Emotional processing and social cognition in Amyotrophic Lateral Sclerosis (ALS) / Motor Neuron Disease (MND)

Watermeyer, Tamlyn Julie

Awarding institution:
King's College London

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Emotional processing and social cognition in Amyotrophic Lateral Sclerosis (ALS) / Motor Neuron Disease (MND)

Tamlyn Julie Watermeyer

Institute of Psychiatry
King’s College London

Thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

November 2013
Abstract

Amyotrophic Lateral Sclerosis (ALS) is a debilitating and life–limiting neurodegenerative disorder that causes progressive muscle atrophy and spasticity. A small proportion of ALS patients experience co–morbid Frontotemporal Dementia (FTD). Milder cognitive–behavioural changes have been noted in ALS patients without dementia. In these patients, deficits in executive functioning, language, memory and behaviour have been documented. Recently, changes to emotional processing and social cognition (EMOSOC) in ALS have also been reported, albeit with inconsistent findings.

The primary aims of the current thesis were i) to delineate the nature and extent of changes in EMOSOC in ALS and ii) to determine the relationship between such changes and interindividual differences in mood, behaviour, personality, empathy and ALS–related executive dysfunction. The results of the study indicate a profile of predominant executive dysfunction, with relative sparing of EMOSOC in non–demented ALS patients. However, the ALS patients did show impaired performance on a task requiring the attribution of thoughts and feelings to characters from cartoons and vignettes. ALS patients’ performance on EMOSOC tasks was predicted by their performance on tests of executive function, above and beyond mood, behaviour, personality and empathy variables.

As a secondary aim, the impact of patients’ cognitive and behavioural changes on ALS caregivers’ outcomes (mood, perceived strain, burden and marital satisfaction) were examined. The data indicated patients’ behavioural dysfunction and functional impairment as key predictors of caregivers’ outcomes. Exploratory analyses revealed differences between patients’ and caregivers’ perceptions of patients’ personality, empathy and behaviour; these differences were associated with caregiver outcomes.

In summary, the current thesis characterises the profile of EMOSOC changes in non–demented ALS and highlights the role of ALS–related executive dysfunction in these changes. It also assesses the relative impact of patients’ disease, cognitive and behavioural changes on ALS caregivers.
Acknowledgements

There are several people I would like to thank for their contribution to this research.

Firstly, many thanks to my supervisors, Professor Laura Goldstein and Professor Richard Brown, for the opportunity to complete this PhD and for their invaluable guidance throughout this process.

I would also like to thank the Medical Research Council, the National Institute of Health Research and the Motor Neurone Disease Association for their generous funding of the project.

I am indebted to an endless list of clinical and research staff based at the various research sites for their assistance with conducting the study. Many thanks are due to my friends and colleagues for their friendship and encouragement. Thank you (and sorry!) to everyone who endured my many irrational prophecies of academic doom.

I would especially like to thank my parents and sister for their support and love throughout my life and their unwavering belief in my potential, a belief which kept me going over these years when I had none left.

Finally, I would like to express my sincerest gratitude to the patients and their spouses who took part in the study. Their enthusiasm, generosity and strength have humbled and inspired me throughout this process and will never leave me. This thesis is dedicated to them, their families and a world free of MND.
“I wake up each morning and find that I am still breathing, and I think to myself
… I’m still winning.”

H.W.
A person living with MND
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<th>Description</th>
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<tr>
<td>AC</td>
<td>Anterior cingulate</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s Disease</td>
</tr>
<tr>
<td>ALS</td>
<td>Amyotrophic Lateral Sclerosis</td>
</tr>
<tr>
<td>ALSFRS–R</td>
<td>Amyotrophic Lateral Sclerosis Functional Rating Scale Revised</td>
</tr>
<tr>
<td>ALS–FTD</td>
<td>Amyotrophic Lateral Sclerosis–Frontotemporal Dementia</td>
</tr>
<tr>
<td>ALS–FTLD</td>
<td>Amyotrophic Lateral Sclerosis –Frontotemporal Lobar Degeneration</td>
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<tr>
<td>ALS–PNFA</td>
<td>Amyotrophic Lateral Sclerosis – Progressive Non–fluent Aphasia</td>
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<tr>
<td>ALS–PPA</td>
<td>Amyotrophic Lateral Sclerosis – Primary Progressive Aphasia</td>
</tr>
<tr>
<td>ALS–SD</td>
<td>Amyotrophic Lateral Sclerosis – Semantic Dementia</td>
</tr>
<tr>
<td>AS</td>
<td>Asperger’s syndrome</td>
</tr>
<tr>
<td>BBs</td>
<td>Bunina bodies</td>
</tr>
<tr>
<td>BDI (–II)</td>
<td>The Beck Depression Inventory (– Second Edition)</td>
</tr>
<tr>
<td>BNT</td>
<td>Boston Naming Test</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood–oxygen–level–dependent</td>
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<tr>
<td>bvFTD</td>
<td>Behavioural–variant–Frontotemporal–Dementia</td>
</tr>
<tr>
<td>CBI</td>
<td>Carer Burden Interview</td>
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<tr>
<td>CD</td>
<td>Cook’s distance</td>
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<tr>
<td>Cho</td>
<td>Choline</td>
</tr>
<tr>
<td>CIU</td>
<td>Correct information units (The Cookie Theft Task)</td>
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<tr>
<td>COWA</td>
<td>Controlled Oral Word Association Test</td>
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<tr>
<td>Cr</td>
<td>Creatine</td>
</tr>
<tr>
<td>CST</td>
<td>Corticospinal Tract</td>
</tr>
<tr>
<td>CT</td>
<td>Computerised Tomography</td>
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<tr>
<td>CVLT</td>
<td>California Verbal Learning Test</td>
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<tr>
<td>DeNDRoN</td>
<td>Dementia and Neurodegenerative Diseases Research Network</td>
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<tr>
<td>D–KEFS</td>
<td>Delis–Kaplan Executive Function</td>
</tr>
<tr>
<td>DLPFC</td>
<td>Dorsolateral prefrontal cortex</td>
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<tr>
<td>DPS</td>
<td>Diaphragm Pacing Simulation</td>
</tr>
<tr>
<td>DSM–IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<tr>
<td>EL</td>
<td>Emotional lability</td>
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<tr>
<td>ELQ (–I)</td>
<td>The Emotional Lability Questionnaire (–Informant version)</td>
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</tbody>
</table>
**EMG**  Electromyography
**EMOSOC**  Emotional Processing and Social Cognition composite
**ERP**  Event Related Potential
**ESS**  Epworth Sleepiness Scale
**FA**  Fractional Anisotropy
**fALS**  Familial Amyotrophic Lateral Sclerosis
**FFM**  Five–Factor Model
**fMRI**  Functional Magnetic Resonance Imaging
**FrSBe (–I)**  The Frontal Systems Behaviour Scale (–Informant version)
**FSIQ (–2)**  Full scale intelligence quotient (–from two subtest estimate of the WASI)
**FTD**  Frontotemporal Dementia
**FTDC**  International Behavioural Variant FTD Criteria Consortium
**FTLD**  Frontotemporal Lobar Degeneration
**FTLD–tau**  FTLD with protein aggregations called tau
**FTLD–TDP**  FTLD with TDP–43 inclusions
**FTLD–U**  FTLD with inclusions that are immunoreactive to ubiquitin
**FUS/TLS**  Fused in Sarcoma/Translocated in Lipsarcoma
**FVC**  Forced Vital Capacity
**GM**  Grey Matter
**GNT**  Graded Naming Test
**HADS**  Hospital Anxiety and Depression Scale
**HD**  Huntington’s Disease
**HFA**  High–functioning Autism
**HOV**  Homogeneity of variance
**ICF**  Intracellular fluid
**IGT**  Iowa Gambling Task
**IQ**  Intelligence Quotient
**IRI (–I)**  Interpersonal Reactivity Index–Informant version
**IVG**  Intravenous immunoglobulin
**LMN**  Lower Motor Neuron
**MAD**  Median Absolute Deviation
**MCI**  Mild Cognitive Impairment
**MD**  Mean diffusivity
**MDI**  Major Depression Inventory
**MIS**  Morris Intimacy Scale
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>MMSE</td>
<td>The Mini Mental State Exam</td>
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<tr>
<td>MND</td>
<td>Motor Neuron Disease</td>
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<td>MR</td>
<td>Multiple Regression</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>MRS</td>
<td>Magnetic Resonance Spectroscopy</td>
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<td>MS</td>
<td>Multiple Sclerosis</td>
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<tr>
<td>MSS</td>
<td>Morris Strain Scale</td>
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<tr>
<td>NAA</td>
<td>N–acetlaspartate</td>
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<td>NART</td>
<td>National Adult Reading Test</td>
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<tr>
<td>NEO–FFI</td>
<td>The NEO Five–Factor Inventory</td>
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<td>NEO–PI</td>
<td>The NEO Personality Inventory</td>
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<tr>
<td>NIPPV</td>
<td>Non–Invasive Positive Pressure Ventilation</td>
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<tr>
<td>NMDA</td>
<td>N–Methyl–D–Aspartic Acid</td>
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<tr>
<td>NPI</td>
<td>The Neuropsychiatric Inventory</td>
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<tr>
<td>OFC</td>
<td>Orbitofrontal cortex</td>
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<td>OSAS</td>
<td>Obstructive Sleep Apnoea Syndrome</td>
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<tr>
<td>PD</td>
<td>Parkinson’s Disease</td>
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<tr>
<td>PEG</td>
<td>Percutaneous Endoscopic Gastrostomy</td>
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<td>PET</td>
<td>Positron Emission Tomography</td>
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<td>PFC</td>
<td>Prefrontal cortex</td>
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<td>PIG</td>
<td>Per–oral Image Guided Gastrostomy</td>
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<td>PLS</td>
<td>Primary Lateral Sclerosis</td>
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<td>PMA</td>
<td>Progressive Muscular Atrophy</td>
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<td>PMC</td>
<td>Primary Motor Cortex</td>
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<td>PNFA</td>
<td>Progressive non–fluent aphasia</td>
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<td>PPA</td>
<td>Primary Progressive Aphasia</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
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<tr>
<td>rCBF</td>
<td>Regional Cerebral Blood Flow</td>
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<td>RIG</td>
<td>Radiologically Inserted Gastrostomy</td>
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<tr>
<td>RME</td>
<td>Reading the Mind in the Eyes Task</td>
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<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
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<tr>
<td>SD</td>
<td>Semantic Dementia or Standard Deviation</td>
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<tr>
<td>SIP</td>
<td>Sickness Impact Profile</td>
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<td>SNIP</td>
<td>Sniff Nasal Inspiratory Pressure</td>
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<td>SOD1</td>
<td>Superoxide Dismutase–1</td>
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<td>Abbreviation</td>
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<tr>
<td>SPECT</td>
<td>Single-Photon Emission Computed Tomography</td>
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<td>SSRI</td>
<td>Selective Serotonin Re-uptake Inhibitors</td>
</tr>
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<td>STAI</td>
<td>State Trait Anxiety Inventory</td>
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<tr>
<td>TARDBP</td>
<td>Transactive response DNA binding protein</td>
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<td>TASIT</td>
<td>The Awareness of Social Inference Test</td>
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<td>TDP–43</td>
<td>Transactive response DNA binding protein of 43 kDa</td>
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<tr>
<td>ToM</td>
<td>Theory of Mind</td>
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<td>TWF</td>
<td>Thurstone Written Fluency Test</td>
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<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>UMN</td>
<td>Upper Motor Neuron</td>
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<td>VBM</td>
<td>Voxel Based Morphometry</td>
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<tr>
<td>VFI</td>
<td>Verbal Fluency Index</td>
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<td>VIF</td>
<td>Variable Inflation Factor</td>
</tr>
<tr>
<td>vMPFC</td>
<td>Ventromedial prefrontal cortex</td>
</tr>
<tr>
<td>VOSP</td>
<td>The Visual Object and Space Perception Battery</td>
</tr>
<tr>
<td>VSAT</td>
<td>Verbal Series Attention Test</td>
</tr>
<tr>
<td>WAIS</td>
<td>The Wechsler Adult Intelligence Scale</td>
</tr>
<tr>
<td>WASI</td>
<td>Wechsler Abbreviated Scale of Intelligence</td>
</tr>
<tr>
<td>WCST</td>
<td>Wisconsin Card Sort Test</td>
</tr>
<tr>
<td>WM</td>
<td>White Matter</td>
</tr>
<tr>
<td>WTAR</td>
<td>Wechsler Test of Adult Reading</td>
</tr>
<tr>
<td>ZBI</td>
<td>Zarit Burden Interview</td>
</tr>
</tbody>
</table>
1. Motor Neuron Disease

