Criteria 1-3 must be answered positively for a PPA diagnosis.

1 Most prominent clinical feature is difficulty with language: e.g., word-finding deficits, paraphasias, effortful speech, grammatical and/or comprehension deficits

2 These deficits are the principal cause of impaired daily living activities: e.g., problems with communication activity related to speech and language, such as using the telephone; or performing routine job responsibilities that require verbal communication

3 Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease.

Exclusion Criteria

Criteria 1-4 must be answered negatively for a PPA diagnosis.

1 Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders: e.g., neoplasm, cerebrovascular disease, hypothyroidism

2 Cognitive disturbance is better accounted for by a psychiatric diagnosis: e.g., depression, bipolar disorder, schizophrenia, pre-existing personality disorder

3 Prominent initial episodic memory, visual memory and visuo-perceptual impairments: e.g., inability to copy simple line drawings

4 Prominent initial behavioral disturbance: e.g., marked disinhibition, emotional detachment, hyperorality or repetitive/compulsive behaviors

Diagnostic Criteria for Nonfluent/Agrammatic Variant PPA (NFAV-PPA)

Also known as progressive nonfluent aphasia (PNFA) and agrammatic PPA or PPA-G

Clinical Diagnosis of NFAV-PPA

At least one of the core features (1 and 2) must be present, and at least two of the following other features (3-5) must be present.

1 Agrammatism in language production

2 Effortful, halting speech with inconsistent distortions, deletions, substitutions, insertions, or transpositions of speech sounds, particularly in polysyllabic words (often considered to reflect "apraxia of speech")

3 Impaired comprehension of syntactically complex sentences

4 Spared single word comprehension

5 Spared object knowledge

Imaging-Supported NFAV-PPA Diagnosis

Both of the following criteria must be present.

1 Clinical diagnosis of NFAV-PPA

2 Imaging must show one or more of the following results:

    1 Predominant left posterior fronto-insular atrophy on MRI

Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET

Appendix 6: Conference Proceedings

Aspects of this work have been presented at national, and international conferences as reported here.

Burke, T., Elamin, M., Hardiman, O. & Pender, N. (2015). Cognitive Deficits in Pure ALS: A Data Driven Approach. Oral presentation presented to the European Network for the Cure of ALS (ENCALS) Dublin

Burke, T., Pinto-Grau, M., Elamin, M., Hardiman, O. & Pender, N. (2015). Social Cognitive Function in ALS Patients. Poster presented at the Neurological Alliance Ireland (NAI) meeting, Dublin

Burke T., Hardiman, O. & Pender, N. (2015). Population based Cognitive Phenotyping in Amyotrophic Lateral Sclerosis. Paper presented at the Psychological Society of Ireland's Early Graduate Conference, NUIG, Ireland.

Burke, T., Elamin, M., Galvin, M., Hardiman, O. & Pender, N. (2015). Caregiver Burden Does Not Affect Patient Survival in Amyotrophic Lateral Sclerosis: Investigating Factors Contributing to Burden. Accepted to American Academy of Neurology (AAN) Annual Meeting, Washington DC.

Burke, T., Pinto-Grau, M., Lonergan, K., Hardiman, O. & Pender, N. (2015). A Prospective Population-based Investigation Of Cross-modal Emotional Processing In Amyotrophic Lateral Sclerosis. Oral presentation accepted to the 26th International Symposium on ALS/MND, Orlando.

Burke, T., Elamin, M., Pinto-Grau, M., Lonergan, K., Hardiman, O. & Pender, N. (2015). Assessing the functional equivalence of verbal and spatial working memory tasks in Amyotrophic Lateral Sclerosis. Psychological Society of Ireland's annual conference.

Burke, T., Elamin, M., Hardiman, O. & Pender, N. (2014). Apathy: The most cogent factor contributing to Caregiver Burden in Motor Neuron Disease. Paper accepted to the Psychological Society of Ireland's Annual Conference, Kilkenny.

Burke, T., Pinto-Grau, M., Elamin, M., Hardiman, O. & Pender, N. (2014). An Isolated Deficit: Social Afective Deficits in Bulbar Onset ALS Patients. [DOI:10.3109/21678421.2014.960176/066]

Burke, T., Elamin, M., Galavin, M., Hardiman, O. & Pender N. (2014). Caregiver Burden Does Not Affect Patient Survival in ALS; Apathy as a Cogent Factor. Accepted to the Neuroscience Ireland CNS conference, Galway.

Burke, T., Wynne, B., O'Brien, C., Elamin, M., Bede, P., Hardiman, O. & Pender, N. (2014). Practice (Effects) Should Make Perfect: Repeated Neuropsychological Assessment of Frontal Lobe Function. Poster accepted to the Psychological Society of Ireland's Annual Conference, Kilkenny.

Burke, T., Elamin, M., Hardiman, O., & Pender, N. (2014). Cognition and Emotional Processing in ALS. Front. Neurosci. doi10.3389/conf.fnins.2014.87.00005

Burke, T., Pinto-Grau, M., Elamin, M., Hardiman, O., & Pender, N. (2014). Preserved Executive Function with Social Cognitive Deficits in ALS. British Neuropsychological Society Spring Meeting, Queen Square, London, March 2014.

Burke, T., Pinto-Grau, M., Elamin, M., Hardiman, O., & Pender, N. (2014). Neuropsychology and MND: Thinking back and Looking Ahead. IMNDA & TCD 'Patient Knowledge Exchange' Event, Dublin, June 2014.

Burke, Pinto-Grau, Lonergan, K., ... & Pender, N. (2014). Inferring Mental States or Inferring Too Much?: Left Fusiform Function and Social Cognition in ALS. Psychological Society of Ireland's Student Congress, Dublin, April 2014

Burke, T., Pinto-Grau, M., Elamin, M., ... & Pender, N. (2013). Emotion and Social Cognitive Assessments in HD and ALS. PSI Annual Conference, Sligo, November 2013

Burke, T., Pinto-Grau, M., Elamin, M., Hardiman, O., & Pender, N. (2013). Neuropsychological Input into the Multidisciplinary Team: What does it involve for Patients? IMNDA/TCD 'Patient Knowledge Exchange' Event, Dublin, June 2013.

Burke, T., Pinto-Grau, M., Hardiman, O., & Pender, N.. (2013). ALS and Affective Theory of Mind: A Neuropsychological Investigation. Psychological Society of Ireland's Conference, Sligo.

Appendix 7: Print Publications Arising from these data

Data contained within this thesis have been successful in being published following peer-review. There are contained here as per the University of Dublin, Trinity College's Thesis Submission Guidelines. As per these guidelines, other publications arising during the time of this thesis have been included, whereby data from this thesis have largely contributed to the publication i.e., cognitive categorization of ALS patients for an EEG study.

Huntington's Disease

9

Tom Burke, Colin P. Doherty, Walter Koroshetz, and Niall Pender

9.1 Introduction

HD results from an expansion of the trinucleotide repeat (Cytosine Adenine Guanine; CAG) causing an expanded polyglutamine chain in the *huntingtin* gene located on chromosome 4p16.3. While there is no unique set of symptoms which indicate the onset in HD, many patients present initially with symptoms that reflect early neurological impairment, such as brief random irregular muscle jerks (chorea), writhing movements (athetosis), difficulty walking and a tendency to fall or clumsiness. Many also present with a range of psychiatric problems including depression and anxiety. The rate of suicide in patients with HD is higher than normal base rates and accounts for 7 % of deaths in non-hospitalised HD patients. According to recent literature, the rate of suicidality between motor-symptomatic, and pre-motor symptomatic gene carriers is equal, with suicidal ideation occurring in an equal number of patients. There are also reports of self-injury, alcohol abuse, criminal offences and marital difficulties. Cognitive impairments such as poor short-term memory, poor concentration, deterioration in work performance and poor judgement have been noted in the early stages. Recent research has identified that HD patients have emerging difficulty with aspects of social cognition before movements become apparent which results in poor inter-personal relationships. As a result of degeneration in the fronto-striatal regions leading to behavioural disinhibition, patients can become aggressive or violent as the disease progresses. It has been recognised that the initial site of deterioration in HD lies within the basal ganglia and that as the disease progresses the damage extends to encompass the cortical structures.

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DOI 10.1007/978-3-319-23309-3_9

burket2@tcd.ie

The Impact of Cognitive and Behavioural Change on QoL of Caregivers and Patients with ALS and other Neurological Conditions.

Burke, T., Galvin, M., Pender, N., & Hardiman, O. (2016). The Impact of Cognitive and Behavioural Change on QoL of Caregivers and Patients with ALS and other Neurological Conditions. In F. Pagnini, & Z. Simmons (Eds.) *Amyotrophic Lateral Sclerosis: Understanding and Optimizing Quality of Life and Psychological Well-Being.* UK: OUP

Abstract

This chapter details the impact of cognitive and behavioural changes on Quality of Life (QoL) in caregivers and patients with ALS and other neurodegenerative conditions. We review the cognitive and behavioural profile of conditions such as Amyotrophic Lateral Sclerosis, Huntington's Disease, Multiple Sclerosis, Frontotemporal Dementia and Alzheimer's Disease, Traumatic Brain Injury, Frontal Brain Tumour, Stroke, and Parkinson's Disease, and investigate their impact on patient and caregiver QoL. We consider the implications for quality of life in ALS and a wider cohort of neurologically compromised patients, explaining the efficacy of intervention strategies. We describe how healthcare providers can optimize holistic care for caregivers and patients with ALS by understanding cognitive and behaviour impairments and their effects on Quality of Life, and how they also learn to facilitate management through interventions and techniques aimed at maximizing QoL.

The chapter concludes with an overview of evidence- and practice-based supports relevant for clinicians, and considers interventions in the presence of patient's cognitive and behavioural impairment.

Keywords: Cognition; Behaviour; ALS; Neurodegeneration; Quality of Life; Intervention.

Introduction

Cognitive impairment is the most consistent neurological complication of acquired and degenerative brain disorders. A high proportion of patients with Amyotrophic Lateral Sclerosis (ALS), Huntington's Disease (HD), Multiple Sclerosis (MS), Frontotemporal Dementia (FTD) and Alzheimer's Disease (AD), Traumatic Brain Injury (TBI), Stroke, and Parkinson's Disease (PD) experience cognitive impairment, often early in their disease course, or before the manifestation of traditional diagnostic criteria. In ALS, for example, cognitive deficits at the early stage of the condition can predict functional decline in patients. Furthermore, measures of cognitive impairment can be used to predict disease trajectory in dementia populations.

Many neurodegenerative diseases also present with behavioural changes that reflect the extent of the underlying disease progression. Combined with cognitive impairment this can represent a significant change from their premorbid state. These deficits can manifest along a continuum from very mild to severe forms, as seen in ALS. Moreover, behavioural and cognitive features may change independently of each other, leading to management challenges for clinical teams caring for such patients, and daily difficulties for the patient's carers.

Compared to classical neurological symptoms such as weakness or sensory loss, and established neuropsychiatric complications such as depression or anxiety, the impact of cognitive deficits and behavioural change on QoL of patients and their primary caregivers has been relatively under investigated. There is accumulating evidence to suggest that patients with neurological disorders may be particularly concerned about changes in their cognitive functioning – although whether this in fact correlates with objective measures of cognitive decline is not yet clear. Available literature suggests that this concern may relate to their perceived impact of the cognitive impairment in their Quality of Life (QoL). While clinical teams often rely on established measures of physical impairment, functional decline, and reduced social participation to quantify the impact of a disease, other variables relevant to QoL such as perceived subjective well-being, life satisfaction, or spiritual fulfilment, are not routinely measured.

The impact of cognitive and behavioural impairment on QoL is complex and multi-directional. This is in part a function of the variability and unpredictability of these impairments. Cognitive domains such as executive function, social cognition, memory, attention, language/communication, combined with behavioural changes such as apathy, disinhibition, or aggression, could impact the perceived quality of life in a patient or caregiver in a multitude of ways. Given that cognitive impairment can be a component both of the neurodegenerations and traumatic brain disorders, it is surprising that their impact on QoL has not been fully elucidated.

Cognitive Impairment and Everyday Function

The World Health Organization identifies six major domains of QoL:

1. **Physical domain**
2. **Psychological domain**
3. **Level of independence**
4. **Social relationships**
5. **Environment**
6. **Personal beliefs**

Considering each of these domains independently, it is clear that cognitive and behavioural impairment secondary to an acquired brain injury or neurodegenerative condition could have a significant impact on a

person's Quality of Life. Both cognitive and behavioural changes can have real-world implications for people, not least of which is their impact on personal and domestic activities of daily living (ADLs). Furthermore, such impairments impact heavily on an individual's ability to pursue, or return to gainful employment. A decline in ability to engage with the requirements of a job can sometimes be the first harbinger of a neurodegenerative condition. The ensuing loss of employment can then represent one of the first assaults on an individual's autonomy, independence and overall QoL. As the impairment progresses, there can be a profound impact on day-to-day activities. For example, visuo-spatial impairment is the most significant predictor of decline in ability to dress, bathe, use the telephone or retain mobility. A decline in these abilities is often seen in early in the course of posterior variants of Alzheimer's disease (Posterior Cortical Atrophy) or with Parkinsonian conditions.

A decline in attention, often reported in traumatic brain injury and many other neurological conditions, may also reduce the capability for awareness of basic personal ADLs such as washing and independent toileting, enjoyment from social relationships, and may even create a health and safety risk in navigating new environments.

Language impairment, which is predominantly a feature in left lateralised frontotemporal dementia, (also known to occur in ALS), is associated with poor communication, both verbally and through the use of communication aids.

Memory impairment, which is relatively uncommon in ALS, can lead to confusion, getting lost in familiar places, potentially hazardous situations e.g., a gas stove may have been ignited and forgotten about, a failure to take prescribed medication or adhere to strict medical regimes, can affect individuals often leading to 1:1 supervision as the disease progresses.

Speed of information processing can have a serious impact on a patient's daily functioning. Many patients struggle to follow conversations, quickly make decisions, or even understand their favourite television programmes. Due to these limitations, many patients begin to avoid social gatherings due to their inability to keep up with rapid social communication. This is often compounded by difficulties with social cognition, which can impact on their ability to understand the intentions and emotional needs of others, as well as produce socially appropriate affection and emotion.

As cognitive dysfunction may also implicate adherence to treatment plans, performance on cognitive testing can provide valuable insights into the patient's daily functioning and enable clinical teams to make suitable arrangements for care and management. This may include discussing prospective treatment options early in the course of a neurodegenerative disease, or as a family unit in the case of sudden TBI. Discussing treatment options early in the course of the disease may reduce health-related stress for patients and their caregivers as the disease progresses.

The Prevalence of Cognitive and Behavioural Change

Amyotrophic Lateral Sclerosis

In recent years there has been an increasing awareness of the relationship between Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD). This overlap has been strengthened by greater volumes of research focusing on the cognitive and behavioural continuum in ALS. On-going genetic discoveries in

particular the C9orf72 variant have also contributed to our understanding of these conditions. Recognizing cognitive and behavioural impairment is an essential component in the management of patients with ALS. Up to 13% of ALS patients present with a comorbid FTD. Due to the triad of physical, cognitive, and behavioural features associated with ALS-FTD, greater caregiver burden and lower QoL in patients have been reported. The most commonly reported cognitive deficit in population-based ALS research is executive dysfunction (in up to 25%), followed by non-executive cognitive deficits i.e., language, memory, visual impairment (14%), with the remainder remaining cognitively intact.

Selective cognitive impairment in the form of verbal fluency deficits, most likely indicating executive dysfunction, appears relatively early on in the course of the disease, and language functions may become more vulnerable as the disease progresses. Planning, organizing information, problem solving, shifting attention, inhibiting behaviour, and negotiating social norms are all examples of executive dysfunction in ALS. Within ALS, higher levels of cognitive impairment specific to executive dysfunction indicate a more rapid disease progression.

Behavioural change can appear early and can precede more classic ALS symptoms. The most prominent behavioural change in ALS is apathy, present in up to 60% of ALS patients, followed by disinhibited and dysexecutive behaviours such as impulsivity. These neuropsychiatric symptoms have been shown to impact on family carers and should be addressed early in the diagnosis and management of ALS. Recent findings suggest that patients with ALS who did not fulfil diagnostic criteria for ALS-FTD may exhibited subtle neuropsychiatric and cognitive changes, which have been shown to implicate caregiver relationships.

Frontotemporal Dementia

The incidence of dementia increases with age, much like ALS, and it presents as a major global health problem impacting people's ability to maintain occupational and social function. However, the age of onset associated with Frontotemporal Dementia (FTD) is much younger than more prevalent dementia syndromes e.g., Alzheimer's disease. FTD is characterised by a number of different sub-phenotypes, the most common of which is the behavioural variant (bvFTD). At the onset of bvFTD, behavioural changes dominate the presenting profile. These behavioural changes are associated with prominent personality changes, early decline in interpersonal conduct (disinhibition). Impairment in regulation of personal conduct, emotional blunting, and loss of insight is known to occur early in the condition. Alongside these behavioural changes, patients often present with severe executive impairment.

As bvFTD advances, patients develop progressive disturbance of executive functions, loss of initiative, reduced mental flexibility, and poor organization. Language can be impaired, but not to the same extent as other FTD variants. Behavioural alterations such as pacing and repetitive stereotyped behaviours may also develop. More severe cognitive impairment and behavioural change at baseline tends to be associated with greater caregiver burden.

Traumatic Brain Injury

A Traumatic Brain Injury (TBI) is a devastating sudden event that can, by definition, have a catastrophic impact on the whole family. The implications of a TBI can be widespread, extending from cognitive, behavioural, and physical impairments, into functional domains such as one's occupation, interpersonal relationships, and leisure

activities. Few studies have incorporated both early- and late-evaluation time points when investigating the prevalence of cognitive and behavioural changes associated with frontal head injury.

The cognitive and behavioural impacts of a TBI have been shown to be widespread and adversely affect an individual's functional ability across a multitude of domains. The three most common events leading to a TBI are falls i.e., falling from a height, vehicle or sport related collisions, and violence or combat injuries. As many TBI patients are young males, the impact can extend to parents, siblings, spouses and children. TBI has a significant impact on occupation and education, with severely injured patients requiring long-term care for many years post injury.

The available literature surrounding TBI is consistent in reporting executive dysfunction, encoding related memory difficulties, difficulties with directed attention, planning, judgement, and errors in decision making. Reports of impairment tend to identify the executive system as distinct components, which are to some extent dissociable. However, it is also known that individual impairment can have negative implications for other cognitive domains. Behaviourally, three main domains are prevalent within the literature. The most commonly reported new onset behaviours include impulsivity, apathy, and inappropriate displays of emotion. Such executive dysfunction has a negative impact on rehabilitation outcomes and subsequent functional ability.

Impaired self-awareness is a commonly reported outcome arising from executive dysfunction within this cohort. A loss of metacognition is a problem that confronts rehabilitation providers and family members, manifesting in limited awareness of cognitive, emotional, and behavioural changes. Difficulties with cognitive and communicative activities are known to characterize disablement after TBI. These limitations present a particular challenge to the assessment of QoL in this cohort.

Brain Tumour

The cognitive and behavioural deficits associated with brain tumours are a function of the tumour type, grade and rate of progression, the location of the tumour, treatment effects (surgical, radiological and pharmacological) and secondary impacts of the tumour (for example, hormonal impairments).

Cognitive abnormalities in those with Central Nervous System (CNS) tumours are common, usually as a direct result of the tumour invasion, but there is an increased awareness of the secondary impact of treatment. Recent studies suggest that both chemotherapy and radiotherapy can also cause cognitive deficits, although focal radiotherapy in patients with glioma is rarely the main reason for cognitive impairment. Neuropsychological effects may occur beyond the local tumour site. Compared with healthy controls, patients with glioma have performed significantly lower on measures of information processing speed, psychomotor function, attention based tasks, working memory, and executive functioning. Cognitive function is also recognised as an independent prognostic factor in the survival of glioma patients, similar to ALS. Neuropsychiatric symptoms and communication difficulties have been strongly associated with high-perceived disease burden.

Stroke

Post-stroke cognitive impairment can occur in approximately 40–55% of patients. Comprehensive neuropsychological testing in 164 stroke patients identified deficits on specific tests measuring executive and sequential aspects of cognition and behaviour. In a follow-up study 2 years post-stroke, significant improvements were noted for all cognitive domains with the largest improvement noted in the attentional system. A small subset of patients accounted for the significant cognitive improvement, as most patients showed no improvement or proceeded to decline further. Post-stroke syndromes are not only cognitive in nature, and can

include hemiplegia, poor balance, visual difficulties, and aphasia. Commonly reported cognitively and behavioural difficulties are displayed in Table 1 based on a cohort of >170 stroke patients, and >140 caregivers. Apathy is a complex concept composed of aspects of cognition, emotion, motor and sensory functions, and is often implicated post-stroke. Clinically, apathy is defined as a lack of, or diminished, emotion, interest, concern, and motivation, manifesting as poor engagement with significant others and in social activities, and a loss of pleasure in usual interests.

Table 1: Common Cognitive and Behavioural Outcome of Stroke.

Cognitive Impairment	**Behavioural Changes**
Forgetfulness	Emotional Lability
Mental slowness	Loss of Initiative
Poor concentration	Irritability
Inability to do things simultaneously	Changed Sexual Drive
Aphasia	Personality Changes
Defects of orientation	Dependent behaviour
Defects of consciousness	Depressed Mood
Apraxia	More Egocentric Behaviour
Agnosia	More Anxious

Apathy is reported to have a negative influence on recovery after stroke particularly in terms of daily functioning and cognitive rehabilitation. Unfortunately, there are few studies examining the effectiveness of cognitive rehabilitation interventions in patients post-stroke. Patients and their families are required to adjust to significant cognitive, behavioural and physical difficulties, which have a substantial impact on functional ability and, in turn, quality of life.

Alzheimer's Disease

The pathology associated with Alzheimer's disease (AD) is initially selective for limbic regions implicating episodic memory, which leads to a presenting cognitive impairment. Rapid loss of information relate to encoding to memory in the early stages of the disease are often seen. Cognitive assessments are used in the early investigations of AD, to investigate the role of cognitive aging, and to screen for a prodromal stage of AD, known as Mild Cognitive Impairment (MCI).

As well as memory related deficits, patients with AD are often impaired on tests of object naming, verbal fluency, and semantic categorization. Deficits in executive function, responsible for the mental manipulation of information, concept formation, problem solving, and directed behaviour occur early in the course of AD and can be present in Mild Cognitive Impairment (MCI), albeit to a lesser extent. Changes in visuospatial function are also apparent on visuo-constructional and perceptual tasks. This may arise from the loss of effective interaction and cortical information processing systems.

The systematic investigation of cognitive performance across major cognitive domains illustrates impairment with memory, attention, executive dysfunction, and visuospatial deficits in the majority of patients. The progressive pattern of cognitive deficits fits with the known pathological staging of AD.

Parkinson's Disease

Cognitive impairment is a non-motor feature of ideopathic Parkinson's disease (PD) and is increasingly recognised as an important and integral feature of the illness. Specific cognitive domains can be affected even in early stages of the disease, and clinical criteria have been suggested to quantify the degree of impairment. Cognitive domains affected include executive performance and visuospatial function, with greater preservation of memory and language. Bradykinesia can result in slowed cognitive functioning and, indeed, many patients report difficulties keeping up with and participating in social activities.

In the case of a Parkinson's Disease Dementia (PDD), functional impairment has been associated with motor severity as well as several non-motor factors such as apathy, depression, and psychosis. As with many of the neurodegenerations, PD is characterised by significant physical disability, postural instability, and gait difficulties.

The presence of dementia significantly increases caregiver burden and decreases quality of life. However, even mild levels of cognitive impairment increased disability and overall functional impairment progresses in tandem with cognitive decline.

Huntington's Disease

Huntington's Disease (HD) is an autosomal dominant neurodegenerative condition characterised by triad of symptoms, which include a movement disorder marked by chorea and athetosis, cognitive impairment, and psychiatric features. While 75% of patients present with neurological features, since the availability of a genetic diagnosis for HD it has become clear that many so-called pre-manifest patients can present with early cognitive or behavioural features. Cognitive deficits consist of impaired executive functions, reflecting early damage to fronto-striatal and fronto-cortical pathways. These deficits include poor planning, problem solving, organisation, and aspects of memory functioning.

These changes in executive function and social cognitive decline are often noticeable at least 2 years prior to the clinical presentation of HD. Cognitive and behavioural deficits are progressive, and the prevalence of severe cognitive impairment or dementia in HD is reported to be between 30 and 50%.

Six main cognitive factors have to be considered when monitoring markers of disease progress, and cognitive indices should be used when monitoring cognitive function in HD. These factors include: (1) speed/inhibition, (2) verbal working memory, (3) motor planning/speed, (4) attention-information integration, (5) sensory-perceptual processing, and (6) verbal learning/memory. Overall, motor planning/speed and sensory-perceptual processing appear to be the most important markers of disease prognosis. In the early clinical stages of the condition, irritability is prevalent. These features are known to deteriorate, and become increasingly disproportionate.

Much like ALS, QoL has been poorly studied in this condition, particularly in relation to cognitive decline and behaviour change. Moreover, as HD is an inherited genetic disorder with almost complete penetrance, it brings its own unique social difficulties. Unaffected family members will have to provide care for parents, spouses and children often on numerous occasions as the disease becomes manifest across generations. This burden takes a terrible toll on the mental and physical health of these carers.

Multiple Sclerosis

Multiple Sclerosis (MS) is one of the most common chronic neurologic diseases in young adults. Cognitive deficits have been reported from 30% to 70% of patients, often in the earliest phases of disease. Even in patients with short disease duration (less than 2 years), discrete impairment of cognitive function may be found in up to

60% on neuropsychological testing. MS negatively affects cognitive domains including executive function and attention, information processing abilities, processing speed, and memory. Cognitive impairment does not simply reflect problems in performing cognitive tasks, but is often associated with reduced functional ability. Cognitive impairment can have a deleterious impact on patients' occupational and social functioning, as well as on their overall quality of life. Cognitively impaired patients show significantly higher depression and anxiety.

Similar to ALS, dysarthria is a common physical feature of MS. It affects approximately 40% to 50% of individuals with the second progressive form of MS and is the most common communication disorder in this population. Speed, strength, range, timing, and accuracy of speech movements involved in speech processes of respiration, phonation, articulation, and prosody are affected.

As MS predominantly affects young people, it can have a devastating impact on their occupational status and careers. Patients may need to retire from work to cope with the variations in the disease course and require carer support at a young age. However, the burden and impact of the disease will vary as a functioning of the disease course with those patients experiencing a primary progressive variant more adversely affected than other variants.

The Impact of Cognitive and Behaviour Change on Patient QoL

Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

In ALS, deficits may present pre-clinically or early in the disease course. Within ALS based research and clinical practice there is an increasing recognition of the importance of categorising a broad spectrum of cognitive impairments associated with the disease. However, there is a dearth of studies investigating the specific role of cognitive impairment on QoL. Quantifying the detrimental impact that cognitive and behavioural changes have on an individual's functional ability, lifestyle, and social interactions can be of value as there is an evolving recognition that cognitive and behavioural changes are likely to negatively impact on personal relationships and consequently threaten social support and reduce QoL.

To date, there has been an absence of longitudinal QoL research that assesses the degree to which burden is influenced by changes in cognitive dysfunction and behavioural change. There may be several reasons for this. Cognitive deficits are conceived as a cumulative loss of function supported by specific systems, and the impact of heterogeneous losses is difficult to study. A further factor is that cognitive deficits are rarely static and are often influenced by the natural history of disease. Longitudinal studies of cognition in ALS indicate that selective cognitive impairment, in the form of verbal fluency deficits, indicating executive dysfunction, appears very early on in the course of the disease, and language functions become more vulnerable as the disease progresses. However, performance on cognitive testing close to the diagnosis of ALS is not predictive of burden or low QoL. Within cross-sectional studies QoL scores, correlate positively with the existence of confiding and emotional support and also correlate negatively with the presence of self-rated everyday cognitive difficulties, as described above.

A lack of insight in patients with ALS is associated with impaired executive skills such as decision-making. This represents a substantial clinical problem, with numerous studies documenting the negative impact of reduced

insight. In a study comparing patients with ALS and those with ALS-FTD, patients with ALS–FTD had a worse compliance for breathing treatments and nutritional supplements. Impaired deficit awareness has increasingly been recognised as a multifaceted neuropsychological problem. This is often assessed within the ALS literature, by relying on patients' subjective reports of difficulties and experiences in daily life, or disease related change using discrepancies between patients' self-report and that of a significant other.

Clinicians can identify those most likely to remain burdened using data routinely collected, based on ALS, ALS-FTD, and FTD research. Through the assessment of cognitive and behavioural change in ALS patients, clinicians may tailor individualised or group-based interventions to enhance and maintain QoL. This may prevent subsequent distress in caregivers and reduce behavioural disturbances in patients.

Traumatic Brain Injury

As a result of the broad cognitive dysfunction following a TBI there are substantial negative consequences in the QoL of both the patient and their family. Parents, siblings, spouses or children might inadvertently become carers. The patient may experience significant limitations in the ability to engage in productive employment or social situations. Independent living can be challenging in many instances. While limits to self-awareness might mitigate the understanding of lifestyle and functional changes, patients and their families may also require intense input from acute and post-acute rehabilitation services to maintain QoL.

Many studies on Traumatic Brain Injury (TBI) report how informants or caregivers rate the QoL of the patient lower than the patient's own self-report. Potential explanatory factors for this discrepancy may be caregiver depression, caregiver burden, and gradual change of the patient's life goals into areas where more control can be exerted. The discrepancy may also be caused by the fact that some patients lack insight in their current symptoms or that patients may be unaware of lost functions, activities and social relationships. However, some studies also suggest that patients rely on social comparison to rate their QoL and that patients might rate themselves high in relation to other patients who are perceived to have a great number of deficits rather than in relation to their former selves.

In TBI, the physical and cognitive impairments produced by the injury are frequently associated with serious functional limitations. Persons with TBI may experience frustration, and a sense of lack of control that exacerbates their difficulties and lowers their QoL. Use of transportation and the freedom to interact with people and pursue one's interests are often restricted due to loss of driving privileges, related cognitive impairment or mobility issues. Communication problems are characteristic of many persons with TBI. Implemented interventions with TBI patients may benefit from using QoL-based outcome measures in conjunction with conventional measures, such as TBI severity.

Brain Tumour

There has been growing interest in the link between cognitive impairment and QoL in brain tumour patients, as more subtle cognitive deficits are being identified. The diagnosis, management, and treatment of brain tumours have a major impact on patients' QoL. Cognitive deficits can prevent brain tumour 'long-term survivors' from returning to premorbid autonomy and their occupation. Moreover, cognitive symptomatology may enhance the burden of other symptoms.

Considering the impact of cognitive deficits on QoL in this cohort, patients also experience secondary symptoms

including (but not limited to) motor deficits, personality changes, aphasia, or visual field defects. These additional symptoms can further impact on patient QoL. Tumour hemispheric laterality, size, and location, have also been reported to be contributory factors associated with lower QoL. This appears to be a consequence of greater cognitive impairment and behavioural change, associated with larger and more aggressive tumours in frontotemporal regions.

A multidimensional approach is considered best when investigating the impact of cognitive and behavioural change on QoL of patients with brain tumours. Measures of well-being which reflect psychosocial and cognitive aspects have been shown to be more appropriate to detect the impact on QoL for both the patient and the family, than traditionally isolated functional instruments.

Stroke

Stroke patients report poorer QoL in the presence of memory and thinking difficulties. Ischaemic stroke patients have reported communication difficulties resulting in lower QoL. Infarct volume, aphasia, impaired motor function, and impaired cognitive function were independently linked with poorer QoL. Cognitive impairment (particularly problems with visual perception and construction), increasing age, and functional dependence, further predicted a reduced QoL. The impact of cognitive impairment on QoL was investigated in 129 patients with ischaemic stroke (64 men; mean age 63.2±14.6 years). Infarct volume, aphasia, impaired motor function, disability relating to ADLs, disturbed global functional health and impaired cognitive function were significantly associated with poorer QoL. In another study of 1572 stroke patients, mean age 69 years (±12 years), cognitive impairment was present in 38%. Cognitive impairment was significantly related to lower functional outcomes and lower QoL. Attention and visuospatial ability were again the cognitive domains most closely associated with QoL.

Alzheimer's Disease

Patients with early AD generally report higher QoL than their informants. This disagreement is sometimes associated with the presence of anosognosia, which may also lead to patients reporting a higher QoL than may be expected. Several other factors, such as dementia severity, memory impairment, and impairments in ADLs have also been reported to have a significant impact on QoL in AD.

Research on determinants of QoL for patients with AD, and interventions to increase QoL are current priorities in dementia care. Recognising the determinants of change in QoL has received much attention, with cognitive performance at the forefront in AD. In a recent study of 104 AD patient and caregiver dyads, and an additional comparison group of 22 patient dyads without cognitive impairment, correlations of patient reported QoL with patient depression scores were significant, alongside satisfaction with life scale reports. Caregiver QoL was correlated with the Neuropsychiatric Inventory total score, distress, and patient MMSE. Patient QoL ratings were higher than caregiver ratings. Both patient- and caregiver-rated QoL scores were lower in patients with cognitive impairment than in the comparison group without cognitive impairment. Similar to these findings, 164 patients-caregiver dyads were recruited to investigate the role of anosognosia on quality of life. With regards to QoL, for AD patients the results showed that lower depression scores and greater anosognosia explained 33% and 10% of the variance in QoL, respectively. That is, greater anosognosia was associated with higher perceived QoL in the patient. However, conversely anosognosia was associated with greater caregiver burden and a greater discrepancy between patient and caregiver ratings of QoL.