1.1. Terminology

Motor Neuron Disease (MND) is a clinical hypernym 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. 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.

Frontotemporal Lobar Degeneration (FTLD) is an umbrella term which refers to a heterogeneous group of neurodegenerative disorders characterised by atrophy of the frontal and temporal lobes of the brain. FTLD corresponds to several overlapping dementia syndromes. As with the MND nomenclature, the terminology for FTLD varies in meaning throughout the literature. Here, ‘FTLD’ will be used to denote the histopathological or neuropathological correlates of its associated cognitive–behavioural syndromes. Frontotemporal Dementia (FTD) will refer to the overarching FTLD–related syndrome that encompasses two sub–syndromes. These sub–syndromes will be referred to as behavioural variant frontotemporal dementia (bvFTD) and the language variants of primary progressive aphasia (PPA).

1.2. Epidemiology

ALS is perceived as a relatively rare disorder. The point prevalence in the 1990’s for Western countries ranges from 2.7 to 7.4 per 100,000 (Worms, 2001), while the United Kingdom (UK) prevalence ranges from 4.02 to 4.91 per 100,000 (Hoppitt et al., 2011). A recent incidence study noted the European incidence rate as 2.1 per 100,000 person years (Logroscino et al., 2010). The disease primarily affects adults in mid–to–late life, with a mean onset age varying between 55 to 65 years (Wijesekera & Leigh, 2009). Juvenile cases of sporadic ALS, where patients are below 25 years of age, are reported in approximately 5% of cases (Aggarwal & Shashiraj, 2006; Myllyla et al., 1979).

There are two patterns of incidence. A disproportionate number of cases are sporadic, but a small proportion (~10% of cases) is familial, showing an autosomal dominant transmission (Byrne & Hardiman, 2010; Leigh et al., 1989). Recessive variants have also been identified (Gros-Louis et al., 2006).
Median survival from symptom onset to death is reported to vary from 20 to 48 months (Chio et al., 2009). The limbs are the most prevalent site of onset (~75% of cases); a minority of patients present with initial bulbar symptoms (~25% of cases), while respiratory onset is rare (Haverkamp et al., 1995). The disease is unrelenting, typically progressing from an initial location to encompass other regions and culminating in respiratory failure and eventual death.

Incidence is 54% higher in men than women in the UK, with a male to female ratio of 3:2. A lifetime risk of disease development is estimated at 1 in 472 for women and 1 in 350 for men (Alonso et al., 2009). The reported gender–ratio varies extensively across studies. In general, higher ratios are reported in clinic–based studies while population data suggest it approaches equality (Abhinav et al., 2007; Logroscino et al., 2008). This disparity might be due to an over–representation of younger patients in clinic registers, as a relationship with age and the sex ratio has been demonstrated. In one study, gender ratios tended towards unity for age groups over 55 years in two European populations (Manjaly et al., 2010). This finding also highlights a possible increased female risk of developing ALS with the advancement of post–menopausal age.

Despite an otherwise uniform world distribution, high risk geographical loci for MND have been detected in Western Pacific countries, such as Guam, the Kii Peninsula and West New Guinea. In the 1950s, incidence rates of MND in these countries were estimated at over 50 – 100 times higher than that of other global regions (Kurland & Mulder, 1954). The MND in these populations can be associated with a Parkinsonism–dementia complex and referred to as ‘Guam syndrome’ (McGeer & Steele, 2011). Post–mortem studies of Guamian patients have revealed neurofibrillary tangles (Rodgers-Johnson et al., 1986), suggesting a degeneration common to Alzheimer’s Disease (AD) and Parkinson’s Disease (PD). The cause of these aggregations remains unknown but the clusters of incidence suggest an environmental trigger. For example, the cumulative consumption of a neurotoxin (β–methyl–amino–L–alanine) found in cycad flour in the Guam diet was posited as a putative predictor in this region (Whiting, 1964). This hypothesis was discounted, but has been recently revived (Borenstein et al., 2009; Steele & McGeer, 2008). Alternatively, a genetic predisposition may be a reasonable explanation for these region–specific incidence rates; yet, to date, only two genes have been identified as potential candidates for susceptibility to this version of the disease (Garruto & Yanagihara, 2009). Intriguingly, incidence rates in Guam appear to have
decreased rapidly since the 1950s (Plato et al., 2003). By contrast, age– and gender–adjusted incidence rates of ALS in the Kii peninsula have increased since the 1960s (Kihira et al., 2012). A change in water resource supply on a small island off the peninsula mainland coincided with a high incidence of 9.45 per 100,000 on the island during 2000 – 2009, supporting the argument for an environmental cause. However, due to the small population of this region, the precision of these estimates might be compromised (95% CI [7.39; 26.29]). Further study in these areas over time is warranted.

1.3. Aetiology

1.3.1 Environmental risk factors

The identification of exogenous risk factors for ALS is challenged by a lack of replication studies and small sample sizes demonstrating insufficient power. As such, no definitive causative environmental factor has been established. Numerous putative risk factors for the development of ALS have been proposed. These include: intense physical activity (Beghi et al., 2010; Chio & Mora, 2012) or rather premorbid lifetime athleticism (Huisman et al., 2013), smoking (Armon, 2009), previous head injury (Chen et al., 2007), military service (Coffman et al., 2005; Horner et al., 2003), low premorbid weight (Scarmeas et al., 2002) and exposure to electromagnetic fields (Bonvicini et al., 2009; Li & Sung, 2003), metals and chemical toxins (Sutedja et al., 2009). Recent years have seen an increase in animal model studies which have isolated numerous putative neurotoxins for the study of neurodegenerative disease aetiology. Such studies have demonstrated that, in animal models at least, environmental neurotoxins can reproduce neurodegeneration, in the absence of genetic co–factors (see Shaw & Hoglinger, 2008).

1.3.2. Genetic risk factors

Alongside the search for exogenous risk factors, research in the genetic aetiology of ALS ensues. Gene hunting in ALS has been prolific in recent years. A description of each ALS gene is beyond the scope of this thesis, but the interested reader is directed to the following online resource for a complete list: ALS Online Genetics Database (ASLoD), http://alsod.iop.kcl.ac.uk (Abel et al., 2012; Wroe et al., 2008).

Research has identified genetic factors underlying both inherited (familial) and, apparent, sporadic ALS (see Section 1.4. for clinical characteristics). Mutations in the superoxide dismutase–1 (SOD1) genes, the transactive response DNA Binding Protein
(TARDBP) genes and the fused in sarcoma/translated in lipsarcoma (FUS/TLS) genes have been documented in both populations (Andersen, 2006; Daoud et al., 2009). Recently, an expansion of the hexanucleotide repeat within gene C9orf72 on chromosome 9.p21.2 has also been implicated in both variants of the disorder (Renton et al., 2011; Shatunov et al., 2010). These findings imply that the boundaries between familial and sporadic forms of the disease may be artificial, if not merely convenient (Hanby et al., 2011).