The role of formal versus informal healthcare settings has been widely researched in AD, compared to other

neurodegenerative conditions. For example total QoL score has been shown to be higher (i.e., better QoL) for patients living at home than for institutionalized patients.

Impaired ADLs predicted lower QoL in the later stages of cognitive impairment, or more severe AD. Behavioural disturbances, especially agitation, appeared to be negatively related to proxy-rated QoL in AD. There appeared to be a negative relation between QoL, ADLs, and cognition, although this is not confirmed in all studies. In longitudinal studies, depressive symptoms were negatively related to QoL, and cognition was positively related to self-rated quality of life. Dependency and depressive symptoms were negatively related to proxy-rated quality of life.

Parkinson's Disease

Cognitive, behavioural, and sleep disturbances are associated with reduced QoL in PD. Non-motor symptoms have been shown to be more important for reduced health-related quality of life than motor symptoms. Fatigue, depression, sensory complaints and gait disturbances emerge as relevant symptoms and should be given corresponding attention in the management of patients with early PD. However, few studies have interrogated the trajectory of cognitive decline in PD, and the relationship between poor cognitive performance and QoL.

A recent study compared 3 groups of people with PD: those with a mild cognitive impairment (PD-MCI), those with a dementia like syndrome (PDD), and those with no cognitive abnormalities (PD-NCA). QoL and disability were measured in 3 groups of participants with PD (PD-NCA, n =54; PD-MCI, n=48; and PDD, n=25). Caregivers (n=102) were assessed using the Zarit Burden Inventory. QoL and caregiver burden were similar in the groups without dementia, but were significantly different than those with PDD. By contrast, disability was progressively greater as cognition declined across the 3 groups. On ADL scale employed in the study, significant impairment was reported alongside the presence of any cognitive impairment. The presence of dementia significantly increases caregiver burden and decreases QoL. However, mild levels of cognitive impairment are correlated with an increase in physical disability and overall functional impairment progresses in tandem with cognitive decline. Unlike ALS, depression and functional ability predict QoL in patients with PD.

Huntington's Disease

In HD, the influence of cognitive and behavioural symptoms on patients' QoL determined the strongest associations with patient self-reported QoL. The role of cognitive and behavioural change on QoL is rather understudied within HD literature, as QoL based research tends to focus on the impact of predictive testing. That being said, executive dysfunction, as reflected in everyday behaviour, has been associated with lower patient QoL. Patient QoL is associated with cognitive performance, according to performance on the MMSE, age, and time since motor symptom onset. Neuropsychiatric symptoms are not directly related to QoL in HD.

In a more comprehensive study of cognition, behaviour, and QoL in 20 genetically confirmed HD patients, QoL was significantly lower for patients who exhibited greater apathy and showed more evidence of executive dysfunction in their everyday behaviour as assessed by the FrsBe.

Multiple Sclerosis

In a study of MS patients, speech accounted for 30.8% of the reported emotional distress, 30.8% of loneliness and isolation, and 38.4% of limitations in communication with family and friends. By contrast, physical symptomatology has not been consistently reported as a predictor of low QoL in ALS. In MS, a significant relationship was found between both memory impairment and executive dysfunction, and QoL. In the early stages of MS, patients with a recent diagnosis tend to report significantly lower scores on both physical and

mental aspects of QoL compared with matched controls. Depression, fatigue and apathy appear to be more common, and more severe in MS compared to controls. In a recent study of MS patients, no correlation was found between cognitive decline and QoL scores, yet patients with MS reported significantly lower physical and mental health related QoL scores. The controls scored significantly higher on all health related QoL sub-scores except for bodily pain. The incidence of fatigue in this cohort was 71% in patients compared to 27% in controls. 46% of patients compared to 18% of controls reported depression. The mean score for apathy was significantly higher among patients.

A longitudinal study of MS patients considered the role of cognitive and behavioural dysfunction in MS patients with a sample of 65 newly diagnosed MS patients followed up over a 7 year period. MS patient's self-reported QoL at baseline was severely reduced in MS patients compared with healthy controls. The independent predictors for QoL composite scores at follow-up were the baseline depression score and the memory impairment. Accordingly, 81.5 % of MS patients worked at baseline and only 54.4 % worked at follow-up. Among the MS patients who did not work at the time of the follow-up assessment, 72.7 % of them were cognitively impaired. Occupational status and its change over time was significantly associated with cognitive deterioration. Memory dysfunction related cognitive impairment in the early stages of MS was correlated with a decreased level in health perception and lower QoL, independent of fatigue, depression and physical disability, which are widely reported in MS.

The Impact of Patient Cognitive and Behaviour Change on Caregivers QoL

Caregivers: "The Unseen Patient"

The heterogeneity of caregiver-patient relationships adds an additional dimension to understanding the complexities associated with the impact of cognitive and behavioural change in neurological conditions on QoL. In general, relationship strain has been correlated to a number of factors including the premorbid relationship quality of patients and caregivers. Loss of intimacy, reduced social contacts, and the extent of change caused by the disease increase tension, worry, and stressful situations for both patient and caregiver.

Family members are increasingly being asked to perform complex tasks similar to those carried out by paid health or social service providers, often at great cost to their own well-being and great benefit to their relatives and society as a whole.

Caregiving presents difficult, sometimes intractable problems, and although through other neurodegenerative conditions, we have learned a great deal about how to describe and characterize the challenges of caregiving, assess its impact on family members, and identify promising intervention approaches, yet more needs to be done. Understanding caregiving stages across the disease trajectories may enable us to develop stage-appropriate preventive intervention strategies that protect the caregiver from adverse outcomes.

Caregiver burden is a multidimensional construct and encompasses both *objective* and *subjective* aspects. Cognitive, behavioural, and neuropsychiatric symptoms are significant factors that contribute to caregiver burden negatively impacting QOL. ALS caregivers with high QOL and low psychological morbidity (i.e., anxiety/depression) are those with a positive problem orientation (viewing problems as opportunities rather than threats) and those whose behavioural response style was rational rather than impulsive, careless, or characterized by avoidance. There is also evolving evidence that caregivers' psychological status may also influence the mental and physical outcome of patients.

The existing caregiving literature in wider neurodegenerative conditions tells us a great deal about who is at risk for negative health outcomes. The significance of caregiving has resulted in extensive research within this area, much of it focused on dementia caregiving. In AD, for example, cognitive deficits and behavioural symptoms of dementia account for approximately 25% of the variance in caregiver distress regardless of how this is measured. Female caregivers reported higher levels of burden than male caregivers.

In general, the various dimensions of caregiver burden are exemplified by ALS, which differs from other neurodegenerations as it can develop at any stage of life, and onset is often insidious, has a rapid decline, and variability in cognitive and behavioural phenotypes. These factors render the multidimensional determinants of caregiving uniquely complex in ALS compared to other neurodegenerative diseases.

Existing data suggests that behavioural change is of great importance as a mediator of caregiver burden and Quality of Life in ALS caregivers. The influence of cognitive change, poses a significant burden to both patients and their carers. However, the presence of cognitive/behavioural changes in ALS patients is often under-recognized by healthcare professionals, and the burden of care associated with these changes is not currently addressed in clinical practice. Moreover, the relentless disease progression typically seen in ALS exemplifies how the factors maintaining and precipitating strain and caregiver burden could change alongside the disease trajectory.

Relatively little is known about transitions into, and out of, the caregiving role. It is therefore necessary to develop methods by which burden and strain in patients or caregivers can be predicted to ensure adequate supports and referral pathways exist.

In ALS, caregiver burden and reduced caregiver Quality of Life is modulated by patients' cognitive and behavioural status, but does not significantly impact patient survival. Highly stressed caregivers show remarkable signs of recovery after the death of their loved one, suggesting that much of the work of dealing with loss occurs before the death. However, during the illness, caregivers are at high risk of developing stress, anxiety, and depression. Anxiety and depression in caregivers have been repeatedly shown to independently affect their QoL. Identifying predictors of anxiety and depression in people with ALS is also important because affective state may be amenable to psychopharmacologic and psychotherapeutic interventions, and depression may contribute to QoL. The concordance between caregiver and patient distress tends to be high. Caregiver mental status can in turn have a great influence on patients. This suggests that attention to the mental health needs of caregivers may not only relieve caregivers' distress but also alleviate patient distress, and improve QoL. Interventions For Cognitive And Behavioural Impairment.

Interventions to address cognitive and behavioural impairments in ALS and other neurodegenerative diseases aim to improve QoL for patients and caregivers. Despite new insights into the psychological issues of patients with neurodegenerative diseases and their caregivers, few studies have investigated possible protective factors against burden, or controlled trials to enhance QoL. In addition to a patient's reaction to their diagnosis, there are a variety of responses experienced by caregivers and the larger family unit. As well as providing care to patients, clinicians should provide appropriate support to the caregivers at the time of diagnosis, during the course of the illness, and post-bereavement.

Interventions can directly and indirectly assist in the management of cognitive and behaviour impairments and contribute to QoL. These include provision of training and support to family caregivers, interventions to maintain ADL functioning, limiting sources of conflict and frustration though redirecting and refocusing the patient, and empowerment of caregivers to change or moderate their interaction with the patient. In addition interventions for caregivers should focus on psychosocial and existential factors such as loss, guilt, resilience, and hope.

Much of the research to date has focused on interventions with dementia cohorts experiencing isolated cognitive impairment. However, the classification of interventions can be problematic as many share common components. Based on a review of patient and caregiver needs, types of interventions, patient resources and individualized consultation or case management, can include practical advice and information. Although this approach does not aim to change individuals' coping styles or beliefs and so can limit long-term efficacy.

Individualised Intervention

Psychotherapy includes individual or group-based psychodynamic, behavioural, and cognitive-behavioural therapy. Psycho-education is the structured presentation of information about dementia, expectable caring issues, stress management, and techniques to manage the patients' behaviour. Psycho-educational interventions for caregivers may improve the symptoms of the patient also, perhaps by training the carer to redirect the patient to avoid escalation of problem behaviour. This can be done on a 1:1 basis, or can be compiemented by sharing experiences in group-based settings.

Many caregivers and family members recount anecdotal evidence noting the therapeutic effect of individualized or group-based music sessions in patients with AD. Beneficial effects have been reported in the areas of behaviour, speech, motor integration and rhythmic movement. In FTD, passive coping strategies were associated with increased caregiver burden and decreased QoL. It has been recommend that FTD caregivers be offered core support that target passive coping strategies. Counselling and support have been shown to significantly delay nursing home placement for persons with AD, improving mood and caregiver quality of life.

Mindfulness Based Stress Reduction (MBSR), which can be administered in an individual or group setting, has been shown to promote a person's ability to cope with the experience and management of negative emotions, mitigating the effects of disease burden, promoting psychological adaptation. Considering both patient and caregivers, people who practice mindfulness have been shown to be more capable of responding to stressful situations without an automatic or otherwise maladaptive reaction i.e., avoidant coping strategies. MBSR has been shown to be a protective factor against caregiver burden in ALS.

In TBI, as in other groups, problem-focused coping strategies are reportedly more successful than emotion-focused strategies, however, this is counter-intuitive to ALS. In MS, knowledge of disease related difficulties (fatigue, communication, pain and depression) may help in prioritizing treatments, and assist in maintaining an optimal QoL. Traditional rehabilitation approaches to dysarthria focus on speech impairment and intelligibility.

In stroke, outcome studies have shown that rehabilitation programs are effective in improving long-term functional status and in decreasing institutionalization. There is a growing interest in post-stroke care as a means

of identifying alternative or compensatory mechanisms that could lead to improved function beyond the expected neural recovery. Compensatory mechanisms to improve post stroke recovery include psychological adaptations such as self-care self-efficacy, which is defined as the confidence a person has in his or her ability to perform relevant self-care activities.

Group based support services

Problem solving and reasoning skills of caregivers are an important determinant of caregiver well-being. Developing group interventions to enhance or teach caregivers new methods of problem solving are beneficial. Support groups provide the opportunity to share personal feelings and concerns, encourage mutuality and validation, and overcome feelings of social isolation. Respite offers substitute care to provide planned, temporary relief to the carer, through group day care, in-home respite, or institutional respite, vacation or emergency respite. Group based psycho-educational programs for family caregivers that target specific problem areas are more effective than other intervention modalities.

In wider neurodegenerative conditions, Cognitive-Behavioural Therapy (CBT) and Peer Support/Counselling group therapy (PSC) aimed to improve mood and QoL and decreasing uncertainty in illness. The mood of the participants in the CBT group improved in terms of anger, tension-anxiety, depression, confusion, and overall mood. The quality of life in this group was significantly improved compared to the other two groups, as was uncertainty in illness.

Cognitive Stimulation Group

Treatment guidelines have been highly critical of cognitive stimulation/training interventions in AD, in view of the risk that cognitive gains may be achieved at the expense of reduced wellbeing and adverse effects. However, treatments for cognitive decline are showing some promise in PD and may influence QoL. In a recent study, a rehabilitation program of 6 weeks including both motor and cognitive training was undertaken with 20 PD patients in the early stages of the illness, who experienced mild cognitive deficits, but not dementia. At the end of the scheduled sessions, the patients showed a significant improvement in verbal fluency, logic memory and on the Raven's matrices tests, when compared with baseline. Improved QoL scores for participants of cognitive stimulation therapy were associated with better mood that was mediated by improvements in cognition.

In a group-based intervention for AD patients, higher QoL was significantly correlated with lower levels of dependency and depression. Improvement in QoL was associated with being female, reduced depression, and increased cognitive function. These results suggest that although QoL in dementia appears to be independent of level of cognitive function, interventions aimed at improving cognitive function can have a direct effect on QoL.

Group Based Exercise Intervention

Several studies have demonstrated a positive impact of exercise on strength, balance, flexibility and QoL in patients with AD, MS, and PD. In a recent study in AD, fifteen patients attended exercise training for three months, which consisted of daily physical exercises supported by music for 30 min/session. They were compared with a group of 10 control patients, who received an equal amount of attention through daily conversation. The assessments were made before, after six weeks of intervention and immediately after the three-month experimental period. The exercise group showed a significant improvement in cognition. This was documented by an increased MMSE mean score of [12.87/15.53], and by a higher median score, rising from 10 to 14 points, on the fluency subset. The control group showed no significant improvement.

Similarly, a study recruited 115 people with early onset AD who were randomised within centres to an exercise

intervention group, and 86 to the control group. At follow-up the intervention group had significantly improved relative to the control group on MMSE, the Alzheimer's Disease Assessment Scale: Cognition, and QoL scales.

In a PD cohort completing an exercise-based intervention, selective benefits were shown for cognitive functioning with improvement of executive function. No significant effects were demonstrated for mood or disease-specific QoL. These results are consistent with previous research demonstrating selective benefits of exercise for executive function among normal ageing adults and PD.

In MS, patients enrolled into an exercise intervention suggested that that cognitive functioning changed over time based on level of fitness. Participants in the physically improved group demonstrated improved performance on measures of executive functioning after 12 weeks of exercise. The results of this study lend support to the hypothesis that change in fitness is associated with improved executive functioning in people with MS.

Multicomponent Interventions

Multicomponent interventions involve combining components from different interventions. Caregivers who possess more cognitive-behavioural resources are more likely to adjust to their caregiving role with fewer emotional difficulties. Combined with psycho-education support and MBSR patients and their caregivers are likely to experience a greater psychological wellbeing and QoL.

Multidisciplinary Approach

Currently, the best treatment available to patients with neurodegenerative conditions is optimal supportive care. In recent years, multidisciplinary ALS clinics have been developed to provide symptomatic and palliative care to patients with ALS. Greater patient numbers in multidisciplinary clinics (MDCs) leads to an accumulation of resources and clinical expertise that facilitates the management of this relatively rare, progressive disease.

MDC care has been shown to improve the mental health and QOL in patients with ALS. The positive effect of multidisciplinary clinics has also been shown to improve median patient survival times, and has considerable importance here in relation to cognitive and behavioural changes. Identification of cognitive decline and behavioural changes in a MDC can lead to a rapid implementation of psychologically tailored interventions for behaviour change. Furthermore, MDCs can offer both formal and informal opportunities for caregivers of patients with ALS, and other neurological conditions, to engage is help-seeking behaviour if necessary. Of patients who attend an MDC, their QoL is elevated in the domains of Social Functioning and Mental Health when compared to those who do not attend, and is independent of the presence of mechanical aids and appliances.