A similar argument can be applied to the boundaries of ALS and FTLD. Mutations in the TARDBP (Borroni et al., 2009), FUS/TLS (Van Langenhove et al., 2010), C9orf72 (Simon-Sanchez et al., 2012) and other genes (see Van Langenhove et al., 2013) have also been associated with forms of FTLD, strongly propounding an aetiological link between the two diseases. In addition, epidemiological evidence indicates that first– and second–degree relatives of ALS patients bear a two–fold increased risk for the development of dementia (Fallis & Hardiman, 2009; Majoor-Krakauer et al., 1994), further implicating a shared genetic susceptibility.

Genotype–phenotype correlations

Evidence for phenotypic variability among patients with distinct genetic mutations exists. For example, SOD1 gene carriers typically show a different site of onset (in the lower limbs) than TARDBP mutation carriers (in the upper limbs) (Millecamps et al., 2010a). ALS patients with C9orf72 expansions are more likely than those with other ALS–related mutations to present with bulbar signs (Chio et al., 2012; Millecamps et al., 2012) and cognitive impairment or FTD (Byrne et al., 2012). In ALS patients with co–morbid FTD, behavioural changes and psychotic features were associated with C9orf72 carriers rather than non–carriers (Snowden et al., 2013). In addition, patients with truncating mutations in the FUS/TLS gene show a more aggressive disease course and a younger age at onset, than those with missense mutations of the same gene (Waibel et al., 2013). The exploration of genotype–phenotype relationships is an exciting and potentially valuable enterprise for research and clinical practice. Some researchers propose the future practicality of stratifying patients in clinical trials or personalising therapeutics on the basis of genotypic information (Al-Chalabi et al., 2012). Although, genetic mutations may not be the sole determinant of the clinical presentation, as phenotypic heterogeneity between and among families with inherited
ALS suggest that environmental or other genetic factors influence symptom predominance and the rate of disease evolution (Millecamps et al., 2010b).

1.4. Clinical characteristics

The hallmark of MND is progressive degeneration of the motor neurons of the motor system, leading to limb weakness and paralysis, speech and swallowing difficulties and respiratory failure. Two types of neurons are relevant: the upper motor neurons (UMNs) and lower motor neurons (LMNs). UMNs arise in the primary motor region and project down the corticospinal tract (CST) to the brainstem where they decussate to the contralateral side of the body and provide impulses to the LMNs. The LMNs originate in the spinal cord and brainstem from where they extend via the peripheral nerves to stimulate the muscles. Please see Figure 1.1. for a simplified illustration of the motor system.

The spectrum of MND presentations encompasses disorders in which degeneration is restricted to the UMNs or the LMNs; or a combination of both, resulting in different MND subtypes. Degeneration of both UMNs and LMNs corresponds to the ALS variant, whilst predominant LMN and UMN degeneration results in Progressive Muscular Atrophy (PMA) and Primary Lateral Sclerosis (PLS), respectively.

1.4.1. Amyotrophic Lateral Sclerosis (ALS)

ALS is the most prevalent form of MND; accounting for approximately 85% of cases (Norris et al., 1993; Talbot, 2002). The term ALS was first conceived by Charcot and Joffroy in the 19th century to describe a combination of UMN and LMN dysfunction. This MND subtype leads to a clinical picture of muscle fatigue, atrophy and spasticity. Muscle cramping and involuntary contractions may precede noticeable muscle weakness and atrophy but are seldomly the presenting symptoms (Wijesekera & Leigh, 2009).

The most common region of symptom onset is in the limbs, where distal or proximal weakness of the upper or lower limb muscles may appear. Patients might experience foot drop or notice focal muscle wasting. Limb onset is more common in men, particularly between the ages of 65 and 84 years. Bulbar onset occurs in approximately 25% of cases and manifests in the form of sialorrhea (excessive drooling), dysphagia (swallowing difficulty), dysarthria (motor speech disorder) and tongue wasting. Bulbar
presentation is more common in older patients, with 43% of patients over the age of 70 presenting with bulbar onset in comparison to 15% for those under 30 years of age (Haverkamp et al., 1995). Approximately 5% of patients present with respiratory onset, showing signs of diaphragmatic weakness in the absence of significant bulbar or limb symptoms (Chen et al., 1996; de Carvalho et al., 1996).

Approximately 10% – 20% of ALS patients survive longer than 10 years (Chio et al., 2009). Population–based research suggests that younger age, a prolonged interval from symptom onset to diagnosis (indicating less aggressive progression) and a predominance of UMN signs are associated with survival times beyond eight years (Zoccolella et al., 2008b). The region of onset is an important prognostic factor, as bulbar onset disease is associated with poorer prognosis compared to limb onset (del Aguila et al., 2003; Zoccolella et al., 2008a). Reduced forced vital capacity (FVC) at diagnosis is also associated with poorer survival (Czaplinski et al., 2006), but respiratory onset disease does not necessarily entail a rapidly progressive decline as comparable survival times between bulbar and respiratory onset patients using ventilation assistance have been found (Shoesmith et al., 2007). Other negative prognostic indicators include symptom progression rate, older age (Logroscino et al., 2008), poor psychosocial status (Johnston et al., 1999; McDonald et al., 1994) and dementia comorbidity (Olney et al., 2005). More recently, a population–based study found that executive dysfunction was significantly associated with reduced survival in a non–demented ALS cohort (Elamin et al., 2011).
Figure 1.1.: Outline of human motor system

1.4.2. Familial Amyotrophic Lateral Sclerosis (fALS)

ALS is generally accepted to be familial if the disease is reported in a first or second degree relative of the respective ALS patient. Epidemiological studies suggest that approximately 0.8% – 13.5% of patients report a family history; however, this prevalence increases to 17% – 23% in genealogical studies (Andersen & Al-Chalabi, 2011). There are several patterns of inheritance including autosomal dominance with complete and incomplete penetrance (Orrell, 2000); as well as recessive transmission (Al-Chalabi et al., 1998; Gros-Louis et al., 2006). In response to the absence of clearly defined criteria for fALS, Byrne and his colleagues propose guidelines for diagnosis to aid epidemiological and genetic research (Byrne et al., 2011). These classify patients into categories of diagnostic certainty, such as ‘definite’, ‘probable’ and ‘possible’ fALS, on the basis of family history, genetics and neurodegeneration (or presence of family history of FTD). Approximately 20% of fALS cases are causally linked to SOD1 mutations (Turner et al., 2013), while TARDBP and FUS/TLS mutations account for 3.0% and 4.4%, respectively (Lagier-Tourenne & Cleveland, 2009; Millecamps et al., 2010b). The C9orf72 expansion is responsible for approximately 40% of fALS (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Clinically, fALS and sporadic ALS are indistinguishable, and, as discussed previously, share common genetic mutations and show similar pathological patterns. However, relative to the sporadic form, the fALS subgroup shows a younger age at onset and typically presents with limb symptomology. Gender distribution is equal between the two groups (Hand & Rouleau, 2002; Li et al., 1988; Mulder et al., 1986).

1.4.3. Primary Lateral Sclerosis (PLS)

PLS is a variant of MND which is characterised by UMN degeneration and absent or minimal LMN symptoms, although electrophysiological evidence of LMN denervation may be present (Le Forestier et al., 2001). It is clinically differentiated from ALS on the basis of a lack of LMN symptoms, such as muscle wasting and fasciculations. Instead, patients typically present with increased muscle tone and spasticity of the limbs (Hudson et al., 1993). Bulbar symptoms at onset are uncommon in PLS (Tartaglia et al., 2007). It is a rare subtype, occurring in approximately 5% – 10% of MND cases. The mean age of onset is between 45 to 54 years (Singer et al., 2007). The gender distribution shows a slight male predominance (Worms, 2001). Cognition was traditionally believed to be intact (Pringle et al., 1992), but recent evidence of cognitive
and behavioural dysfunction comparable to that seen in ALS has been reported (Grace et al., 2011).

Over time the disease may progress and severity of an isolated region may worsen or LMN symptoms might develop (Floeter & Mills, 2009). Some PLS cases, may progress to meet criteria for ALS (Bruyn et al., 1995). Prognosis is typically better in PLS than ALS, with survival times reported at over 14 years. The disease progression is insidious and includes periods of accelerated decline and stability (Floeter & Mills, 2009; Tartaglia et al., 2007). The differentiation of MND patients with and without LMN signs appears to be an important indicator for prognosis. Patients with PLS who present or develop even subtle signs of LMN or electromyography (EMG) abnormalities show shorter survival compared to patients with exclusive UMN involvement (Gordon et al., 2009). It is difficult to distinguish PLS from the ALS subtype early in the disease course, as classical ALS might initially present without noticeable LMN signs. For this reason, some authors recommend a period of 3 to 4 years without LMN signs for a definitive PLS diagnosis (Gordon et al., 2006; Pringle et al., 1992; Tartaglia et al., 2007).

Whether PLS and ALS are distinct disorders or different clinical presentations of the same disease remains controversial. Due to the relative rarity of PLS, few studies examining common pathological mechanisms with ALS are available. Nonetheless, case reports have noted occurrences of familial ALS and PLS phenotypes within the same families (Brugman et al., 2005; Praline et al., 2010), suggesting common genetic factors promoting motor degeneration. However, structural differences in white matter (WM) changes between the two disorders have been observed (Iwata et al., 2011), indicating distinct underlying pathology.

1.4.4. Progressive Muscular Atrophy (PMA)

The PMA subtype is characterised by the degeneration of the spinal motor neurons and exclusive lower motor neuron (LMN) involvement, such as muscle atrophy and weakness, almost always in the limbs. However, as the disease evolves, patients may develop typical ALS, which includes bulbar and upper motor neuron symptoms. Approximately 5% – 10% of MND patients are classified as suffering from PMA (Maragakis, 2010; Norris et al., 1993; Traynor et al., 2000b). In comparison to ALS, PMA is associated with a later age at diagnosis (Maragakis, 2010) and better prognosis, with survival times of approximately 200 months from symptom onset. The gender bias
is more marked in PMA, as a male to female ratio of 2:1 is consistently reported. A third of PMA cases survive beyond five years and 12% beyond 10 years according to a population–based study (Norris et al., 1993; Visser et al., 2007). Cognitive involvement is not strongly associated with the disease. An early neuropsychological study found that, unlike their ALS sample, PMA patients did not show cognitive impairment (Wicks et al., 2006); while, a larger study did find deteriorated performance on tasks of executive function and memory in their PMA sample (Raaphorst et al., 2011).

The disease is considered a distinct nosological entity under current diagnostic criteria (Brooks et al., 2000), but recent evidence suggesting common clinical, genetic and pathological characteristics with ALS may endorse PMA as a clinical position within a broader ALS spectrum. A histological study of 18 PMA patients reported CST degeneration as a prevalent feature (50%) in their sample upon autopsy. In addition, ALS–associated ubiquitinated inclusions were also found in the spared motor neurons (Ince et al., 2003). Moreover, recent evidence has identified genetic mutations common to familial and sporadic ALS subtypes, such as SOD1, in patients presenting with isolated LMN signs (van Blitterswijk et al., 2012).

1.4.5. ALS–Frontotemporal Lobar Degeneration (ALS–FTLD)

The broad clinical heterogeneity of ALS is exemplified by its possible co–morbidity with another neurodegenerative condition, FTLD. This disease is characterised by focal atrophy of the frontal and anterior temporal lobes of the brain. It is associated with distinct syndromes of cognitive and behavioural dementias, defined here collectively as frontotemporal dementia (FTD). ALS–FTLD patients show the typical physical symptoms of ALS, with concomitant cognitive and/or behavioural changes common to FTD. These symptoms may follow, precede or present simultaneously with motor symptoms. FTD is divided into two variants: behavioural–variant–Frontotemporal Dementia (bvFTD) and Primary Progressive Aphasia (PPA). The two variants are associated with distinct behavioural and language–dominant symptoms respectively; an overlap of these symptoms has been reported in ALS–FTD (Bak & Hodges, 2004; Bak et al., 2001; Caselli et al., 1993; Mitsuyama & Takamiya, 1979). PPA, itself, is divided into two subtypes: progressive non–fluent aphasia (PNFA) and semantic dementia (SD). These FTLD–dementia subtypes are illustrated in Figure 1.2.

FTD is the second most common dementia for adults under 65 years of age, showing an estimated prevalence of 10 – 20 per 100,000 and an incidence of 3.5 – 4.1 per 100,000
Prevalence rates for FTD in ALS vary from 5% – 18% (Goldstein & Leigh, 1999; Lomen-Hoerth et al., 2003; Neary et al., 1990; Ringholz et al., 2005). Approximately 15% of FTD patients develop ALS symptoms following a diagnosis (Burrell et al., 2011; Lomen-Hoerth et al., 2002). Due to the variable nomenclature used in published studies, it is difficult to discern if these rates include all the FTD syndromes, or are weighted towards a particular variant. There is an impression of a predominant bvFTD profile in ALS–FTD (Lillo et al., 2010; Neary et al., 1990), but this might reflect the limited study of language in ALS.

**Figure 1.2.: Subtypes of Frontotemporal Lobar Degeneration (FTLD) associated dementias**

![Subtypes of FTLD](image)
Risk factors for the development of FTD in the course of ALS have not been determined, but some evidence suggest that bulbar–onset (Giordana et al., 2011; Neary et al., 2000) and presence of the C9orf72 gene mutation (Gijselinck et al., 2012; Whitwell et al., 2012) may increase patient susceptibility. The identification of co–morbidity in ALS is of great clinical relevance. Relative to classical ALS patients, ALS–FTD patients show a more aggressive disease course and reduced median survival times (Gordon et al., 2010; Olney et al., 2005). Furthermore, the predominant FTLD phenotype occurring alongside ALS holds important implications for disease progression, as language–dominant ALS–PPA has been associated with bulbar symptomology and shorter survival than ALS–bvFTD (Coon et al., 2011). The clinical characteristics of each syndrome are described below. Diagnostic criteria for ALS–FTD are detailed in Section 1.5. An overview of the literature regarding the cognitive and behavioural profiles of ALS–FTD is provided in Chapter 2, Section 2.1.

A. ALS–behavioural–variant–Frontotemporal Dementia (ALS–bvFTD)

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, perseverative and sterotyped 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 common (Ikeda et al., 2002; Woolley et al., 2007a). Visuospatial and memory functions are typically preserved (Neary et al., 1998; Neary et al., 2005). 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).

B. ALS– Primary Progressive Aphasia (ALS–PPA)

ALS may also present concurrently with Primary Progressive Aphasia (PPA) in a phenotype referred to as ALS–PPA. Two subtypes of PPA have been associated with
ALS, namely progressive non–fluent aphasia (PNFA) and semantic dementia (SD). The former subtype is a disorder of expressive language, characterised by agrammatism (ungrammatical sentence construction), phonemic paraphasia (mispronunciation) and anomia (word retrieval failure). Word comprehension remains intact. In contrast, SD is a disorder of language meaning, in which patients display impaired naming and word comprehension; fluent speech but reduced content. Perceptual disorder, such as prosopagnosia (impaired face recognition) and associative agnosia (impaired object identification) may also be present (Neary et al., 1998; Neary et al., 2005). Each subtype is associated with distinct areas of cerebral atrophy: PNFA is associated with asymmetric atrophy of the left hemisphere, whilst SD is correlated with bilateral atrophy of the middle and inferior temporal neocortex (Neary et al., 2005). SD and bvFTD symptoms may overlap, with some SD patients displaying social disinhibition, a lack of insight and reduced empathy as the disease progresses (Grossman, 2010; Rosen et al., 2006).

1.5. Diagnosis & diagnostic criteria

1.5.1. Amyotrophic Lateral Sclerosis (ALS)

As no accepted biomarkers for the disease currently exist, ALS diagnosis is established on the basis of characteristic features and the exclusion of possible mimic syndromes. Clinical, genetic, neuroimaging and electrophysiological data are used to aid and corroborate diagnosis. Symptoms indicative of combined upper and lower motor neuron impairment, which cannot be accounted for by co–morbid disease processes are suggestive of ALS. The El Escorial Revised criteria (Brooks et al., 2000) classifies patients into four categories: “Clinically Definite”; “Clinically probable”; “Clinically probable–laboratory supported”; and “Clinically possible” (see Table 1.1.). However, these criteria may fail to identify a large proportion of patients who, in the early stages of the disease, do not show clinical signs of UMN involvement, but may have ALS or a related variant. Furthermore, early detection of UMN signs with EMG is difficult (Rowland & Shneider, 2001). As a result, it has been suggested that these standards are more useful for research settings (Silani et al., 2011). Clinical practice might benefit from recently devised guidelines which combine the current criteria with expanded electrophysiological data. Known as the Awaji–Criteria (AC; de Carvalho et al., 2008), these standards suggest the inclusion of fasciculation potentials, characteristic of ALS, as evidence for developing denervation in the context of chronic neurogenic changes.
Earlier detection of ALS and greater diagnostic sensitivity for AC relative to the \textit{El Escorial Revised Criteria} has been demonstrated (Boekestein \textit{et al.}, 2010; Carvalho & Swash, 2009; Okita \textit{et al.}, 2011), yet the latter remains the current gold standard of ALS diagnosis for research purposes (Dengler, 2012).

\textbf{Table 1.1.: The El Escorial Revised Criteria for the diagnosis of ALS} (adapted from Brooks \textit{et al} 2000)

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

1.5.2. \textbf{ALS–Frontotemporal Dementia (ALS–FTD)}

The diagnosis of ALS–FTD is complex, due to the heterogeneous presentation of co–morbid disease. ALS patients may experience mood and behavioural changes as a response to the emotional implications of a terminal diagnosis. Language or speech may appear compromised as a result of motor dysfunction. It is thus important that the perceived changes represent a marked departure from the patient’s premorbid state and that physical impairment is accounted for at diagnosis (Strong \textit{et al.}, 2009). Although not designed for use in ALS, criteria for FTD are commonly used to confirm co–occurrence of the disease (Gregory \textit{et al.}, 1999; McKhann \textit{et al.}, 2001; Neary \textit{et al.}, 1998). The 1998 International Consensus Criteria for FTLD proposed by Neary and colleagues (see Table 1.2.) are widely used in research and practice. Core clinical features for the distinct sub–syndromes of FTD are outlined (Neary \textit{et al.}, 1998).
Common to all sub–syndromes, an insidious onset and gradual progression of symptoms must be present. Beyond this criterion, each sub–syndrome is associated with distinct core features; the profiles of which are disproportionally behavioural or language–related for bvFTD and PPA, respectively. Supportive features, although not mandatory, are also listed to affirm the diagnosis. Motor neuron disease symptoms are categorised under an extension of the clinical diagnostic features. Formal neuropsychological testing, electroencephalography (EEG) and brain imaging are used to corroborate the clinical diagnosis, but are not a prerequisite.