Accessing appropriate services and support can make a crucial difference. Studies among patients with dementia in general, show that behavioural problems are significant predictors of exhaustion leading to caregivers' mental and physical health problem

QoL Assessment Facilitating Intervention

QoL measures can be used to identify and prioritise problems and issues of clinical relevance; facilitate communication; screen for potential problems as particularly psychological and social issues can be overlooked unless specifically asked about; facilitate shared clinical decision making; monitor changes or response to treatment; and train new staff. Furthermore, assessing QoL in patient cohorts can have a positive therapeutic

effect due to greater introspection into positive aspects of one's life. Indeed, assessment of individualised QoL may be seen itself as an intervention, with the potential to influence the quality of life of that individual through self-evaluation and reflection, and/or their appraisal of QoL as the respondent identifies life domains of importance to them.

QoL does not necessarily diminish as neurodegeneration worsens, but continues to be strongly influenced by the resident's mood and interaction with their environment. Improvement in cognition and mood may lead to increased QoL. The routine use of QoL as an outcome measure for people with dementia in care homes is indicated to identify the benefits of clinical interventions and treatments, and to assess the impact of the disease process on individuals through the course of the illness.

Behavioural Impairment and Suggested Interventions

Given the prevalence of cognitive and behavioural impairment in the neurodegenerations, and particularly in ALS, FTD, and TBI, adjustments to roles and responsibilities, interaction styles, and to activities of daily living may be beneficial in reducing caregiver burden and increasing QoL. Reconfiguring existing roles within the family could reduce frustration or irritation if cognitive impairment is a prominent feature. If the patient is experiencing executive dysfunction and not able to reliably make decisions, they should still participate in less demanding ways.

Informally observing patterns of behaviour noting recurring negative changes may identify patterns of restlessness and fatigue. Some patients have been reported to become excessively tired by the end of the day and react with anger when demands upon them become overwhelming. Creating a predictable, structured schedule and a calm environment is helpful.

The spouse caregiver is often the 'target' of the patient's irritability and may need breaks and respite from caregiving responsibilities. When lack of empathy is present in a patient, the primary intervention is education and support to the family about the nature of ALS-FTD related change. This symptom of behavioural change can be confusing and frustrating without proper psycho-education. If new onset behaviours include sensitivity to external stimulus, when engaging in activities of daily living then aim to sit in more private and secluded sections of restaurants and waiting rooms to reduce overstimulation.

Furthermore, recommendations for routine management and care for patients with behavioural deficits can be summarised as follows:

- Explain clearly that cognitive and behavioural changes are part of the condition.
- Give a clear structure to the patient's day and make it as predictable as possible. To keep a routine is very important for the patient to be able to initiate and engage with daily activities.
- Give the patient enough time to make decisions and offer limited choices and closed ended questions. The "little and often" rule applies. Give the patient small amounts of information regularly rather than overload them with too much detail or content.
- Encourage the patient to make lists to help organize activities that may need to be done during the day.
- Avoid distractors in the room to help with concentration.
- Encourage the patient to use calendars, memory aids or phone alarms to help him remember appointments or recall to take the medication.

- Simplify communication to enhance patient's comprehension: speak clearly using a simple and straightforward language, break sentences into short phrases containing not too much information, and slow down when speaking.
- In patients with increased irritability, look for triggers or predictors that may prompt bursts of anger (tiredness, hunger, etc.) and try to prevent them. In cases of anger outburst, remain calm and avoid arguments, acknowledging the patient's irritability. It is also important to eliminate environmental stimuli that may be annoying for the patient such as loud noise, inadequate temperatures, etc.
- Avoid surprises that may create confusion or agitation and keep the environment calm and controlled. If visitors are expected, make sure that the patient is aware of this. If large gatherings provoke agitation or irritability in the patient, avoid them.
- Patient contact with the public may need to be supervised. It is recommendable that the patient frequents places where people are aware of the condition. Sometimes, to gain understanding from the public when visiting crowded places such as waiting rooms or restaurants, families are suggested to bring a small business-size card which clarifies that the patients suffers from a medical condition that affects behaviour.

For care planning, it is crucial to consider the additional complication of also dealing with the physical symptoms. Therefore, recommendations to enhance safety are also essential:

- Ensure that all family members understand that cognitive and behavioural changes are part of the condition.
- Encourage the family to supervise walking and transfers, especially in the case of impulsive patients, to reduce the risk of falls.
- Self-care and hygiene may also need to be supervised.
- Supervise eating, especially in the case of patients with swallowing difficulties. Patients with FTD may exhibit difficulties in swallowing associated with executive impairment rather that true dysphagia, and this should be taken into account. Patients may fail to follow the advice of limiting solid foods or not placing too much food in the mouth. If impulsive eating is observed, encourage the patient to count the number of times the food is chewed before swallowing it. If food cravings or hyperorality are present, portions need to be limited and cupboards or refrigerators may need to be locked. It is recommendable to keep safe foods visible and handy, and remove the less suitable ones from the patient's access.
- When dealing with impulsive patients, items that may be a risk of harm for the patient need to be removed.
- Make sure that the family is aware of future appointments and that these will be attended.
- Encourage caregivers and family to continue safe activities that the patient enjoys.
- Treatment options and preferences may need to be discussed with the patient as soon as possible in the course of the disease. As some patients may lack proper ability to judge their care needs or may lack insight about their deficits, it is advisable (or mandated in the case of ALS-FTD) to include the family in these discussions. It is important that the patient feels his/her preferences are validated to enhance adherence to care options. Moreover, family members also need to be aware of these preferences to reflect them when making decisions down the line.
- Caregiver involvement may also be mandatory when facing financial or legal issues.

- It is very important to set realistic expectations. Care plans for ALS patients with cognitive and behavioural deficits may need to be simplified to be in line with the patient's current abilities. Thus, it may not be possible for those with cognitive and behavioural impairment to comply with interventions such as non-invasive ventilation. Additionally, those with severe executive impairment or dementia may not be suitable for gastrostomy insertion. There is no definitive evidence that gastrostomy improves survival, and the risks of an invasive procedure must be carefully balanced against the projected benefits. Finally, some patients may not be able to manage some alternative communication devices such as tablets, which are suitable for ALS patients without cognitive and behavioural deficits.

Finally, we present some recommendations for care for caregivers of patients with cognitive and behavioural deficits:

- Effective caregiving requires that caregivers themselves receive practical and emotional support.
- Routine cognitive-behavioural screening can identify patients who require full neuropsychological examination, and identify caregivers in need of early, targeted interventions.
- Identification of caregiver needs will allow for the better management of those needs, leading to a reduction of overall burden and greater caregiver empowerment. While taking into account that patients' and caregivers' perspectives might differ from those of the health professionals involved in their care.
- ALS caregivers need to become aware that patients may change their behaviour over time, and to be able to face the modification of their interpersonal relationship.
- Patient's behavioural impairment can affect interpersonal and social relationships, reducing closeness, communication, and sharing viewpoints.
- Set realistic expectations for caregivers. For example, without insight a person cannot be expected to change their behaviour, the environment around the impaired person must change.
- To address the complex needs of caregivers, a detailed appraisal of the cognitive, behavioural and motor disability of the patient must be accompanied by detailed analysis of the psychological, emotional and capacity for resilience of the caregiver.
- Consideration of the possible positive aspects of caregiving is also important, as support and interventions for caregivers' should also enhance the positive aspects of their role that could reinforce their well-being and reduce the impact of caregiving in stress and burden.

Conclusions

Cognitive, and especially behavioural changes, significantly impact on QoL of patients with neurological disease and on their carers. This is congruent with other areas of medicine where perceived memory difficulties, poor concentration and impaired problem solving are important predictors of low QoL. In the neurodegenerative conditions, cognitive and behavioural impairment can present at different stages of a disease, and can manifest in varying forms, depending on the region of brain involvement and the nature of the underlying pathology. For example, executive impairment may implicate other cognitive processes if compromised, as disruptions to the supervisory attentional systems can negatively impact memory via encoding, lexical fluency, and orientation. Similarly, patterns of behavioural change are a function of the neurological pathways that are affected by the illness, and can range from extreme apathy to disruptive disinhibition, and accordingly require different types of

tailored intervention. While a range of interventions have been described that can help to support the QoL of patients and carers, there is no "one size fits all", and there is an urgent need for further research into the longer term impact of cognitive and behavioural change on QoL of patients and carers, such that an evidence base for effective targeted interventions can be generated.

Supplementary Online Resources

www.theaftd.org/life-with-ftd/support-for-caregivers

www.ftdsupportforum.com

www.nia.nih.gov

www.bluefieldproject.org

www.dementiatoday.com

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Behavioural Subphenotypes in Amyotrophic Lateral Sclerosis: A Population Based Factor Analysis Approach.

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Running Title: Distinct Behavioural Subphenotypes in ALS

Abbreviations: ALS = amyotrophic lateral sclerosis; BBI = Beaumont Behavioural Inventory; bvFTD = behavioural variant frontotemporal dementia; PCA = Principal Component Analysis

Abstract

Objective: Amyotrophic Lateral Sclerosis (ALS) is a clinically heterogeneous neurodegenerative disorder associated with cognitive and behavioural impairment. The primary aim of this study was to identify behavioural subphenotypes in ALS using a custom designed behavioural assessment tool (Beaumont Behavioural Inventory, BBI).

Methods: A cross-sectional population-based research design was applied to examine behavioural data from ALS patients (n=317) and healthy controls (n=66). Patients were screened for the *C9orf72* repeat expansion. A sub-cohort of ALS patients completed an extensive cognitive assessment battery (n=65), to investigate predictors of behaviour change. Principal component analysis (PCA) determined factors associated with altered behaviour. Survival data were extracted from the Irish ALS register.

Results: No behavioural changes were reported in 180 patients (57%); 95 patients had Mild-Moderate behavioural change (30%); 42 patients met the cut-off for Clinically Severe Behavioural Change (13%), suggestive of a bvFTD diagnosis. The most frequently endorsed behaviours in ALS were reduced concern for hygiene (36.8%), irritability (36.2%), new unusual habits (33.4%), and increased apathy (31.1%). Five independent behavioural factors were identified through factor analysis. Social cognitive performance was predictive of behaviour change (p=.031), yielding an R^2=.188. Severity of behaviour change was not associated with survival (p=0.198).

Interpretation: These data imply the presence of distinct sub-phenotypes of behavioural change in ALS most likely reflect subcategories of extra-motor network disruption.

Keywords: motor neuron disease; behavioural change; executive function; social cognition

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a clinically and genetically heterogeneous neurodegenerative disorder, of which cognitive and behaviour impairment are core features. [1-6] Executive dysfunction is present in up to 50% of ALS patients, alongside behavioural features associated with frontotemporal dementia (FTD). [7,8] Approximately 13-15% of ALS patients presenting with severe behaviour change meet consensus criteria for behavioural variant frontotemporal dementia (bvFTD)[9], which negatively impacts on patient survival.[7]

Behaviour change is under-reported within the ALS literature[8,9], as studies often lack a robust methodological design to infer generalizable results.[10-13] A recent systematic review of 21 studies found that mild to moderate behavioural changes are present in 17% – 88% of ALS patients without overt dementia.[4] The most commonly reported behaviour changes in ALS patients are apathy, which is present in up to 60% of patients[12,14], followed by disinhibition[15] and irritability. Direct comparisons of ALS and bvFTD patients suggest that behavioural symptoms are significantly less frequent in ALS[16], though changes in behaviour are qualitatively similar between the two groups.[15] However, significant correlations between executive dysfunction and behavioural change have been found[12,13] and co–morbidity of symptoms is reported.[9,17,18] Behaviour changes are also shown to occur independently of cognitive dysfunction.[19]

The anatomical degeneration of cortical regions associated with behavioural regulation has been documented in ALS studies[20,21] and have included orbitofrontal, anterior cingulate[19], and prefrontal cortical regions[22]. Extensive extra-motor pathology has also been demonstrated in ALS cohorts with no detectable behavioural or cognitive change, which most likely reflects pre-symptomatic grey matter alterations[23]. Multi-parametric imaging studies of the *C9orf72* genotype demonstrate orbitofrontal, Broca's area and cingulate pathology as well as marked white matter degeneration in the genu of the corpus callosum.[24] Correlative imaging studies of behavioural change in ALS demonstrated that apathy scores correlate with bilateral orbitofrontal cortex atrophy, decreased frontal fractional anisotropy[21], and accumbens nucleus atrophy.[25] Notwithstanding, there have been few population based studies of sufficient magnitude to definitively subcategorize behavioural sub-phenotypes in ALS, and to determine whether severity of behavioural change affect clinical outcome.

The aims of this study were to examine behavioural change in a large population based cohort of ALS patients using a recently validated behavioural instrument[26]; to determine whether distinct sub-phenotypes of behavioural change can be discerned based on known patterns of network disruption; to consider the cognitive predictors of behavioural change; to investigate whether behavioural change correlate with clinical parameters of disease; and to examine the impact of behavioural change on survival.

Material and Methods

Participants

Recruitment of ALS patients (n=317) and healthy controls (n=66) was undertaken using both clinic-based recruitment, and through the Irish ALS Register.[27] Recruitment protocols have been described previously in detail.[6] A sub-cohort of patients underwent neuropsychological assessment outlined in detailed in Table 1. All patients were tested within 7.66 ±10.54 months of diagnosis, and 22.09 ±16.07 months of first symptom (See

Table 2 for further details). Clinical stage was estimated using the King's Staging Criteria.[28,29] Matched healthy controls were recruited as part of a volunteer network (n=66). Inclusion criterion included possible, probable or definite ALS based on the revised El Escorial Criteria[30] with supported neurophysiology. Exclusion criteria included neurological conditions associated with cognitive or behavioural change, and/or high dose psychotropic medications. Patients with a diagnosis of ALS-FTD were included, however, FTD patients without overt symptomatology of ALS were not included in this study. All but 9 of 317 patients were screened for the *C9orf72* expansion.

[Tables 1 and 2]

All participants provided written consent as per the approved protocol. The work was approved by the Beaumont Hospital Ethics Committee and meets the standards and requirements of the Declaration of Helsinki.

Cognitive, Behavioural and Functional Assessment

A sub-cohort of participants (n=65) was assessed using an extensive battery of standardized neuropsychological measures (Table 1) sensitive to cognitive changes in ALS.[6] This cohort underwent cognitive testing as part of a larger study investigating cognitive dysfunction in a population-based cohort of ALS patients. These patients were recruited using the outlined protocol, and were incident based ALS patients. A 41-item proxy-report behavioural questionnaire was employed (The Beaumont Behavioural Inventory; BBI), which was custom designed and validated for use with ALS patients.[26] The BBI has high internal consistency (Cronbach's =.89), and high sensitivity and specificity (87.9% and 78.8% respectively) for identifying mild behaviour change, and using a cut-off score of 22.5 can identify ALS-FTD (90% sensitivity; 96% specificity). The presence of symptoms is graded on a scale of 1 to 3 (mild; moderate; severe). The results are then categorised based on the total score (No Behavioural Dysfunction $\leq$6; Mild Behavioural Change 7-22; Severe Behavioural Dysfunction $\geq$23).

The revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) is a clinically validated tool used to document disease progression over time and was utilized in this study to compare disease severity within patient groups.[31]

Statistical Analysis

Group comparisons were undertaken using independent sample t-test and ANOVA with multiple comparison considered. Logistic regression was used to investigate the value of cognitive scores in predicting behavioural impairment. The predictive value of the model was estimated using the C statistic. All tests were two-tailed and alpha was set at 0.05. IBM Statistical Package for the Social Sciences (SPSS) 21.0 was used for analyses.

Factor Extraction

With regards to statistical power, n=100 is the minimum number required to undertake a factor analysis.[32] However, five respondents per-item has also been suggested.[33] This study meets both criteria for sufficient sample size. Principal Components Analysis (PCA) examined the interrelationship of variables.[34] To decide upon the number of emerging factors, Kaiser's criterion for factors with an eigenvalue of >1 was employed.

Results

Prevalence of Behavioural Change

Of the total ALS cohort (N=317), 180 patients (57%) had no behavioural dysfunction (BBI ≤6), 95 patients (30%) had mild-moderate behavioural impairment (BBI=7-22), and 42 patients (13%) had severe behavioural dysfunction (BBI ≥23) as illustrated in Fig 1.

Bulbar-onset disease had no effect on overall behavioural impairment (p=0.643) but was associated with higher rates of Emotional Lability (56.5% versus 40.8%, p=0.002). No significant association between behavioural impairment and gender, site of onset, or disease-duration, was observed.

[Fig 1]

The most frequently described new onset behaviour in ALS was emotional lability (44%; $p<0.001$), followed by reduced concern for hygiene (36.8%; $p<0.001$), irritability (36.2%; $p=0.002$), new 'unusual habits' (33.4%; $p<0.001$), and increased apathy (31.1%; $p<0.001$). The classification of 'unusual habits' was determined by caregivers, who outlined behaviours that were previously uncharacteristic of the person. The remaining behavioural changes can be seen in Table 3, alongside the caregiver endorsement of mild, moderate, and severe change.

[Table 3]

Within the patient cohort, ALS patients without behavioural impairment (n=180), with mild behavioural impairment (n=95), and severe behavioural impairment (n=42) were stratified to investigate the most common types of behaviour change. Patients exhibiting *mild behaviour change* were also reported to have emotional lability (57%), apathy (48%), and an altered sensory perception to external stimuli (41.1%), according to their primary caregiver. This cohort further exhibited new onset unusual habits (44.7%) and less concern for hygiene (52.1%). Patients with *severe behavioural impairment* were reported to be more apathetic (87.5%), not as aware of mistakes as before (82.5%), more impulsive (82.9%), and less responsive to others' needs (71.4%). Through the itemisation of the scale in table 4, it can be seen that many of the same new-onset behaviours are endorsed across all groups, with higher frequency in the severely impaired group.

[Table 4]

ALS patients were stratified by King's Staging Criteria. Behavioural reports were significantly different between King's stages ($p=0.016$). Post-hoc analysis showed, on a group level, that caregivers of patients in Stage 4 reported significantly greater behavioural change in patients, compared to caregivers of patients in Stage 1, as illustrated in Fig 2.

[Fig 2]

Cognitive Function as a Predictor of Behaviour change

A sub-cohort of ALS patients underwent detailed cognitive evaluation (n=65). Twenty-four patients had evidence of single- or multi-domain cognitive impairment (36%). Of those who were cognitively intact (n=41), 30% had evidence of mild-moderate behavioural change (n=12), with 7% reported to have severe behavioural

impairment (n=3). Executive dysfunction was more likely to be in evidence in those with behavioural impairment (p=0.001). Spearman correlation analyses revealed that patients exhibiting severe behavioural impairment performed poorly on the Stroop Colour-Word Interference Task (r=-.549, p<0.0001), VFI (r=0.504, p<0.0001) and to a lesser extent, the Brixton Spatial Anticipation task (r=-0.300, p=0.036). Supplementary table 1 reports pertinent cognitive outcome data for this sub-cohort in greater detail.

Severe behavioural impairment was significantly correlated with poor scores on The Reading the Mind in the Eye Test (RMET), which is a task of social cognition (r=-0.453, p=0.002). A binary logistic regression model defined a predictive value of abnormal performance on the Stroop task, verbal fluency index and RMET for behavioural impairment (p=0.011, C-statistic=0.794, n=33). A significant predictor of behavioural dysfunction in this model was impaired performance on the RMET (p=0.031, odds ratio=8.8, 95%CI 1.2-63.7). A linear regression model was then created to include cognitive outcome data, and the HADS (Supplementary table 1). The only significant predictor within the battery of tests was the RMET (p= 0.031), yielding an individual R^2= .188, with the total battery considered yielding R^2= .616.

Principal Component Analysis of Behavioural Change

As shown in table 5, five independent factors were identified, which, from a neuropsychological perspective, map onto distinct fronto-striatal and fronto-temporal circuits. Although the BBI focuses on dysexecutive behaviour, the first factor in the model accounts for the greatest amount of variance, which describes a broad range of disinhibited items of the scale (i.e., acts without thinking; acts inappropriately; excessively stores food in mouth; and hyperorality), The second reflects a clustering of items related to an irregularity of reward and impulse control (i.e., eats much more, is less picky about food, smokes more, is more distractible, etc.). The third reports dysexecutive behaviours (i.e., aggressive behaviour, irritability, less concern about hygiene, less concern for others, and social behaviours). The fourth details a group of behaviours focusing around cognitive rigidity (i.e., overly concerned with neatness, aligning things a certain way, checking clocks/switches). The final is reflective of behavioural changes likely to be seen within ALS-FTD, and are characterised by their neuropsychiatric nature (i.e., visual and auditory hallucinations, new bizarre beliefs, hoards/hides/collects things, and handles things for no apparent reason). Many of the behaviours apparent in Factor 5 were represented within the *C9orf72* positive group. Supplementary Table 2 shows the breakdown between ALS patients and healthy controls based on the factor loading, and the comparative result.

[Table 5]

The *C9orf72* Expansion and Behaviour Change in ALS

C9orf72 hexanucleotide repeat screening was undertaken in 308/317 ALS patients (97.16%). Of the patients who had not undergone genetic testing, 7 had no significant behaviour change, and 2 fell within the mild-moderate range. Forty of the ALS patients tested (12.98%) were positive for the *C9orf72* hexanucleotide repeat expansion. These patients were significantly younger at time of testing compared to patients without the genetic expansion (59.8±9.0 versus 63.7±11.26, p=0.037).

The presence of the positive *C9orf72* gene expansion was associated with greater caregiver endorsement on the BBI, although 40% of these patients had no significant behaviour change (n=16). 40% were reported to have

Mild-Moderate behavioural change; the remaining 20% (n=8) were within the Clinically Severe Behavioural Change group. Four patients with the *C9orf72* gene expansion had evidence of cognitive impairment, two within the Mild-Moderate behaviour change group, and two within the Clinically Severe Behavioural Change group.

C9orf72 positive patients were less aware of mistakes (45% versus 22.7%; p=0.007); were more aggressive (25% versus 15.5%; p=0.026); reported seeing/hearing things/people (7.7% versus 1.7%; p=0.031); demonstrated new bizarre beliefs (14.3% versus 3.5%; p=0.024); and showed evidence of hoarding, hiding, or collecting objects (15% versus 5.8%; p=0.045).

ALS Patient Survival and Behaviour Change

Of the total cohort of 317 patients tested, 175 are deceased. Of these, 85 had no behavioural change; 65 had mild-moderate behavioural change, and 25 patients were within the clinically severe range. As seen in Fig 3, there was no significant difference between the groups at the beginning of the survival curve (Breslow p=0.105), middle (Tarine-Ware p=0.139), or end (Log Rank p=0.198), implying that behaviour change, as assessed early in the disease, was not a predictor of survival.

[Fig 3]

Discussion

The aim of this study was to examine behavioural change in a large population-based cohort of ALS patients using a validated disease specific behavioural scale. Our data confirms those of previous studies that emotional lability is a frequent finding in ALS (44%). Other common behavioural changes included a reduced concern for hygiene (36.8%), increased irritability (36.2%), new unusual habits (33.4%), and increased apathy (31.1%). As noted previously, 37% of patients with behavioural change were cognitively normal.

Emotional lability, or "pseudobulbar affect" is recognized as a manifestation of extensive upper motor neuron pathology, and is generally considered separately to other types of behavioural change. In our cohort, increased rates of emotional lability were associated with bulbar onset disease, which is congruent with other studies. Emotional lability is considered to be a disconnection between mechanisms which mediate emotions and associated motor responses, and primarily presents secondary to lesions, atrophy, or injury to the cortico-limbic-subcortico-thalamic-ponto-cerebellar network.[35]

The majority of patients exhibiting mild behaviour change had evidence of emotional lability (57.4%). Apathy was also commonly reported (48.4%). This cohort further exhibited new onset unusual habits (44.7%) and less concern for hygiene (52.1%). Patients with severe behavioural impairment exhibited apathy (87.5%); were not as aware of mistakes as before (82.5%), more impulsive (82.9%), and less responsive to others' needs (71.4%). Clinically relevant behavioural changes were also noted i.e., increased sensitivity to sensory stimuli (>28%), likely resulting from pathophysiological changes in the afferent system.[36]

Our findings concur with previous findings which suggest that behavioural changes in ALS are qualitatively similar regardless of whether a patient presents with mild or more severe behaviour change.[8,15] These qualitative similarities likely represent shared disrupted neurologic pathways, with greater atrophy resulting in increased

behavioural severity as seen with other neurodegenerative conditions.[47] Notwithstanding, some behaviours i.e., hallucinations, were almost exclusively present in the clinically severe behavioural change group (See tables 3 and 4).

Our findings extend those of previous studies both by the large size of the study population, and by our data-driven observations indicating that specific behavioural sub-phenotypes can be discerned in ALS to a greater extent than previously reported.[9,38] By mapping from a neuropsychological perspective the altered behaviours onto known anatomic pathways, the behavioural categories broadly reflect differential impairments within the corticostriatal circuits known to be compromised in ALS. For example, the neuropsychological categorization of behaviours with within Factor 1 are reflective of disruptions in pathways involving medial prefrontal and orbitofrontal cortices, as well as the anterior insula.[39,40] Behaviours characteristics within Factor 2 implicate orbitofrontal and anterior cingulate pathways[41,42]; and those within Factor 3 are reflective of disruptions in the right lateral orbitofrontal and right dorsolateral prefrontal l regions [43-45]. The clusters of behavioural change within Factor 4 are associated with alterations in the dorsolateral prefrontal cortex and temporolimbic networks[46]. Behaviours described by Factor 5 are not predictive of specific neuroanatomical pathways but are closely associated with the *C9orf72* expansion which is known to implicate extensive cortical and subcortical frontotemporal regions.[24] See supplementary Fig 1 for a graphical illustration of the behavioural schema.

Further analysis of behavioural impairment in in ALS demonstrated that changes occurred a mutually exclusive manner, which adds validity to the findings (see Table 5). This is evident through the statistical convergence i.e., Factor 1: "Lack of Embarrassment", and "Acts Inappropriately in Public" occurred together. Moreover, the statistical divergence of the scale items illustrates the exclusivity of these behavioural changes between different factors i.e., Factor 1: "More Withdrawn", and Factor 2: "Seeks Social Contact".

One of the mostly widely accepted non-dysexecutive behavioural sub-phenotype in ALS[2,47] relates to Factor 5, which from a neuropsychological perspective is predictive of more extensive network disruption. In our study cohort, this constellation of behavioural change was associated primarily with the presence of the *C9orf72* expansion..[47] In our cohort, 20% (n=8) of the *C9orf72* positive patients met the cut-off score for clinically severe change, which according to the BBI is suggestive of bvFTD.[26]

Extensive cognitive assessments were conducted with a sub-cohort of ALS patients (n=65). Although 37% of patients with behavioural change were cognitively normal, there were significant correlations between the measures of executive function (Stroop Colour-Word Interference Task, VFI and the Brixton Spatial Anticipation task) and severe behavioural change. Notably, these tasks are dependent on the integrity of multiple fronto-striatal circuits, requiring both inhibition of unwanted responses and close error monitoring.[48] More severe behavioural impairment also correlated with lower scores on the RMET, which was a reliable predictor of behavioural change in ALS.

Overall these data confirm the relationship between executive function and severe behavioural change and also confirm that behaviour changes in ALS are associated with frontal pathology. Indeed, the strongest predictor of behavioural change in our neuropsychological model was a measure of social cognition, which anatomically correlates with core circuitry involving the dorsolateral prefrontal cortical regions and the anterior cingulate.[49]

Although primarily cross-sectional in nature, the large population based sample permitted an assessment of the relationship between behavioural change and disease stage as defined by the Kings Staging System. Our findings suggest that while physical disability may contribute to milder degrees of behavioural impairment, it is unlikely to be a major determinant of overall behavioural impairment. We found no significant differences on survival between the groups with and without behavioural impairment, in contrast to our previous findings that executive impairment is a significant negative prognostic indicator.

This study has limitations. The data are drawn from a cross-sectional analysis albeit with survival data. Although this study incorporated a relatively large cohort of *C9orf72* positive patients, larger samples with differing behavioural profiles are required. Notwithstanding, this study, which to our knowledge is the largest analysis of behavioural change in ALS to date and facilitates for the first time a factor analysis of behaviour, has identified a characteristic behavioural phenotype associated with the *C9orf72* repeat expansion, and at several further behavioural sub-phenotypes which map onto distinct neuroanatomical pathways. These factors represent the psychometric and statistical clustering of the items on the scale, and further external validation studies are needed.

Our neuropsychology-based analyses support the hypothesis that behavioural sub-phenotypes in ALS reflects differential disruption of extra-motor networks involving fronto-striatal, orbitofrontal and anterior cingulate pathways and indicate that the neuropsychological profile of ALS patients that manifest as behavioural change is heterogeneous ,reflecting differential disruption of neuroanatomic circuits. Further longitudinal studies are currently underway to assess the interaction between behavioural change and clinical staging, and between neuropsychological changes and those observed by neuroimaging.

Disclosure Statement and Conflict of Interest

Mr. Tom Burke, Ms Marta Pinto-Grau, Dr Peter Bede, Ms. Katie Lonergan, Dr Alice Vajda, Dr. Russell McLaughlin, Mr. Mark Heverin, and Dr Niall Pender have nothing to disclose. Prof Orla Hardiman has received fees for consultation work from Biogen Idec, Cytokinetics and Novartis. She serves as Editor-in-Chief of Amyotrophic Lateral Sclerosis. The authors report no conflict of interests.

Contribution of Authors

TB contributed to the process of data collection, analysed the data and wrote the manuscript; PB, AV, RLM, KL, MOS, and MPG contributed to the process of data collection, edited, and revised the intellectual content of the manuscript; NP supervised the neuropsychological and statistical aspects of the study and revised the manuscript from a neurocognitive and behavoural perspective; and OH supervised all clinical aspects of the study in all stages of development and revised the manuscript from a clinical perspective.

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Table 1: Details of the neuropsychological battery

Executive dysfunction	*Impairment that is two SD below the mean for healthy controls on at least two executive tasks*
Stroop Colour-Word Test	(a) Priming trial: patients presented with a multi-coloured list of colour names and asked to read as many words as they can in 2 minutes. (b) Inhibitory trial: a similar list is presented but colour names (e.g., 'blue') are printed in an ink colour not denoted by the name (e.g., red). Correct responses in two minutes are recorded. Non-executive factors (including bulbar disability) contribute equally to both trials. The difference in scores between the two trials represent the number of responses 'lost' due to the delay imposed by the extra executive demands in the inhibitory trial.
Brixton Spatial Anticipation Test	A rule attainment based task whereby the rule in operation, cannot be identified by any perceptually salient aspect of the stimuli. It consists of pages showing the same basic array of 10 circles set in two rows of five, with each circle numbered from one to 10. The changes in position are governed by a series of simple rules, which vary without warning.
Backward digit span	A measure of auditory attention and working memory. This test is composed of trials where examinees are read strings of digits and are asked to repeat them back aloud.