These criteria indicate good predictive value of ante mortem FTLD pathology (Knopman et al., 2005; Pijnenburg et al., 2008) and high sensitivity has been demonstrated (Knopman et al., 2005), although this is variable (Mendez & Perryman, 2002; Piguet et al., 2009; Rascovski et al., 2007). Some authors have questioned the sensitivity of these guidelines for their under–specification of some features, the number and nature of exclusion features, and their inflexible structure, which may lack sensitivity to early–stage bvFTD or variable symptom presentation (i.e. by requiring patients to meet all 5 core features) (Rascovski et al., 2011). Consequently, revised guidelines for the diagnosis of bvFTD have been proposed by the International Behavioural Variant FTD Criteria Consortium (FTDC) (Rascovski et al., 2011). These expand upon the earlier specifications and provide three levels of diagnostic certainty under a hierarchy of ‘definite’, ‘probable’ or ‘possible’ bvFTD (See Table 1.3.). The ‘possible’ classification specifies that patients must show three out of six core features of bvFTD, eliminating the distinction between core and supportive features. ‘Probable’ bvFTD patients must meet criteria for the ‘possible’ diagnosis, but must also show functional decline and imaging results consistent with bvFTD. Together these classifications are deemed most useful to distinguish early bvFTD from other FTLD phenotypes and AD. ‘Definite’ bvFTD is reserved for patients who show core disease features and neuropathological or genetic evidence of FTLD. In keeping with the original consensus, the FTDC guidelines acknowledge motor neuron disease symptoms as possible overlapping features. A comparison of the original and revised criteria against retrospective neuropathological data, showed improved bvFTD sensitivity for the revised classification in a large cohort of patients (n=137; Rascovski et al., 2011), while a later report showed that the revised criteria showed high sensitivity and specificity for early-onset bvFTD when applied to a larger (n=156) autopsy-confirmed cohort (Harris et al., 2013).
Table 1.2.: Core criteria for the diagnosis of FTLD subtypes (adapted from Neary et al, 1998)

<table>
<thead>
<tr>
<th>Behavioural–variant frontotemporal dementia</th>
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<tbody>
<tr>
<td>1. Insidious onset and gradual progression</td>
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<tr>
<td>2. Early decline in social interpersonal conduct</td>
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<tr>
<td>3. Early impairment in regulation of personal conduct</td>
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<tr>
<td>4. Early emotional blunting</td>
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<tr>
<td>5. Early loss of insight</td>
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<table>
<thead>
<tr>
<th>Progressive non–fluent aphasia</th>
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<tbody>
<tr>
<td>1. Insidious onset and gradual progression</td>
</tr>
<tr>
<td>2. Non–fluent spontaneous speech with at least one of the following:</td>
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<tr>
<td>Agrammatism, phonemic paraphasias, anomia.</td>
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<table>
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<tr>
<th>Semantic dementia</th>
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<tr>
<td>1. Insidious onset and gradual progression</td>
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<tr>
<td>2. Language disorder: fluent empty spontaneous speech, loss of word meaning, manifest by impaired naming and comprehension and semantic paraphasias and/or</td>
</tr>
<tr>
<td>Perceptual disorder: prosopagnosia (impaired recognition of faces) and/or associative agnosia (impaired recognition of objects)</td>
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<tr>
<td>3. Preserved perceptual matching</td>
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<td>4. Preserved single word repetition</td>
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<td>5. Preserved ability to read aloud and write orthographically regular words</td>
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</table>
Table 1.3: Revised international criteria for the diagnosis of bvFTD (adapted from Rascovsky et al, 2011)

| The following symptom must be present to meet criteria for bvFTD: |
| 1. shows progressive deterioration of behaviour and/or cognition by observation or history |

**Possible bvFTD**

| Three of the following behavioural/cognitive symptoms must be present to meet criteria: |
| 1. Early behavioural disinhibition; one of the following symptoms must be present: |
| 1.1. Socially inappropriate behaviour |
| 1.2. Loss of manners or decorum |
| 1.3. Impulsive, rash or careless actions |
| 2. Early apathy or inertia; one of the following symptoms must be present: |
| 2.1. Apathy |
| 2.2. Inertia |
| 3. Early loss of sympathy or empathy; one of the following symptoms must be present: |
| 3.1. Diminished response to other people’s needs and feelings |
| 3.2. Diminished social interest, interrelatedness or personal warmth |
| 4. Early perseverative, stereotyped or compulsive/ritualistic behaviour; one of the following symptoms must be present: |
| 4.1. Simple repetitive movements |
| 4.2. Complex, compulsive or ritualistic behaviours |
| 4.3. Stereotypy of speech |
| 5. Hyperorality and dietary changes; one of the following symptoms must be present: |
| 5.1. Altered food preferences |
| 5.2. Binge eating, increased consumption of alcohol or cigarettes |
| 5.3. Oral exploration or consumption of inedible objects |
| 6. Neuropsychological profile: |
| 6.1. Deficits in executive tasks |
| 6.2. Relative sparing of episodic memory |
| 6.3. Relative sparing of visuospatial skills |

**Probable bvFTD**

| All of the following symptoms must be present to meet criteria: |
| 1. Meets criteria for possible bvFTD |
| 2. Exhibits significant functional decline |
| 3. Imaging results consistent with bvFTD |

**Definite bvFTD**

| Criterion 1. and either criterion 2. or 3. must be present to meet criteria: |
| 1. Meets criteria for possible or probable bvFTD |
| 2. Histopathological evidence of FTLD on biopsy or at post mortem |
| 3. Presence of a known pathogenic mutation |
1.5.3. Non–demented Amyotrophic Lateral Sclerosis with cognitive impairment (ALSci) and/or behavioural impairment (ALSbi)

Strong and colleagues’ consensus criteria (2009) provide a unified framework which subtypes the range of cognitive impairment apparent in ALS patients. This framework provides clinicians and researchers with definite impairment cut–off criteria and advises the discernment of appropriate clinical control variables which might account for impairment (for example, mood, co–morbid disease and other disease symptoms, such as respiratory dysfunction). In clinic, should cognitive screening suggest dysfunction, a full neuropsychological assessment would be required to make a formal diagnosis of impairment. Currently, six categories of cognitive impairment are acknowledged in ALS. Here, only ALSci and ALSbi categories are introduced, but Table 1.4. illustrates the criteria for all subtypes of ALS–related cognitive dysfunction.

A. ALSci

ALSci characterises patients who do not fulfil current FTD dementia (or another dementia syndrome) but who perform at or below the 5th percentile on at least two distinct standardised neuropsychological measures sensitive to executive functioning, when compared to age– and education–matched norms from healthy controls. The guidelines recommend the assessment of other cognitive domains such as language, memory, attention and visuoperception in order to exclude the possibility of other cognitive conditions.

B. ALSbi

The ALSbi category describes patients who do not meet criteria for bvFTD, but who are rated by caregivers as having at least two non–overlapping behavioural changes, as measured by either the Neary et al FTD criteria (Neary et al., 1998; Neary et al., 1990) or Hodges et al bvFTD criteria (Gregory et al., 1999).

In cases where patients present with both executive dysfunction and behavioural change, concurrent ALSci and ALSbi diagnoses may be warranted. These criteria have encountered criticism, mostly regarding their failure to address the heterogeneity of cognitive impairment that has been documented in ALS (Goldstein & Abrahams, 2013). Since the recommended assessment for impairment is weighted towards executive function, this might compromise the detection of deficits in other cognitive domains, such as language dysfunction which can occur alongside or independent of executive
dysfunction (Taylor et al., 2013). Furthermore, deficits in emotional processing and social cognition have been shown in ALS patients (see Chapter 2, Section 2.3.) but there is no consensus on whether or how these should be assessed. Finally, these criteria await validation in ALS population studies.

Table 1.4.: Criteria for cognitive and behavioural impairment in ALS (adapted from Strong et al, 2009)

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<tr>
<td></td>
<td>ALS patient meeting criteria for either Neary et al criteria or Hodges et al criteria for bvFTD</td>
<td>ALS patient meeting Neary et al criteria for PNFA</td>
<td>ALS patient meeting Neary et al criteria for SD</td>
<td>ALS patient meeting at least two non–overlapping supportive diagnostic features from either Neary et al criteria or Hodges’ et al criteria for bvFTD</td>
<td>ALS patient with evidence of cognitive impairment at or below 5th percentile on at least two distinct tests of cognition that are sensitive to executive functioning</td>
<td>Patient with primary FTLD diagnosis with evidence of MND–type degeneration insufficient to be classified as ALS</td>
<td></td>
<td>ALS with dementia, not typical of FTD</td>
<td>ALS patient with concurrent dementia and/or parkinsonism occurring in hyperendemic foci of the Western Pacific</td>
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1.5.4. Differential diagnosis

There are many conditions with features that closely resemble ALS, further complicating the diagnosis process. These ‘mimic syndromes’ are suspected on the basis of unusual symptomatology, an atypical presentation of symptoms or a stable disease course (Traynor et al., 2000a). Population–based studies have estimated that up to 10% of ALS diagnoses may in fact be other disorders (Davenport et al., 1996; Traynor et al., 2000a). Here, two disorders which are most commonly misdiagnosed as ALS (Traynor et al., 2000a) are briefly described, but this does not exhaust the list of possible mimic disorders.

Kennedy’s Disease, also known as X–Linked bulbospinal neuronopathy or spinal and bulbar muscular atrophy, is a genetic disorder caused by a trinucleotide repeat in the androgen receptor gene (Finsterer, 2010). Its clinical features include slowly progressive lower motor neuron signs in the bulbar and proximal limbs. Differentiation from ALS is demonstrated on nerve conduction examinations in which Kennedy’s disease does not show sensory nerve action potentials, characteristic of ALS (Hardiman et al., 2011). Genetic testing is also conducted to distinguish the two diseases. The disease is progressively slower than ALS and life expectancy is not greatly affected (Finsterer, 2009).