	The length of the digit strings is incrementally increased over successive trials.
Category fluency	Patients were asked to name as many animals as they could think of in 1 minute (spoken only).
Phonemic verbal fluency	Written/spoken, number of words starting with letter 'S' generated in 5 minutes and number of four letter words starting with letter 'C' generated in 4 minutes. Verbal Fluency Index used to adjust for disability.
Memory dysfunction	*Impairment that is two SD below the mean for healthy controls on at least four* of the parameters highlighted using +*
Logical Memory (LM)	+LM1 (immediate recall), +LM2 (delayed recall) and +LM retention (retention)
Verbal Paired Associate (VPA)	+VPA1 (immediate recall), +VPA2 (delayed recall) and +VPA retention (retention)
Auditory Delayed Recognition Task	+Sum of total recognition scores on Logical Memory and Verbal Paired Associates
California Verbal Learning Tests	+Total of five trials, +short delay free recall (immediate recall) +long delay free recall (delayed recall)
Rey-Osterrieth Complex Figure test	Non-verbal memory: parameters used: +immediate and +delayed recall trials
Language dysfunction	*Impairment that is two SD below the mean for healthy controls on this task.*
Boston Naming Test	
Visuospatial dysfunction	*Impairment that is two SD below the mean for healthy controls on copy trial of this task.*
Rey-Osterrieth Complex Figure Test	

Table 2: Baseline demographics of participants Mean±SD

Demographic Variable	Healthy Controls (N=66)	ALS (N=317)	*p*
Age at assessment	61.39 ±13.67	63.00±11.13	.333
Males %	45%	51%	.023
Years of Education	13.51±3.76	12.91±3.77	.252
Disease onset (%)			
Spinal Onset	-	56.7	-
Bulbar Onset	-	23.2	-
Respiratory	-	2.9	-
Time since diagnosis (months)	-	7.66±10.54	-
Disease duration (months)	-	22.09±16.07	-
Total ALSFRS-R (±SD)	-	35.17±7.88	
Bulbar Total	-	9.42±2.96	-
Spinal Total	-	15.23±5.88	-
Respiratory Total	-	10.51±2.40	-
Disease Staging (as per King's criteria)			
Stage 1	-	21%	-
Stage 2	-	18%	-
Stage 3	-	14%	-
Stage 4	-	47%	-

Table 3: Total ALS cohort's behavioural change on BBI (n=317)

BBI Symptom	No Change	Mild	Moderate	Severe
Increased Irritability	63.8%	20.4%	13.2%	2.6%
Less Aware of Physical Senses	84.1%	6.3%	8.3%	1.3%
Difficulties with Conversation	76.2%	14.5%	6.6%	2.6%
Not Aware of Mistakes	75%	14.1%	7.9%	3.0%
Less reactive to difficulties	68.9%	12.9%	13.6%	4.6%
Acts without thinking	73%	10.9%	8.6%	7.6%
Emotional Lability	56%	21.5%	15.6%	6.8%
Lack of appropriate embarrassment	77.5%	13.2%	6.6%	2.6%
Less Concerned about others	80.3%	10.5%	4.3%	4.9%
More Selfish Behaviour	87.1%	7.9%	3.0%	2.0%
New Unusual Habits	66.6%	20.5%	9.3%	3.6%
More Withdrawn	82.3%	10.5%	5.2%	2.0%
Perseverative Speech	81.4%	13.1%	4.6%	1.0%
Less Concerned about Hygiene	63.2%	22.4%	7.9%	6.6%
More Aggressive	83.6%	9.2%	5.2%	2.0%
Obsessive Counting	96.4%	2.6%	.3%	.7%
Excessively Storing Food in mouth	92.8%	4.6%	2.3%	.3%
Eats Much More	89.5%	6.5%	3.6%	.3%
Hyperorality	97.7%	1%	1%	.3%
Overly Sensitive to Stimuli	71.9%	15.7%	10.1%	2.3%
New Food Preferences	81.8%	13%	3.9%	1.3%
Less Picky about Food	86.6%	9.5%	2.3%	1.6%
Difficulty with everyday language	92.6%	2.7%	3.1%	1.6%
Smokes More	92.6%	2.7%	3.1%	1.6%
Change in Sexual Interest	85.9%	5.2%	3.3%	5.6%
Sees/Hears Things/People	97.8%	.7%	.7%	.7%
New Bizarre Beliefs	95.6%	1.5%	2.9%	0%
Repetitious Behaviour	82.6%	9.8%	4.6%	3.0%
Repeats Phrases again and again	88.8%	5.3%	4.0%	2.0%
Dislikes Change in Routine	82.5%	11.4%	4.2%	1.9%
Seeks Social Contact	89.5%	5.2%	4.2%	1%
Constantly Aligns things	88.8%	6.6%	3.3%	1.3%
Overly Concerned with Neatness	95.7%	2.3%	2.0%	0%
Constantly Checking Clocks etc.	93.1%	4.6%	1.6%	.7%
Shows Less Emotion	84.3%	8.5%	4.6%	2.6%
Acts Inappropriately in Public	94.4%	2.6%	2.6%	.3%
Developed Unusual Rituals	99.7%	.7%	0%	0%
Hoards, Hides, or Collects Things	93.1%	3.9%	2.6%	.3%
Handles Things for No Reason	97.1%	1.6%	1%	.3%
More Distractible	77.5%	13.4%	4.6%	4.6%
Mimics/Repeats Words/Phrases	93.1%	4.0%	1.3%	1.7%

Bolded text implies significantly different to controls, at a group level, where $p<.05$.

Table 4: ALS cohort stratified by behavioural category, displaying % of endorsed items per group.

BBI Symptom	No Behaviour Change (n=180)	Mild-Moderate Behavioural Change (n=95)	Clinically Severe Behavioural Change (n=42)
Increased Irritability	35.7%	32.6%	46.3%
Less Aware of Physical Senses	3.6%	22.3%	53.8%
Difficulties with Conversation	7.7%	36.8%	60%
Not Aware of Mistakes	4.7%	36.8%	82.5%
Less reactive to difficulties	8.3%	48.4%	87.5%
Acts without thinking	7.7%	36.8%	82.9%
Emotional Lability	28.7%	57.4%	76.2%
Lack of appropriate embarrassment	6.5%	33%	65%
Less Concerned about others	.6%	30.5%	71.4%
More Selfish Behaviour	1.8%	19.1%	43.9%
New Unusual Habits	19.8%	44.7%	66.4%
More Withdrawn	3.6%	21.1%	68.3%
Perseverative Speech	6.5%	26.3%	51.2%
Less Concerned about Hygiene	17.2%	52.1%	82.9%
More Aggressive	2.4%	21.1%	61.9%
Obsessive Counting	0%	3.2%	20%
Excessively Storing Food in mouth	0%	9.5%	31%
Eats Much More	5.9%	13.7%	22%
Hyperorality	.6%	0%	14.6%
Overly Sensitive to Stimuli (Noise)	15.3%	41.1%	51.2%
New Food Preferences	5.3%	33.7%	35.7%
Less Picky about Food	1.8%	26.3%	31.7%
Difficulty with everyday language	8.4%	27.7%	65.9%
Smokes More	4.9%	9.4%	14.3%
Change in Sexual Interest	7.9%	17.1%	33.3%
Sees/Hears Things/People	0%	3%	11.8%
New Bizarre Beliefs	0%	9.1%	17.6%
Repetitious Behaviour	4.1%	25.5%	53.7%
Repeats Phrases again and again	0%	12.8%	53.7%
Dislikes Change in Routine	4.1%	25.6%	54.8%
Seeks Social Contact	1.2%	12.6%	43.9%
Constantly Aligns things	.6%	13.4%	48.8%
Overly Concerned with Neatness	.6%	4.3%	20%
Constantly Checking Clocks etc.	.6%	8.5%	29.3%
Shows Less Emotion	1.2%	22.3%	61%
Acts Inappropriately in Public	0%	4.2%	31.7%
Developed Unusual Rituals	0%	1.1%	2.6%
Hoards, Hides, or Collects Things	.6%	6.3%	35%
Handles Things for No Reason	0%	0%	22%
More Distractible	4.7%	35.8%	65.9%
Mimics/Repeats Words/Phrases	0%	5.3%	39%

Table 5: Item loading and relevant cross-loading into five identified components

		Identified BBI Components				
	Beaumont Behaviour Inventory Questions	1	2	3	4	5
	Repeats Words/Sentences Said By Others	**.745**				
	Not Aware of Mistakes	**.647**				
	Excessively Stores Food in Mouth	**.632**				
	More Withdrawn	**.607**	.442			
	Lack of Embarrassment	**.594**				
1	Acts without Thinking	**.580**				
	Difficulties with Conversation	**.564**				
	Difficulty with Everyday Language	**.550**			.471	
	Less able to React to Difficulties	**.549**				
	Hyperorality	**.541**				
	Repeats Phrases again and again	**.520**	.482			
	Acts Inappropriately in Public	**.481**				
	Obsessive Counting*	**.306**				
	Seeks Social Contact		**.672**			
	Shows Less Emotion		**.623**			
	More Distractible/ Unable to Concentrate		**.539**			
2	New Food Preferences		**.502**			
	Dislikes Change in Routine		**.448**			
	Smokes More		**.415**			
	Eats Much More*		**.270**			
	Less Picky About Food Preferences*		**.245**			
	New Unusual Habits			**.621**		
	More Aggressive			**.617**		
	Less Concerned About Others		.496	**.543**		
	Increased Irritability			**.497**		
	Perseverative Speech			**.478**		
3	More Selfish			**.474**		
	Less Concerned about Hygiene	.460		**.464**		
	Emotional Lability			**.444**		
	Repetitious Behaviour*			**.383**		
	Overly Sensitive to Sensations (Noise)*			**.371**		
	Less Aware of Physical Sensation*			**.326**		
	Developed Unusual Rituals*			**.297**		
	Overly Concerned with Neatness				**.751**	
4	Constantly Aligns Things in a Certain Way				**.720**	
	Constantly Checking Clocks/Switches		.477		**.483**	
	Change in Sexual Interest				**.441**	
	Sees/Hears Things/People					**.839**
5	Handles Things for No Apparent Reason					**.736**
	New Bizarre Beliefs					**.674**
	Hoards, Hides, or Collects Things					**.586**
	Variance explained	24.4%	6.2%	5.7%	4.6%	4.1%

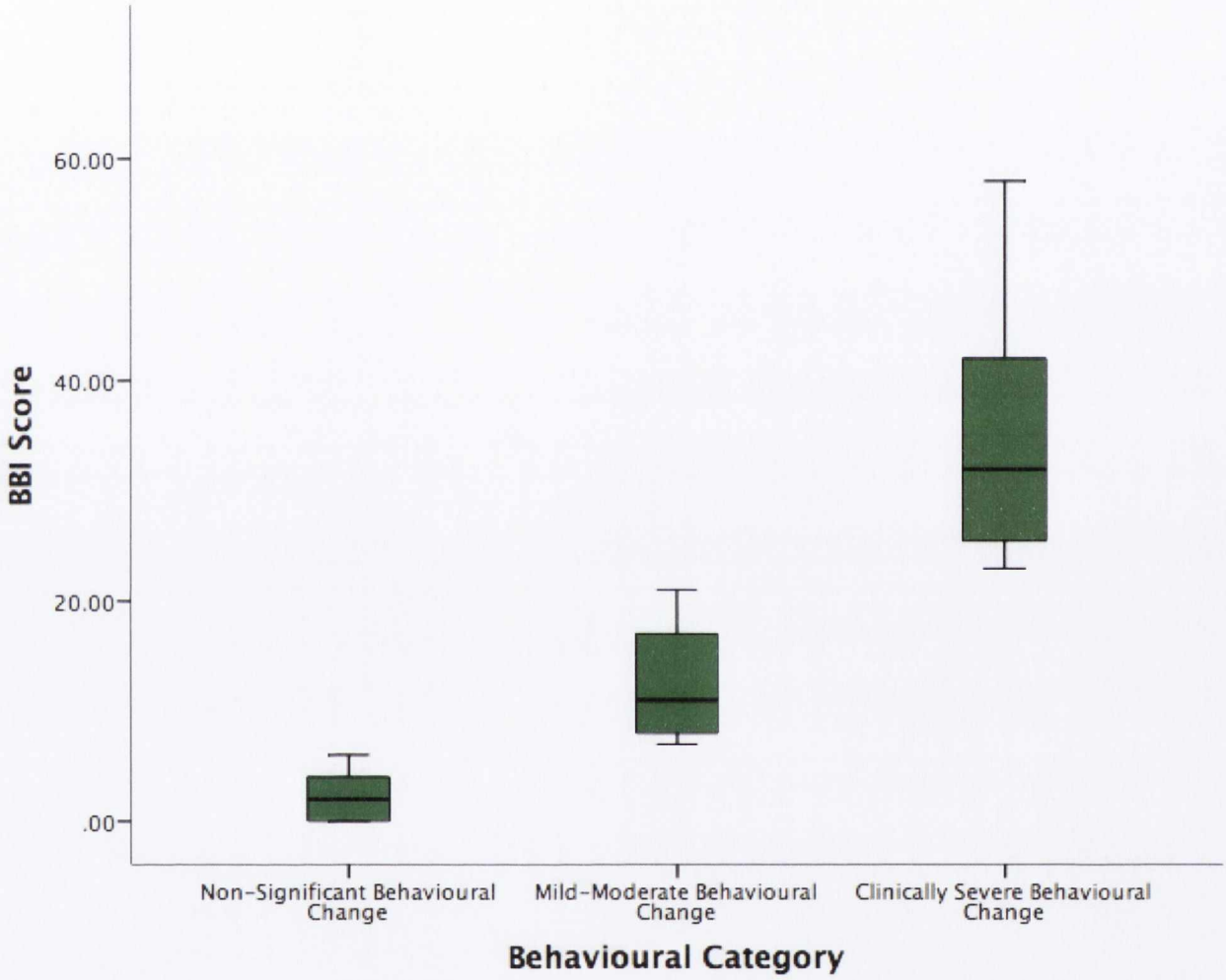
Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization.
*Factors which are considered weak, which do not load ideally to an individual factor.

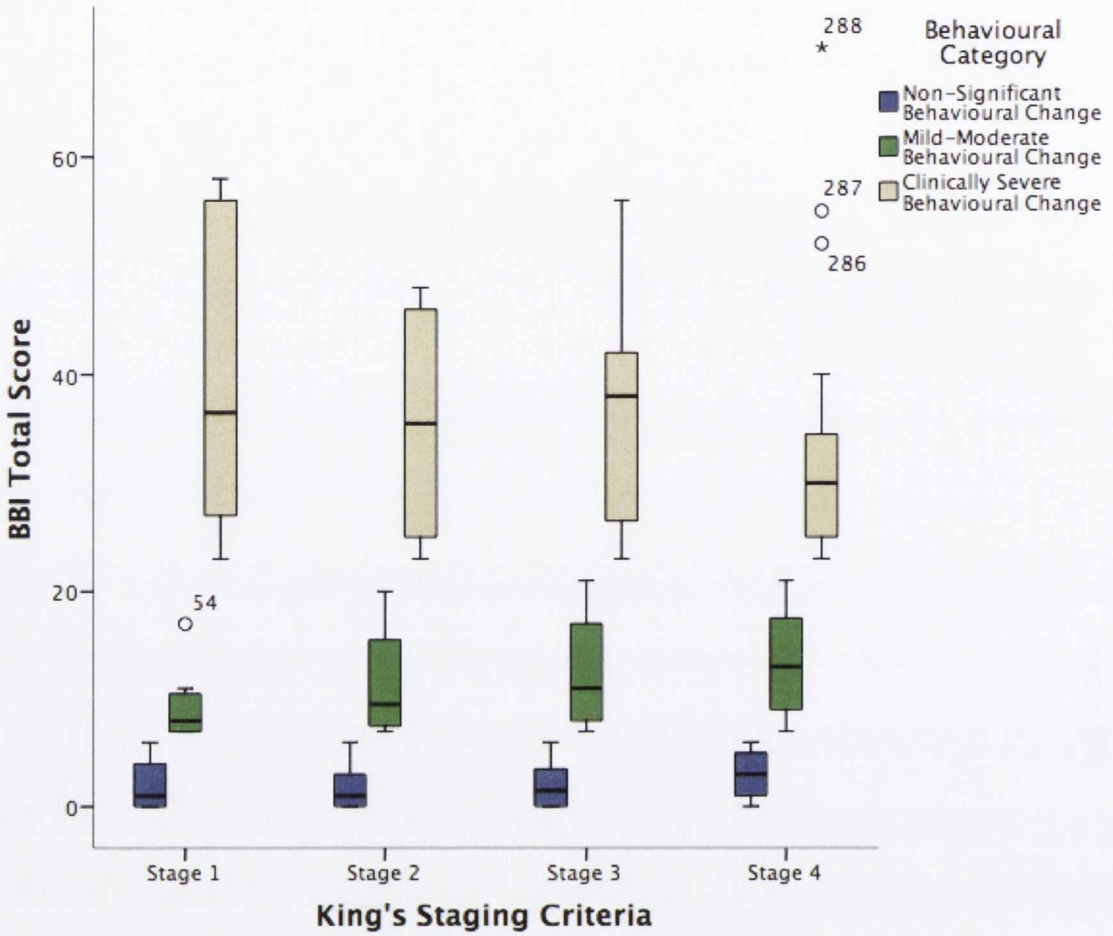
Figure Legends:

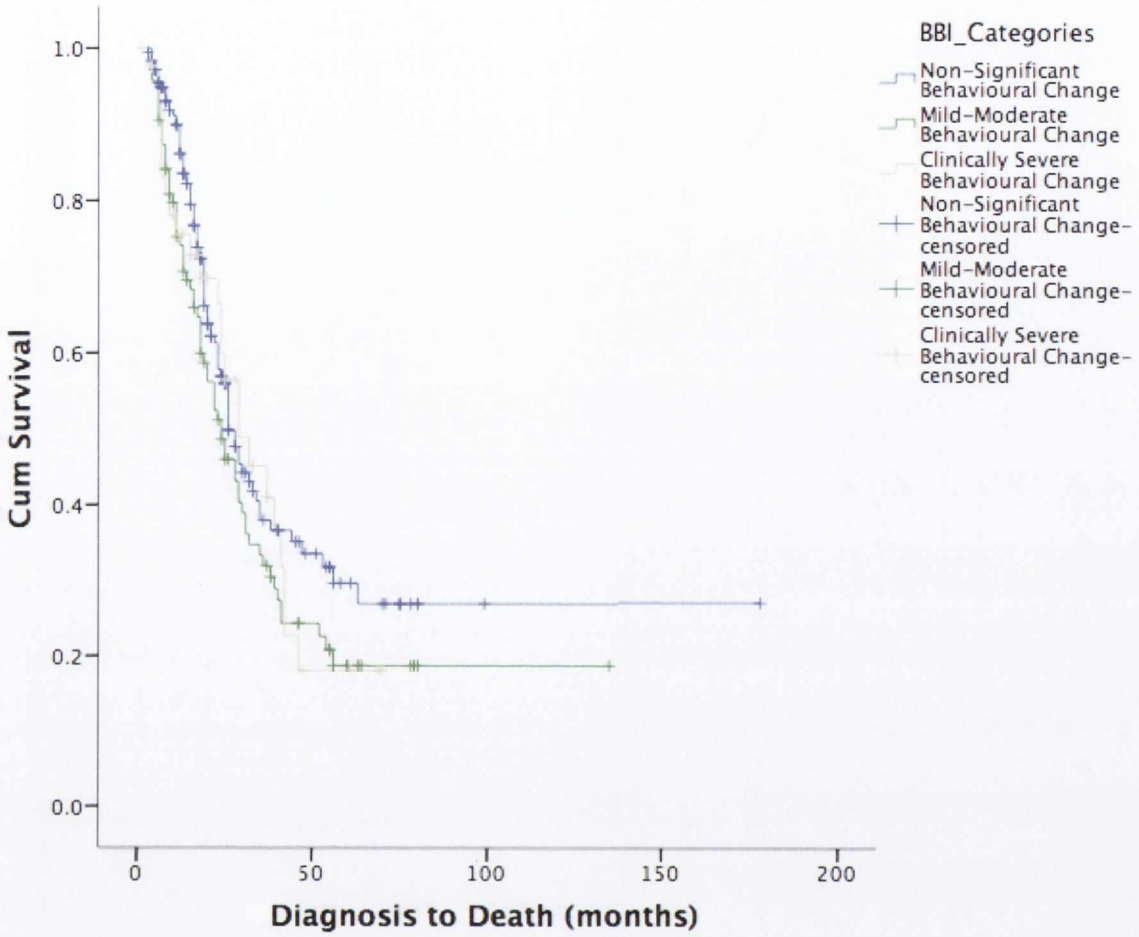
FIGURE 1: Box-plots representing the behavioural data stratified by severity as non-significant behavioural change (n=180), Mild-Moderate behavioural change (n=95), and clinically severe behaviour change (n=42).