Another ALS–like disorder is multifocal motor neuropathy with conduction block. This is a slowly progressive condition presenting as asymmetric muscle weakness, selective involvement of the finger extensors and in some cases the presence of antiganglioside antibodies. The condition can be remediated with the introduction of intravenous immunoglobulin (IVG) treatment (Federico et al., 2000). In practice, IVG may be prescribed to patients presenting with ALS symptoms to rule out an immunopathological mechanism (Radunovic et al., 2007).

1.6. Neuropathology

1.6.1. ALS

As previously described in Section 1.4., ALS is characterised by relative degrees of upper and lower motor neuron degeneration of the motor system. UMN pathology may encompass astrogliosis (neuronal scarring) in the grey matter (GM) and subcortical WM of the motor cortices, as well as axonal loss and demyelination in the CST (Ince et al.,
1998a). Early studies suggested depopulation of UMNs in the primary motor cortex (Brownell et al., 1970; Nihei et al., 1993). However, later stereological investigations found no significant difference in the number or size of these neurons in this region (Gredal et al., 2000; Toft et al., 2005). LMN pathology may manifest as neuronal loss in the brainstem and ventral horn of the spinal cord (Ince et al., 1998a).

At the molecular level, pathological hallmarks include abnormal neuronal and glial cytoplasmic inclusions in surviving neurons. Hyaline conglomerate inclusions are one type of body which may dislodge neuron contents, such as the nucleus (Ince et al., 1998b). These inclusions are rare and associated with SOD1 mutation carriers (Kokubo et al., 1999). More prevalent are Bunina bodies (BBs), inclusions which are specific to ALS and occur in approximately 86% of cases (Piao et al., 2003). They are granule–like bodies found in spinal anterior horn cells (Hirano, 1996). BBs tend to occur alongside ubiquitin–immunoreactive intraneuronal inclusion bodies, within the same cell (Mori et al., 2010). The relationship between these inclusion types is undetermined. In 2006, the protein TARDBP of 43 kDa (TDP–43) was identified as a major component of these ubiquitinated inclusions in a majority of ALS and FTLD cases (Arai et al., 2006; Neumann et al., 2006). TDP–43 is an amino acid nuclear protein encoded by the TARDBP gene and which functions for ribonucleic acid (RNA) metabolism (Buratti & Baralle, 2009). TDP–43 inclusions are principal protein deposits in a high proportion of ALS cases, occurring in all 102 cases in one report (Piao et al., 2003). Some familial ALS cases resulting from SOD1 mutations have shown absent TDP–43 pathology (Mackenzie et al., 2007), raising the possibility of distinct pathologies underlying the disease. TDP–43 inclusion bodies are morphologically and functionally similar to FUS/TLS inclusions. The displacement of either inclusion in the cytoplasm of neurons might lead to loss of typical function of the nuclear protein, a gain of toxic function in intracellular fluid (ICF) or both (Lagier-Tourenne & Cleveland, 2009). FUS/TLS inclusions have been reported in ALS patients with and without FUS/TLS mutations (Deng et al., 2010; Vance et al., 2009), implying a role of FUS/TLS in the pathogenesis of sporadic and other familial forms of the disease.

Pathology is not necessarily restricted to the motor system in ALS. Immunohistochemical surveys of extra–motor pathology in ALS patients have revealed TDP–43 and other inclusions in regions such as the nigro–striatal system, the cerebellum, amygdala, hippocampus and neocortex (Geser et al., 2008; Geser et al., 2009; Mackenzie et al., 2006; Neumann et al., 2006; Tan et al., 2007). Furthermore,
extra–motor functional and structural changes in non–demented ALS patients have been documented in the frontotemporal regions; the corpus callosum, hippocampus and amygdala. These observations support the proposal that ALS is a multisystem disorder extending beyond the motor system.

1.6.2. ALS–FTLD and FTLD

In FTLD, distinct neuropathological changes are associated with each variant. This pattern of change is replicated in the various subtypes of ALS–FTLD. In bvFTD, atrophy of the mesial and orbital frontal regions occurs early in the disease course, typically progressing to encompass the temporal pole, hippocampal formation, dorsolateral cortex and basal ganglia (Kril et al., 2005; Piguet et al., 2011). Similarly, ALS–bvFTD is associated with prominent neuronal loss, gliosis, spongiosis and atrophy of the frontal and temporal cortices, the hippocampus, amygdala, striatum and basal ganglia (Chang et al., 2005; Coon et al., 2012; Ferrer et al., 1991; Garraux et al., 1999; Mackenzie & Feldman, 2004; Yoshida, 2004). The extent of cerebral pathology in the frontal cortex, in particular, has been shown to differentiate ALS–bvFTD patients from ALS patients without dementia (Murphy et al., 2007a; Talbot et al., 1995; Wilson et al., 2001).

The PPA variants of FTLD are associated with differential pathology. PNFA is associated with predominant left fronto–insular degeneration, while SD is related to bilateral atrophy of the anterior temporal areas (Gorno-Tempini et al., 2011). Likewise, PNFA and SD in ALS patients show common patterns of neuropathology associated with each FTLD phenotype, in addition to the typical motor patterns of ALS (Bak et al., 2001; Caselli et al., 1993; Davies et al., 2005; Kim et al., 2009; Yokota et al., 2006).

Much like ALS, the molecular pathology of FTLD is heterogeneous. A proportion of FTLD patients show protein aggregations or deposits called tau (FTLD–tau). In other cases, tau deposits are undetected and instead inclusions which are immunoreactive to ubiquitin are present (FTLD–U) (Cairns et al., 2007; Josephs et al., 2011). As in ALS, TDP–43 forms the main component of these inclusions (FTLD–TDP) (Arai et al., 2006; Neumann et al., 2006). Subtypes of TDP inclusions are associated with different phenotypes of FTLD. Consequently, Mackenzie and colleagues offer an FTLD classification system based on ubiquitin pathology (Mackenzie et al., 2011). A small minority of FTLD patients have neither tau nor ubiquitin–positive inclusions (Mackenzie et al., 2006).
A comparison of TDP–43 pathology between patients with ALS, ALS–FTD and FTLD–TDP showed an accordant pattern of pathology involving motor, frontotemporal and parietal regions. The extent and severity of neocortical pathology was greater in FTLD–TDP and ALS–FTLD patients compared to ALS patients. Clinical symptoms were related to predominant distribution and burden of TDP–43 pathology (Geser et al., 2009). This continuum of TDP–43 pathology between the diseases substantiates the hypothesis that ALS and FTLD are expressions of the same disease process, with motor dysfunction and cognitive–behavioural impairment present on opposite sides of the clinical spectrum (Ince et al., 1998a; Mackenzie & Feldman, 2005). Similarly, FUS/TLS pathology has been indicated in ALS, ALS–FTLD and the bvFTD variant of FTLD (Deng et al., 2010; Neumann et al., 2009; Urwin et al., 2010), furthering the argument for a common pathogenesis.

1.7. Neuroimaging in ALS

1.7.1. Motor system dysfunction

In keeping with neuropathological features of ALS, structural change along the CST and motor cortex has been observed using conventional and novel Magnetic Resonance Imaging (MRI) techniques (Abe, 1997; Charil et al., 2009; Cheung et al., 1995; Goodin et al., 1988; Roccatagliata et al., 2009). Involvement of the posterior limb of the internal capsule of the CST has been commonly noted in post–mortem and MRI studies of ALS patients (Goodin et al., 1988; Smith, 1960; Wang et al., 2006); a recent study suggests that measures of WM degeneration in this area acts as a prognostic indicator (Menke et al., 2012). Voxel–based morphometry (VBM) has reported grey matter (GM) loss in the precentral gyrus (Chen & Ma, 2010; Roccatagliata et al., 2009), which correlates with disease progression rate (Verstraete et al., 2010). GM volume loss in this region appears to correspond to functional disability, as a comparison of patient onset groups revealed that bulbar–onset and limb–onset patients showed differential atrophy in the bulbar segment and limb segment of the motor homunculus, respectively (Bede et al., 2012).

Altered metabolite concentrations in primary motor cortex (PMC) and brain stem has also been documented. Magnetic Resonance Spectroscopy (MRS) allows for the non–invasive measurement of tissue metabolites, such as N–acetlaspartate (NAA), choline (Cho) and creatine (Cr) (Turner et al., 2012). Studies have found decreased NAA and
Cr levels but increased Cho concentrations in the PMC of patients compared to controls (Bowen et al., 2000; Gredal et al., 1997; Mitsumoto et al., 2007; Pohl et al., 2001; Schuff et al., 2001). Altered metabolite concentrations, including glutamate, are also documented in the brain stem (Hanstock et al., 2002; Pioro et al., 1999). PMC metabolite concentrations correlate with disease severity, disease progression and UMN impairment (Abe et al., 2001; Mitsumoto et al., 2007; Pohl et al., 2001). Similarly, brainstem NAA/Cr ratios are found to be lower in patients with bulbar weakness (Cwik et al., 1998).

1.7.2. Extra–motor involvement

Early imaging studies of extra–motor structural changes using Computerized Tomography (CT) in ALS produced inconsistent findings. One of the earliest studies to adopt CT alongside neuropsychological testing revealed that 57% of their ALS sample (8/14) displayed cerebral atrophy (David & Gillham, 1986). Later larger CT studies with samples including other MND variants (e.g. PMA, ALS–FTD) would challenge (n=18 ALS, n=17 PMA; Gallassi et al., 1989) and support these results (n=19 ALS, n=3 ALS-FTD; Kato et al., 1993) concerning cortical atrophy.