FIGURE 2: ALS patient behavioural data stratified by King's stage, and trichotomised by behavoural severity. ALS patients were classified by the King's staging criteria as follows: Stage 1, 21%; Stage 2, 18%; Stage 3 14%; Stage 4, 47%. In Stage 1, 77% had no behavioural change (1.84±2.0), 13% were in the Mild-Moderate change category (9.37±3.46), and 10% were in the clinically severe range (39.50±14.57); Stage 2, 67% of patients had no behavioural change (1.63±1.93), 24% had Mild-Moderate behavioural change (11.41±4.92), and 8% were within the clinically severe range (35.50±12.34); Stage 3 patients recorded mostly no behavioural change (50%: 2.1±2.22), with 32% in the Mild-Moderate range (12.38±4.83), and 18% (36.28±11.78) in the clinically severe range; Stage 4, 46% of the cohort has no behavioural change (2.93±2.09), 40% exhibited Mild-Moderate behavioural change (13.34±4.48), with 14% within the clinically severe range (33.57±12.64).

FIGURE 3: Survival data of ALS patients (n=175) stratified by the severity of behavioural change.


60.00
40.00
20.00
.00
BBI Score
Non-Significant Behavioural Change
Mild-Moderate Behavioural Change
Clinically Severe Behavioural Change
Behavioural Category


288
287
286
54
Behavioural Category
Non-Significant Behavioural Change
Mild-Moderate Behavioural Change
Clinically Severe Behavioural Change
BBI Total Score
60
40
20
0
Stage 1
Stage 2
Stage 3
Stage 4
King's Staging Criteria


BBI_Categories
Non-Significant Behavioural Change
Mild-Moderate Behavioural Change
Clinically Severe Behavioural Change
Non-Significant Behavioural Change-censored
Mild-Moderate Behavioural Change-censored
Clinically Severe Behavioural Change-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
Diagnosis to Death (months)

Supplementary Table 1: Additional data on the sub-cohort completing the cognitive assessment

Clinico-demographics	Mean ±SD
Age at assessment	64.87±10.83
Disease duration	23.30±14.52
Time from diagnosis	10.47±11.26
Years of Education	12.77±3.21
O2 Statistics	96.87±1.54
CO2 Statistics	5.34±.766
Spinal onset	64.9%
ALSFRS-R Total	36.71±6.58
ALSFRS-R Bulbar	9.45±3.44
ALSFRS-R Respiratory	11.17±1.51
Cognitive Assessment	
WTAR predicted FSIQ*	101.55±10.28
Ravens Coloured Progressive Matrices§	26.08±8.09
Boston Naming Test (Form B)§	22.75±5.76
Verbal Fluency Index[b]	1.23±.41
Semantic Fluency§	15.49±7.38
Brixton Spatial Anticipation Test^	4.54±2.41
Digit Span Forward[a]	12.93±2.42
Digit Span Reverse[a]	11.51±4.29
Stroop Colour-Word Interference Task (EF)[b]	33.47±25.04
Reading the Mind in the Eyes§	21.09±6.70
HADS Anxiety§	5.13±4.14
HADS Depression§	3.04±3.05

*standard score; §cumulative score; ^transformed within test normative data; [a]scaled score; [b] transformed weighted score

Supplementary Table 2: Frequency of all reported behaviours in the ALS cohort versus healthy controls

BBI Questions	**ALS (n=317)**	**HC (n=66)**	***p* value**
Repeats Words/Sentences Said By Others	6.9%	0%	.052
Not Aware of Mistakes	25%	10.6%	**.009**
Excessively Stores Food in Mouth	7.2%	0%	**.039**
More Withdrawn	17.7%	7.6%	**.018**
Lack of Embarrassment	22.5%	3%	**.002**
Acts without Thinking	27.1%	6%	**<.001**
Difficulties with Conversation	23.8%	7.6%	**.007**
Difficulty with Everyday Language	22.2%	9.1%	**.039**
Less able to React to Difficulties	31.1%	7.6%	**<.001**
Hyperorality	2.3%	0%	.253
Repeats Phrases again and again	11.2%	3.1%	**.032**
Acts Inappropriately in Public	5.6%	0%	.070
Obsessive Counting*	3.6%	1.5%	.334
Seeks Social Contact	10.5%	3.1%	**.043**
Shows Less Emotion	15.7%	1.5%	**.004**
More Distractible/ Unable to Concentrate	22.5%	7.7%	**.011**
New Food Preferences	18.2%	9.1%	**.035**
Dislikes Change in Routine	17.5%	4.6%	**.008**
Smokes More	7.4%	1.6%	.071
Eats Much More*	10.5%	1.5%	**.023**
Less Picky About Food Preferences*	13.4%	0%	**.005**
New Unusual Habits	33.4%	7.7%	**<.001**
More Aggressive	16.4%	3%	**.010**
Less Concerned About Others	19.7%	1.5%	**.002**
Increased Irritability	36.2%	18.2%	**.002**
Perseverative Speech	18.6%	1.5%	**.001**
More Selfish	12.9%	0%	**.006**
Less Concerned about Hygiene	36.8%	4.6%	**<.001**
Emotional Lability	44%	7.5%	**<.001**
Repetitious Behaviour*	17.4%	3.1%	**.004**
Overly Sensitive to Sensations (Noise)*	28.1%	1.5%	**<.001**
Less Aware of Physical Sensation*	15.9%	3%	**.004**
Developed Unusual Rituals*	.7%	0%	.512
Overly Concerned with Neatness	4.5%	1.5%	.233
Constantly Aligns Things in a Certain Way	11.2%	4.6%	.111
Constantly Checking Clocks/Switches	6.9%	4.6%	.310
Change in Sexual Interest	14.1%	0%	**.003**
Sees/Hears Things/People	2.2%	0%	.699
Handles Things for No Apparent Reason	2.9%	3%	.992
New Bizarre Beliefs	4.4%	0%	.565
Hoards, Hides, or Collects Things	6.9%	1.5%	.176

*Factors which were considered weak during the component loading. **Bolded** text highlights significance between healthy controls and ALS patients, whereby p<.05.

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2016; 1–6

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RESEARCH ARTICLE

Survival analysis of geospatial factors in the Irish ALS cohort

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Abstract

Variations in environmental risk factors potentially influence incidence and progression in complex multifactorial diseases. Few studies have examined the association of survival in amyotrophic lateral sclerosis (ALS) with environmental geospatial variables. Here we use data from the Irish ALS cohort to perform such an analysis. Geographic data sources were used to generate small area values for four geospatial variables (population density, social deprivation, distance to coast, and distance to ALS multidisciplinary (MDT) clinic) for each ALS case on the Irish ALS register. These were combined with follow-up data and used as covariates in Royston-Parmar regression survival analysis including age of onset, site of onset, diagnostic delay, riluzole prescription and MDT clinic attendance as covariates. One thousand, two hundred and thirty-two patients with median survival of 2.31 years from disease onset were included. After addition of the individual geospatial variables in turn, none of the four variables was found to be associated with survival with a p-value <0.05. The results may reflect the public healthcare system that provides riluzole prescription and access to the MDT to all patients free of charge, and is also congruent with our recent finding that social deprivation is not associated with ALS incidence in Ireland.

Key words: *ALS, spatial epidemiology, survival, geospatial variables, prognosis, environment*

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative condition with poor prognosis. The incidence is approximately 2–3 per 100,000 people in European populations (1). The only drug effective at improving prognosis is riluzole (2). Non-invasive ventilation confers a survival and quality of life benefit (3,4) as does attendance at a specialist multi-disciplinary clinic (5).

The clinical phenotype of ALS is heterogeneous. There is evolving evidence of a multi-step pathogenic process in which both genetic and environmental factors are likely to play a role (6), although the nature of any gene-environment interactions in pathogenesis and disease course remains to be determined. From an environmental perspective, exposures that increase the incidence risk of ALS might also increase the rate of progression of the disease and hence impact negatively on survival. However, few studies have investigated the effect of spatially structured environmental factors on ALS survival.

In this study, we sought to explore this area by examining the influence of several geospatial factors on the survival of Irish ALS patients. Geospatial factors examined were population density (previously associated with ALS survival) (7), social deprivation (known to be an important factor in survival in breast cancer and other diseases (8,9)), distance of address of usual residence to the coast (coastal residency was previously reported to be associated with improved survival) (7) and finally distance to the multidisciplinary ALS care team (MDT) (patients attending the MDT have improved survival) (5).

Methods

Data sources

Survival characteristics of the Irish ALS cohort have been well described (5,10). For the current analysis an updated survival analysis data-set was generated with follow-up on all patients to at least July 2014. Due to the previously described effects of missing

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PLOS | ONE

RESEARCH ARTICLE

Functional Connectivity Changes in Resting-State EEG as Potential Biomarker for Amyotrophic Lateral Sclerosis

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Abstract

Background

Amyotrophic Lateral Sclerosis (ALS) is heterogeneous and overlaps with frontotemporal dementia. Spectral EEG can predict damage in structural and functional networks in frontotemporal dementia but has never been applied to ALS.

Methods

18 incident ALS patients with normal cognition and 17 age matched controls underwent 128 channel EEG and neuropsychology assessment. The EEG data was analyzed using FieldTrip software in MATLAB to calculate simple connectivity measures and scalp network measures. sLORETA was used in nodal analysis for source localization and same methods were applied as above to calculate nodal network measures. Graph theory measures were used to assess network integrity.

Results

Cross spectral density in alpha band was higher in patients. In ALS patients, increased degree values of the network nodes was noted in the central and frontal regions in the theta band across seven of the different connectivity maps ($p<0.0005$). Among patients, clustering coefficient in alpha and gamma bands was increased in all regions of the scalp and connectivity were significantly increased ($p=0.02$). Nodal network showed increased assortativity in alpha band in the patients group. The Clustering Coefficient in Partial Directed Connectivity (PDC) showed significantly higher values for patients in alpha, beta, gamma, theta and delta frequencies ($p=0.05$).

Discussion

There is increased connectivity in the fronto-central regions of the scalp and areas corresponding to Salience and Default Mode network in ALS, suggesting a pathologic disruption

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Routledge
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Retrospective investigations of practice effects on repeated neuropsychological measures of executive functioning

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(*Received 7 April 2014; accepted 21 April 2015*)

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The present study aimed to investigate the degree to which serial testing may impact neuropsychological test scores following serial evaluation of executive function. Healthy control data were retrospectively analysed, recruited as part of a longitudinal study of cognitive impairment in amyotrophic lateral sclerosis. As part of a larger battery of tests, participants were assessed using The Brixton Spatial Anticipation Test (n = 31), Backward Digit-span (n = 22), The Stroop Colour-Word Test (n = 30) and Phonemic Fluency (n = 29). Participants completed the tests on three occasions at 6-month intervals. Results showed no statistically significant difference between any of the measures of executive function over the three time points. Further covariate analyses showed that intellectual ability was not a confounding variable when investigating practice effects, as previously reported in literature. In an Irish cohort, participants did not show statistically significant changes over time on neuropsychological tests, either positively or negatively. Although these findings should be considered exploratory due to sample size, the wide age range and the retrospective nature of analysis, the data suggests practice effects did not significantly influence the test results in this cohort when assessed at 6-month intervals. Implications relative to these findings are discussed.

Keywords: neuropsychology; Ireland; executive-function; practice-effects

Introduction

Standardised neuropsychological testing is commonly used to assess individuals' cognitive abilities in diverse clinical and non-clinical settings. Neuropsychological tests can be used to monitor change in patients' underlying condition over time, or to measure responses to treatment-based interventions. However, there is growing concern that a patient's scores may be artificially inflated due to practice effects during serial testing. Practice effects are defined as increases in a person's test score from initial presentation to subsequent presentations, in the absence of intervention (Wilson, Watson, Baddeley, Emslie & Evans, 2000).

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CASE REPORT

Atypical social cognitive processing in premotor Huntington's disease: a single case study

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Background. We report the case of a 52-year-old male with pre-motor Huntington's disease (HD) who has undergone detailed clinical and neuropsychological examination. This patient's negative symptomatology and behavioural change are having a detrimental impact on his social, occupational and interpersonal life, in the absence of motor symptoms.

Methods. The patient has undergone repeat neuropsychological testing (T1 aged 50; T2 aged 52) with particular focus on executive function and social cognition on repeat testing.

Results. This case details a specific manifestation of HD relating to behavioural, psychiatric and social affective deficits.

Conclusions. This case illustrates how social cognitive changes can occur in HD, months and even years prior to the onset of motor features and how such unrecognized deficits can have a deleterious impact on an individual's functional ability and lifestyle, before the disease is traditionally considered to have become manifest.

Received 24 August 2015; Revised 18 September 2015; Accepted 29 September 2015

Key words: Affect deficit, empathy, Huntington's disease, social-cognition.

Introduction

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder characterized by chorea, cognitive decline and psychiatric illness, with associated behavioural difficulties (Walker 2007). HD is reported to have an incidence of 6.4/100 000 in Northern Ireland (Morrison *et al.* 1995), although prevalence is unknown in the Republic of Ireland. HD is caused by a trinucleotide repeat expansion (CAG) in the *huntingtin* gene located on chromosome 4p16.3 (Huntington's Disease Collaborative Research Group 1993). Subtle cognitive decline has been reported before the onset of motor features in patients with genetically confirmed HD (Henley *et al.* 2012; Paulsen *et al.* 2013), although the focus herein is on social-affect deficits, specifically as social cognition can deteriorate over the course of the disease (Sprengelmeyer *et al.* 2006; for a review of global cognitive decline in prodromal HD, see Paulsen *et al.* 2013).

Social cognition refers to the cognitive processes associated with social interaction, which encompass the ability to recognize, process, and express emotions (Ekman 1992; Ekman 1993). These have been shown to be problematic in neurodegenerative diseases (Müller & Bekkelund 2013), including HD (Johnson *et al.* 2007). Some studies maintain that poor performance on tasks that examine the recognition of emotional stimuli, by patients with HD, may be due to task difficulty rather than specific social affective dysfunction associated with emotional processing (Midlers *et al.* 2003). However, impairment has been noted in the recognition of certain emotions in patients with HD, such as sadness and disgust, using a range of stimuli in different modalities (Snowden *et al.* 2008). Modalities such as facial recognition of emotion (Calder *et al.* 2010) and prosodic tone in an individual's voice (Snowden *et al.* 2003) have evidenced deficits in emotive processing in patients with manifest HD (Henley *et al.* 2012).

Social cognition is theorized to be a sub-element of the executive system (Damasio & Maurer 1978); however, there is an increasing body of evidence suggesting that social cognition is characterized by its own subcomponents referred to as 'Theory of Mind' (ToM; Sprengelmeyer *et al.* 2006). ToM is further categorized into 'cognitive' and 'affective' subtypes. Cognitive ToM governs the recognition that others may have knowledge and beliefs, which are different to one's own (Abu-Akel & Shamay-Tsoory 2011), whereas affective ToM is the ability to infer another's emotional state and modulate socially appropriate behaviour accordingly (Shamay-Tsoory & Aharon-Peretz 2007).