Studies of Single–Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) were applied in ALS patients and obtained comparable results. Both techniques rely on the detection of radiation emitted from injected radioisotopes (e.g. glucose) in the brain, allowing the quantification of cerebral changes, such as oxygen or glucose metabolism and blood flow (Turner et al., 2012). Using SPECT, Ludolph, Elger & Böttger (1989) demonstrated global cortical reduction, as well as multifocal reduction in the frontotemporal areas, of 17 ALS patients. Findings of frontotemporal dysfunction correlates in non–demented ALS have since been corroborated by others using this technique (Abe et al., 1997; Abe et al., 1993; Waldemar et al., 1992; Waragai et al., 1997). One of the first comparative SPECT studies of ALS, ALS–FTLD and FTD patients found that, relative to controls, all patient groups showed a common pattern of reduced regional cerebral blood flow (rCBF) in the bilateral anterior and medial orbitofrontal cortex (OFC), anterior and medial frontal cortex and bilateral anterior temporal lobes. Neuropsychological impairment and cerebral abnormalities were present in ALS patients but both were more pronounced and widespread in the ALS–FTLD and FTD patients (Talbot et al., 1995), implying a
continuum of pathology between the diseases and suggesting a positive relationship between extra–motor dysfunction and cognitive impairment in ALS patients.

Functional MRI (fMRI) data have also indicated multisystem involvement in ALS. Analysis of resting state brain networks in 20 ALS patients and controls found significant deactivation in both the sensorimotor and default–mode networks in patients only (Mohammadi et al., 2009). The latter network is an interconnected neural system comprising of frontal, parietal and temporal regions, showing high activity during rest and reduced activity during cognitive tasks (Raichle & Snyder, 2007). In this study, decreased volumes in the lateral and prefrontal cortex (PFC), the inferior parietal and posterior cingulate cortex in patients relative to controls were found, indicating significantly weaker functional connectivity. Earlier studies have correlated activation patterns with neuropsychological indices in ALS patients. These studies are discussed alongside neuropsychological investigations of ALS in Chapter 2.

Studies of GM in extra–motor areas complement fMRI findings in ALS. Chang and colleagues (2005) compared patients with ALS, ALS–FTD and controls using VBM. A reduction in GM volume in the frontal (left middle and inferior frontal gyri, frontal pole, ventromedial frontal cortex) and temporal (bilateral superior temporal gyri and right temporal pole) regions, as well as the left posterior thalamus was observed in all patients versus controls. On direct comparison of ALS–FTD patients with ALS patients, the former group showed a greater degree of atrophy in the left frontal gyri. Thus, in keeping with Talbot et al’s (1995) SPECT observations, a frontotemporal pattern of atrophy was found in both groups, supporting the purported pathological continuum between ALS and ALS–FTLD.

Changes in WM were not reported in the above study. This is in contrast with previous MRI investigations (Abrahams et al., 2005a; Ellis et al., 2001; Kassubek et al., 2005; Senda et al., 2011), but in keeping with others (Agosta et al., 2009; Agosta et al., 2007; Filippini et al., 2010; Tsujimoto et al., 2011). These discrepant findings may be due to heterogeneous processes underlying ALS, resulting in no apparent distinct degenerative profile. Alternatively conventional MRI may lack sensitivity to WM changes compared to other advanced techniques. Diffusion Tensor Imaging (DTI) has been proposed as a more robust method of detection (Turner & Modo, 2010). This relatively new technique allows for the in vivo assessment of WM integrity by probing the diffusion of water molecules along WM tracts. Two indices are used to estimate diffusion. The first index,
fractional anisotrophy (FA), measures the degree of diffusion anisotrophy and relates to the alignment of cellular structures. The second, Mean diffusivity (MD), is an index of the directionally averaged magnitude of diffusion and reflects the integrity of local neural tissue (Wang et al., 2011). A meta-analysis which pooled 8 whole-brain voxel-based DTI studies that compared FA differences between non-demented ALS patients and controls revealed that, relative to controls, patients showed FA reductions in the bilateral frontal WM and cingulate gyrus. The results showed robustness and high replicability, remaining after jackknife sensitivity analysis was applied (Li et al., 2012). Other DTI studies, which were not included in the meta-analysis, have supported changes to WM in the parietal lobes and corpus callosum, thalamus, hippocampal formation and insula (Ciccarelli et al., 2006; Filippini et al., 2010; Sach et al., 2004; Sage et al., 2007).

1.8. Clinical management

Although ALS remains incurable, many of the symptoms of the disease are treatable. Disease management is therefore focussed 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).

1.8.1. Musculoskeletal and otolaryngological symptoms

In addition to muscle weakness and fasciculations, cramping and spasticity may also occur in ALS. Clinic or community-based physical therapy may be available to supplement symptom management alongside pharmacological treatments. Cramps may be relieved through prescription of quinine sulphate, phenytoin and carbamazepine, while baclofen, tizanidine, dantrolene sodium and benzodiazepines can be helpful to relieve spasticity.

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 amitriptyline, a tricyclic antidepressants. In addition, botulinum toxin injections into the parotid and submandibular glands are effective for
pronounced secretions (Jackson et al., 2009). Radiation therapy applied to the salivary glands has also been trialled in ALS for sialorrhea control with satisfactory results, although side effects including nausea and throat soreness were reported in some patients (Harriman et al., 2001).

1.8.2. Emotional lability

Emotional lability (EL), also known as “pseudobulbar affect”, is described as involuntary episodes of contextually inappropriate or exaggerated outbursts of laughter, crying or smiling often without corresponding patient affect (Parvizi et al., 2009). The episode is often incongruent with the patient’s emotional state and/or incommensurate to the emotional valence of the eliciting stimulus. These inappropriate displays may be difficult to suppress, causing patients social embarrassment. Further, the condition is largely misunderstood by the patients’ caregivers, causing secondary distress. The disorder is associated with various neurological conditions; in ALS an estimated prevalence as high as 71% has been reported (Palmieri et al., 2009). It is also more common in patients with bulbar symptomatology (Moore et al., 1997; Newsom-Davis et al., 1999; Palmieri et al., 2009). Various tools have been developed for the assessment of EL. The Emotional Lability Questionnaire (ELQ; Newsom-Davis et al., 1999) has been developed for the specific assessment of EL in ALS for use in research or clinical settings (see Chapter 4).

The exact pathophysiology of EL is unknown, but the available evidence implicates disruption to the cortico–pontine–cerebellar circuit, which includes motor, limbic and association cortices (Miller et al., 2011; Parvizi et al., 2009). Treatment of EL has primarily involved the prescription of selective serotonin re–uptake inhibitors (SSRIs) and tricyclic antidepressants which are thought to act on neurotransmitters involved in the relevant circuit. A novel agent, ‘Nuedexta’, which is a combination of dextromethorphan and quinidine sulphate, has been developed for the treatment of EL. The precise mechanisms of the drug’s action are undetermined but it is believed to modulate glutamatergic transmission (Miller et al., 2011). A placebo–controlled trial of the drug in ALS and Multiple Sclerosis (MS) patients experiencing EL found a significant reduction in episode rate and symptom severity over a 12 week period for both groups. In general the drug was well tolerated, but adverse effects did include diarrhoea, dizziness and nausea (Pioro et al., 2010).
1.8.3. Depression and anxiety

The presence of depression and anxiety is understandable but not inevitable in the face of a terminal disease diagnosis such as ALS (See Chapter 2, Section 2.2.3.). No controlled studies of antidepressant benefit in ALS exist; however, in practice, tricyclic antidepressants or SSRIs may be prescribed for depression, while anxiety is treated with bupropion or benzodiazepines. Caregivers may also experience changes in mood state (see Chapter 3). Supportive counselling may benefit both patient and their families as they cope with the patient’s increasing disability.

1.8.4. Cognitive and behavioural changes

There is mounting evidence for cognitive and behavioural change in ALS. The degree of these changes may vary from mild to frank dementia (see Chapter 2). Detection of impairment is important as evidence suggests that executive dysfunction is a negative prognostic indicator in ALS (Elamin et al., 2011) and associated with reduced compliance with palliative care methods (Bede et al., 2011; Olney et al., 2011). Furthermore, behavioural impairments are associated with increased burden and reduced QoL of ALS caregivers (Chio et al., 2010).

Screening tests for cognitive and behavioural impairment in ALS have been developed (e.g. Abrahams et al., 2013; Woolley et al., 2010b), and a verbal fluency task, which accounts for motor impairment (Abrahams et al., 2000), is available for use in clinical settings. Comprehensive neuropsychological testing is required to determine impairment or dementia comorbidity. Behavioural impairment can be assessed using self and informant–rated scales (See Chapter 2, Section 2.2.2). Management of behavioural symptoms might include behaviour modification and/or atypical antipsychotics and SSRIs in standard doses (Gordon, 2011). However, no studies have evaluated the effects of behavioural and pharmacological interventions on such symptoms.

1.8.5. Respiratory function

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. Practice parameters recommend the introduction of non–invasive ventilation when FVC or SNIP measures fall below 50% and 40cm H20, respectively (Andersen et al., 2007; Miller et al., 2009). At this juncture, Non–invasive Positive Pressure Ventilation (NIPPV) may be prescribed to alleviate respiratory symptoms. NIPPV simulates physiological function by artificially inflating the lungs and assisting with respiration. NIPPV compliance of more than four hours per day was associated with enhanced quality of life (QoL) and a survival benefit of approximately seven months in patients without severe bulbar dysfunction (Bourke et al., 2006).

Invasive procedures may be elected to compensate for advanced respiratory impairment when non–invasive ventilation is no longer effective. Tracheostomy insertion is such a procedure and requires a respiration tube to be implanted into the trachea for the direct oxygenation of the lungs. One–year survival rates after this treatment option vary between 65.0% – 78.9% and mean and median survival are reported as 10.6 and 21 months, respectively (Sancho et al., 2011; Vianello et al., 2011). Perceived QoL of patients receiving this treatment is comparable to non–treated patients and patients receiving NIPPV (Kaub-Wittemer et al., 2003; Vianello et al., 2011). In contrast, caregivers of tracheostomy patients rate their own QoL lower than their patient’s QoL and report a high level of care burden compared to caregivers of NIPPV patients (Gelinas et al., 1998; Kaub-Wittemer et al., 2003), possibly reflecting the increased assistance required for tracheostomy in relation to non–invasive measures.