Social breakdown and interpersonal difficulties are common features of HD, and these may be mediated by

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RESEARCH ARTICLE

Discordant performance on the 'Reading the Mind in the Eyes' Test, based on disease onset in amyotrophic lateral sclerosis

TOM BURKE[1,2], MARWA ELAMIN[2], PETER BEDE[2], MARTA PINTO-GRAU[1,2], KATIE LONERGAN[1,2], ORLA HARDIMAN[2,3] & NIALL PENDER[1,2,4]

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Abstract

Executive dysfunction is a core feature of amyotrophic lateral sclerosis (ALS) and is associated with brain atrophy in cortical and subcortical regions. Social cognitive deficits may also be a prominent feature of ALS. This study investigated executive, and social cognitive performance, in a population based cohort of patients with ALS, stratified by disease onset. Participants were recruited as part of a population based study investigating cognitive decline in ALS. Patients carrying pathogenic C9orf72 hexanucleotide repeat were excluded. Participants were stratified based on bulbar ($n = 20$) or spinal ($n = 39$) disease onset ($n = 59$). Matched healthy controls were used to generate culturally specific comparative data for within-patient analyses ($n = 59$). Results showed that ALS patients performed significantly worse than controls on a number of measures of executive function. When sub-stratified by disease onset, there was a significant difference between bulbar- and spinal-onset patients with respect to the 'Reading the Mind in the Eyes' Test scores ($p < 0.001$). Conversely, standardized scores of executive function did not differ between the patient groups. In conclusion, patients performed significantly worse than matched controls on measures of executive function. Bulbar-onset ALS patients evidenced more social-affective deficits compared to spinal-onset patients, with matched performance on measures of executive function.

Key words: *ALS; neuropsychology; social cognition; executive function*

Introduction

Cognitive impairment as an integral part of some forms of motor neuron disease (MND) has been interpreted as the fifth major clinical presentation of MND, alongside bulbar, cervical, thoracic, and lumbosacral (1). Cognitive impairment, primarily in the executive domain, occurs in up to 50% of incident patients with amyotrophic lateral sclerosis (ALS), with deficits in language, emotional processing and social cognition also documented (2–5). Additional impairment of language has also been reported in prevalent cases, particularly in those with bulbar-onset disease (6). The presence of executive impairment is associated with poor outcome, including a more rapid decline in motor function as measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS), and is associated with cortical atrophy on neuroimaging (4,7–12).

Executive dysfunction is known to occur secondary to ALS, and there is increasing evidence of impairment in social cognition in ALS implicated by frontal and temporo-parietal lobe dysfunction associated with social cognitive processes (13). Social cognition can be studied using instruments such as the social faux pas recognition test, the Judgment of Preference Test, The Reading the Mind in the Eyes Test, and through the use of social vignettes. The social faux pas recognition test evaluates the appropriateness of responses in a social context based on reading individual stories and answering questions posed by the examiner. ALS patients have been found to be significantly impaired compared to control participants on this measure, and it is also time-consuming, without appropriately controlling for motor disability. However, in many instances, patients are also impaired on other measures of dorsolateral prefrontal functioning, including verbal

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ORIGINAL COMMUNICATION

Caregiver burden in amyotrophic lateral sclerosis: a cross-sectional investigation of predictors

Tom Burke[1,2] · **Marwa Elamin**[2] · **Miriam Galvin**[2,3] · **Orla Hardiman**[2,4] · **Niall Pender**[1,2,5]

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Abstract The objective of the study was to investigate whether cognitive and behavioural impairment in Amyotrophic Lateral Sclerosis (ALS) contributes to caregiver burden, and whether carer burden affects patient outcome. Thirty-three dyads of incident patients with ALS and their primary caregivers ($n = 33$) completed a series of measures to determine cognitive and behavioural profiles, (patients) and carer burden (carers) to investigate the psychological impact of ALS, and the impact of behavioural change since the onset of ALS. Caregivers were divided into high- and low-burden groups using previously established norms. High burden in carers was associated with significantly higher apathy ($p = 0.009$), disinhibition ($p = 0.005$), and executive dysfunction ($p = 0.015$) in patients. Regression analyses for burden confirmed significant predictors such as change in apathy ($r = 0.390$, $F = 5.19$, $p = 0.03$), disinhibition ($r = 0.530$, $F = 11.32$, $p = 0.002$), and executive dysfunction ($r = 0.372$, $F = 4.66$, $p = 0.039$), with total behaviour change contributing to 31 % of caregiver burden ($r = 0.563$, $F = 4.17$, $p = 0.015$). Total distress as measured by the Hospital Anxiety and Depression Scale was also a significant predictor of caregiver burden, contributing to 38.5 % of variance ($r = 0.621$, $F = 18.79$, $p < 0.000$). Caregiver burden did not affect survival ($p = 0.496$). Caregiver burden in ALS is modulated by patient's cognitive and behavioural status, but does not significantly impact patient survival.

Keywords Amyotrophic lateral sclerosis · Neuropsychology and behaviour · Burden and quality of life · Survival and prognosis · Health services research

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Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of an unknown aetiology, limited treatment, with a rapidly progressive and fatal trajectory. ALS leads to progressive neurodegeneration and paralysis with death from respiratory failure within 3 years of symptom onset in the majority of patients [1].

Caregiver burden has been reported to be a consequence of physical impairment worsening congruently with disease trajectory [2], although recent reports also implicate cognitive, behavioural and neuropsychiatric symptoms as significant factors contributing to caregiver burden [3–6]. It has been suggested that caregivers' psychological status may influence the mental and physical outcome of patients

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RESEARCH ARTICLE

Measurement of Social Cognition in Amyotrophic Lateral Sclerosis: A Population Based Study

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Data Availability Statement: In line with our ethical approval, data contained within this study is made available to all interested researchers upon request; requests should be submitted to Dr. Alice Vajda, Research and Data Manager, Trinity Biomedical Sciences Institute, Dublin, Ireland (vajdaa@tcd.ie), and will therein be released to interested researchers without delay.

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disease. Executive dysfunction is common in patients with ALS, with up to 50% of patients performing within an impaired range. There is evidence that social cognitive deficits associated with ALS are a function of deficits in executive function. The 'Reading the Mind in the Eyes' Test is a recognized test of social cognitive function, although the reliability of this instrument remains to be established. Methodology: Patients with ALS (n = 106), and age and IQ matched controls (n = 50) were recruited and asked to perform the Reading the Mind in the Eyes Test as part of an on-going population-based study of cognitive function. ALS patients were sub-stratified based on the presence, and/or extent of executive dysfunction. Results: Cronbach's Alpha of .73 was observed, indicating good reliability on this measure. Split-half reliability analysis further confirms these findings ($p = 0.826$). The Reading the Mind in the Eyes test had excellent psychometric properties when discriminating between ALS patients who are cognitively intact, and those who have executive impairment, with an overall medium difficulty. There was a large magnitude significant difference between patients and controls ($p< 0.001$; $\eta^2 = .19$). Post-hoc analysis revealed that controls performed significantly higher than patients with executive impairment ($p< 0.001$), and patients with single executive deficits ($p = 0.002$). Conclusion: Executive dysfunction impacts on social cognitive performance. This study contributes not only to the psychometric knowledge of this measure, but also to the usability, efficacy, and reliability of social cognitive assessment in ALS. Using population-specific normative data, we confirm the Reading the Mind in the Eyes Test is a reliable measure of social cognitive processes in ALS.

Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and fatal neurodegenerative disorder. Cognitive impairment, specifically executive dysfunction is common in patients with ALS,

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RESEARCH PAPER

What does the ALSFRS-R really measure? A longitudinal and survival analysis of functional dimension subscores in amyotrophic lateral sclerosis

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ABSTRACT

Introduction ALS functional rating scale (revised) (ALSFRS-R) is the most widely used functional rating system in patients with amyotrophic lateral sclerosis (ALS). However, heterogeneity in ALSFRS-R progression renders analysis challenging. We have explored the characteristics of total ALSFRS-R, and ALSFRS-R subscores in longitudinal and survival models, to determine whether subscore analysis enhances the precision of the instrument.

Methods All cases with ALSFRS-R scores on the Irish ALS register were included. ALSFRS-R subscores were defined for bulbar, motor and respiratory domains. Longitudinal models were used to visualise fitted total ALSFRS-R and ALSFRS-R subscore progression. In addition, the prognostic value of convenience and computed ALSFRS-R slope and subscore slopes were compared.

Results 407 incident cases were identified with a complete ALSFRS-R measure. 233 (57%) patients were male, and 125 (31%) had bulbar-onset disease. ALSFRS-R bulbar and motor subscore slopes provided a better fit in prognostic models when combined over the total ALSFRS-R slope. Longitudinal analysis revealed that the ALSFRS-R motor subscore deteriorated earlier in spinal-onset disease over bulbar-onset disease, while in bulbar-onset disease the ALSFRS-R bulbar subscore deteriorated earlier and faster than in spinal-onset disease.

Discussion Our analysis builds on previous knowledge of ALSFRS-R subscores. Decline in ALSFRS-R motor subscores in patients with spinal-onset disease, and decline in ALSFRS-R bulbar subscores in patients with bulbar-onset disease, may predate reported disease onset dates. Respiratory subscores were not prognostically informative after adjustment for bulbar and motor subscores. These results provide robust evidence that the ALSFRS-R should not be reported as a single combined score, but rather as domain specific subscores.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder with a typically poor prognosis, although progression is recognised to be highly variable.[1] In the absence of an established biomarker, the rate of decline on the ALS functional rating scale (revised) (ALSFRS-R) has become the most commonly used measure of progression by clinicians in research and in clinical trials. The ALSFRS was designed as a 10-item functional score across fine and gross motor, bulbar and respiratory functional domains.[2 3] This was later extended to the ALSFRS-R by including extra respiratory scores to better capture the respiratory functional domain.[4] The longitudinal analysis of change in ALSFRS-R, which is generally considered to be linear for the majority of the illness, is complicated both by heterogeneity[5] and by longitudinally informative censoring due to dropout of more ill patients, and/or the mortality of patients over time.[6] This problem has led to the development of alternative measures, such as the Combined Assessment of Function and Survival, a non-parametric ranked score combining functional and survival outcomes for use in clinical trials in ALS.[7]

The rate of change of the ALSFRS-R, or 'ALSFRS-R slope', has gained widespread acceptance as a prognostic indicator.[8–10] However, a recent Rasch analysis of the ALSFRS-R has identified multidimensionality within the score and suggests that the use of subscores corresponding to bulbar, motor and respiratory domains may be superior to the use of a single combined score.[11] Until now, the prognostic value of these subscores has not been evaluated.

Using data from the Irish ALS register, our aims were to explore the prognostic and longitudinal characteristics of ALSFRS-R functional subscores, defined by the Rasch analysis of Franchignoni *et al*.[11 12]

METHODS

Case ascertainment

We identified all incident cases from the Irish population-based register[13 14] for whom at least one ALSFRS-R measurement was available. A small number (n=8) of respiratory onset cases were excluded, as this group was too small for analysis. We then collated demographic, clinical, survival information and longitudinal ALSFRS-R measurements. Information included: gender, age and site of onset, diagnostic delay, revised El-Escorial category, attendance at the multidisciplinary team (MDT) clinic and Riluzole use. ALSFRS-R scores were generated by physiotherapy and medical assessors, all of whom had undergone standardised training using online tools developed by the NEALS and ENCALS groups for clinical trial purposes.

Definition of ALSFRS-R subscores

The Rasch analysis carried out by Franchignoni *et al*[11] determined that the ALSFRS-R scale

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RESEARCH ARTICLE

Identifying behavioural changes in ALS: Validation of the Beaumont Behavioural Inventory (BBI)

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Abstract

Objective: Behavioural changes are an important part of amyotrophic lateral sclerosis (ALS). However, most tools do not account for the influence of motor impairment. Furthermore, they do not fully measure the broad range of behavioural changes specific to ALS. This study aimed to develop and validate an ALS specific behavioural inventory, the Beaumont Behavioural Inventory (BBI). *Methods*: The BBI was validated in a cohort of ALS patients ($n = 85$) and 78 age-, gender-, and education-matched controls. The scale was validated against the Frontal Systems Behaviour Scale (FrSBe) and The Frontal Assessment Battery (FAB) for convergent validity, and against other non-behavioural measures to assess discriminant validity. Reliability was assessed with Cronbach's alpha. *Results*: The instrument showed high internal consistency (Cronbach's alpha value =0.891). BBI scores highly correlated with the FrSBe and moderately with the FAB. However, the measure was independent from non-behavioural measures. Using a cut-off score of 7 for mild behavioural changes, the BBI displayed high sensitivity and specificity (87.9% and 78.85%, respectively). The cut-off score for moderate changes, consistent with a diagnosis of ALS-FTD, is set at 22.5, showing 90% sensitivity and 96% specificity. *Discussion*: The BBI is a sensitive and specific tool to assess the entire behavioural spectrum of ALS.

Key words: *ALS, behaviour, validation, BBI, neuropsychology*

Introduction

Amyotrophic lateral sclerosis (ALS) is a clinically and genetically heterogeneous neurodegenerative disorder, which involves extramotor frontotemporal mediated changes. Thirteen percent of ALS patients develop severe behavioural changes consistent with behavioural-variant frontotemporal dementia (ALS-FTD) (1). The literature also suggests that a subgroup of non-demented ALS patients experience behavioural changes, which can be independent of the presence of cognitive changes (ALSbi) (2). However, reports on the prevalence of more subtle behavioural changes in ALS vary considerably depending on the sample size, patient cohort, behavioural instruments, and the diagnostic criteria used (1–5).

Behavioural changes in ALS have important implications for disease management, survival and caregiver burden (6), and it is important to assess changes in behaviour as part of the neuropsychological evaluations of ALS. Although behaviour is ideally assessed by detailed family interviews, this is not always practicable in a multidisciplinary clinic setting, and there is an urgent need for a behavioural inventory that includes the wide range of behaviours characteristic of frontotemporal dysfunction. As behavioural symptoms observed in ALS mirror those characteristic of FTD, and these two conditions have been placed in the same clinical continuum (7,8), some behavioural questionnaires designed for the use in FTD have been employed to assess behaviour in ALS (9–11). However, these tools do not account for the confounding effects

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RESEARCH ARTICLE

Screening for cognitive dysfunction in ALS: validation of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) using age and education adjusted normative data

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Abstract

Background: Cognitive and behavioural changes are an important aspect in Amyotrophic Lateral Sclerosis (ALS). The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) briefly assesses these changes in ALS. *Objective:* To validate the ECAS against a standardised neuropsychological battery and assess its sensitivity and specificity using age and education adjusted cut-off scores. *Method:* 30 incident ALS cases were assessed on both, ECAS and neuropsychological battery. Age and education adjusted cut-off scores were created from a sample of 82 healthy controls. *Results:* ECAS composite scores (Total, ALS Specific and Non-Specific) were highly correlated with battery composite scores. High correlations were also observed between ECAS and full battery cognitive domains and subtests. The ECAS Total, ALS Specific and Non-Specific scores were highly sensitive to cognitive impairment. ECAS ALS-Specific cognitive domains also evidenced high sensitivity. Individual subtest sensitivity was medium to low, suggesting that caution should be used when interpreting these scores. Low positive predictive values indicated the presence of false positives. *Conclusions:* Psychometric properties of the ECAS using age and education adjusted norms indicate that the ECAS, when used as an overall measure of cognitive decline, is highly sensitive. Further comprehensive assessment is required for patients that present as impaired on the ECAS.

Key words: *Cognition, ALS, screen, ECAS, validation, standardisation*

Introduction

Amyotrophic lateral sclerosis (ALS), the most common form of Motor Neuron Disease (MND), is now recognised as a multisystem disease also affecting cognition and behaviour. Population-based studies of cognitive impairment in ALS have reported that approximately 15% of patients meet criteria for the diagnosis of Frontotemporal Dementia while 30% of non-demented ALS patients have some degree of cognitive impairment (1,2). However, the nature and degree of cognitive impairment in ALS varies across patients. The most prevalent impairment in ALS is executive dysfunction, in particular verbal fluency, followed by social cognition and language (3,4). However, detailed neuropsychological batteries are time consuming and often inappropriate in a multidisciplinary clinic setting. There is a need, therefore, for a brief, sensitive clinic-based instrument that allows for the screening of cognitive difficulties in ALS (5).

To characterise the neuropsychological changes in ALS, some authors have adapted available behavioural and cognitive screening tools (6–8) while others have developed screening tools specifically for ALS (9–11). However, these tools exclude various cognitive domains that may be affected in ALS, and most do not adapt for physical disability, thus limiting their utility as sensitive screening tools.

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (12) is a brief multi-domain cognitive screening tool designed specifically to assess cognitive performance in patients with ALS. The ECAS has been developed not only to determine the presence of cognitive impairment but also to quantify the severity and the nature of the deficits. The ECAS covers a range of cognitive domains in order

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