As advances in technologies for respiratory management ensue, ALS patients may benefit from novel treatment options. Diaphragm Pacing Simulation (DPS) is a relatively new technique in which electrodes are implanted into the diaphragm and
routed percutaneously to a control unit. This unit provides the stimulus for diaphragm contraction thereby simulating ventilation (Onders et al., 2009a). An initial assessment of DPS safety in ALS patients showed encouraging results in patients with intact phrenic nerves, while trials to date indicate that DPS use may delay the need for a ventilator by two years (Onders et al., 2009b). DPS has also been associated with reduced apnoeas and hypopnoeas during REM sleep, improving sleep efficiency (Gonzalez-Bermejo et al., 2012).

1.8.6. Nutritional status

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), while a longitudinal analysis indicates that patients with a weight loss of only 5% from diagnosis experience a twofold increase in mortality risk (Marin et al., 2011).

Many factors may contribute to malnutrition and weight loss including dysphagia; reduced upper limb strength which restricts eating function and consumption; suppressed appetite from anxiety or depression and constipation as a result of medication use, bowel immobility or reduced fluid intake. Additionally, hypermetabolism is often associated with the disease (Bouteloup et al., 2009), further complicating weight management. Moderate feeding difficulties may be overcome through the use of adaptive eating utensils; the modification of food or liquid consistency for easier swallow; postural advice to prevent asphyxiation or par–enteral feeding. As dysphagia and immobility become more problematic, enteric feeding by gastronomy becomes necessary to supplement oral intake.

Percutaneous endoscopic gastrostomy (PEG) is an enteral 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 compared to those declining it (Spataro et al., 2011). Since the procedure requires sedation, the insertion of an endoscopic tube and the ability to lie flat, it is not advised for patients experiencing pronounced respiratory insufficiency or sialorrhea. Morbidity risk increases if the procedure is performed when FVC is below 50% (Kasarskis et al., 1999); it is therefore advised that PEG is fitted
prior to the event of this threshold. Radiologically inserted gastrostomy (RIG) is a suitable alternative for patients with respiratory dysfunction as sedation and endoscopy is not required. Per–Oral Image Guided Gastrostomy (PIG), a hybrid technique of both PEG and RIG procedures, is a recent advance in enteral feeding procedures. Compared to PEG, no significant survival differences were observed for either procedure in one study, but no life–threatening complications were reported for patients in either procedure group (Chavada et al., 2010), suggesting the safety and efficacy of PIG as an alternative method of nutritional management in ALS.

1.9. Disease modification

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. Other pharmacological mechanisms of the drug have been posited to encompass the disruption of the N–methyl–D–aspartate (NMDA) receptor action, the blockade of $\text{CA}^{2+}$ and $\text{NA}^{+}$ channels and the modulation of gamma–amino–butyric acid (GABA) systems, although its precise neuroprotective actions are unknown (Cheah et al., 2010). A Cochrane Library meta–analysis of four randomised placebo–controlled trials including 1477 ALS patients indicated that a dosage of 100mg/day of Riluzole was associated with a prolonged median survival of 2 – 3 months in patients experiencing symptoms of less than five years, a FVC greater than 60% and an age of less than 75 years (Miller et al., 2007). A deceleration in progressive muscle weakness was demonstrated in one study (Bensimon et al., 1994), but not replicated in subsequent trials (Bensimon et al., 2002; Lacomblez et al., 1996). Another study reported a small positive benefit on limb function, which persisted when the data were combined in a meta–analysis (Lacomblez et al., 1996). Imaging data revealed an increase of 6% in the N–acetylaspartate/Choline (NAA/Cho) ratio in the primary motor cortex of 11 patients after three weeks administration of the drug. In comparison, untreated patients showed a 4% reduction in this ratio over the same period (Kalra et al., 1998). However, no corresponding improvement in functional or symptomatic indices in the treatment group was observed over the study period. The drug is shown to be well tolerated, even in elderly or advanced–staged patients (Bensimon et al., 2002). Nonetheless, adverse effects may include fatigue, nausea, dizziness and diarrhoea. In addition, elevated liver enzyme
levels may also occur and thus regular monitoring of liver functioning is required (Gordon, 2011).

1.10. 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 and related neurodegenerative diseases. It highlighted the on–going interdisciplinary efforts which have so far converged to support the suggestion of ALS relationships with FTLD at genetic, neuropathological and neuropsychological levels. The primary focus of the current thesis concerns the profile of neuropsychological change in non–demented ALS patients; Chapter Two provides a detailed review of the literature in this area. As a secondary focus, the thesis will examine the effect such change has on the ALS caregiver; studies pertaining to research in this area are reviewed in Chapter Three.
2. Literature Review – Cognition and behaviour in ALS

As highlighted by Chapter One, the evidence for ALS as a multisystem disorder is compelling; not least because of extra–motor involvement documented by neuroimaging and neuropathological studies, but also because of the apparent aetiological overlap with other neurodegenerative conditions, as indicated by genetic research. This chapter will provide further evidence to support this notion through a critical review of studies reporting neuropsychological change in ALS. A subsidiary focus of the review is the overlap of cognitive and behavioural symptoms in ALS with FTLD syndromes. With this in mind, Section 2.1. outlines the main findings of cognitive and behavioural changes in ALS–FTLD. The key objective of this chapter will be to delineate the cognitive (Section 2.2.1.) and behavioural (Section 2.2.2.) profiles of ALS and specifically the emotional processing and social cognition deficits (Section 2.3.) that have been reported in the disease. Evidence for a relationship between executive dysfunction and deficits in emotional processing and social cognition is also explored (Section 2.3.2.4.). An overview of the literature concerning caregiving in ALS is provided in Chapter Three.

2.1. Cognitive and behavioural changes in ALS–FTLD

As outlined in Chapter One, the criteria for the separate syndromes ALS–FTD are characterised by behavioural and/or language changes. This section will review neuropsychological findings of ALS–FTD. The few studies which have assessed neuropsychological function in ALS–FTD patients have included case reports or very small patient groups, leading to reduced generalizability of their findings. The majority of these studies predate the establishment of current ALS–FTD and FTD diagnostic criteria (e.g. Neary et al., 1998; Rascovsky et al., 2011; Strong et al, 2009) and the standards for dementia diagnosis vary between them. Furthermore, many lack controls for motor disability. Despite these caveats, a profile of neuropsychological change for these patients has emerged. Studies investigating profiles for behavioural and language variants of ALS–FTD will be considered separately.

2.1.1. ALS–bvFTD

Converging findings from studies of ALS–bvFTD patients support a predominant pattern of impaired executive functioning and behavioural change. In particular, cognitive impairments are elicited on measures of verbal fluency, attention, inhibition, set–shifting and concept formation. Table 2.1. summarises these findings by study and
year. Memory impairments are reported less consistently (Gentileschi et al., 1999; Liu et al., 2009; Neary et al., 1990). Visuoperception is consistently reported as intact (Gentileschi et al., 1999; Moretti et al., 2002; Neary et al., 1990; Peavy et al., 1992), while language dysfunction has been suggested using measures of confrontation naming (Gentileschi et al., 1999; Liu et al., 2009; Neary et al., 1990; Peavy et al., 1992). Errors, such as semantic and phonemic paraphasias, have been noted in some studies (Gentileschi et al., 1999; Neary et al., 1990; Vercelletto et al., 1999), suggesting overlapping symptoms of PPA. Although executive dysfunction dominates the cognitive profile of ALS–FTD, language dysfunction has been found in several recent studies of these patients (see Section 2.1.2). The relationship between executive and language impairment, and the overlap of ALS–bvFTD and PPA, within ALS–FTD is of on–going enquiry.

Case reports have described ALS–bvFTD patients as showing marked personality change, becoming increasing socially disinhibited, irritable and aggressive. Increased egocentrism, sterotyped gestures, and reduced ‘warmth’ or empathy are also reported, alongside a lack of insight into or concern for their deterioration (Gentileschi et al., 1999; Liu et al., 2009; Moretti et al., 2002; Peavy et al., 1992; Vercelletto et al., 1999). The more florid behavioural displays may, paradoxically, culminate in a period of inertia, apathy, emotional flatness and social withdrawal (Liu et al., 2009; Neary et al., 1990; Peavy et al., 1992). These case descriptions of ALS–bvFTD patients resonate with those from the bvFTD literature (Neary et al., 1998; Neary et al., 2005; Tartaglia et al., 2008). Three major behavioural subtypes of FTD have been proposed (see Figure 2.1.), on the basis of clinical presentation and underlying neuropathological distribution of the frontal and temporal lobes (Snowden et al., 2001). A disinhibited subtype is characterised by overactivity, distractibility and disinhibition and associated with predominant pathology of the orbitofrontal lobes and anterior temporal neocortex. A second rare subtype shows predominant ritualistic and sterotyped behaviours (stereotypic–type), reflective of pathology in the striatum and temporal cortex. The apathetic subtype is characterised by apathy, inertia and loss of volition, associated with more widespread frontal lobe pathology including the DLPFC. Neary et al describe patients with disinhibited–type bvFTD as becoming increasingly more apathetic with time (Neary et al., 2000). This is similar to the pattern of behaviour described in ALS–bvFTD patients above, suggesting early orbitofrontal pathology in the disease with increasing dorsolateral involvement at later stages. However, it is not certain if
increasing physical disability in these patients may partially explain this change from a disinhibited to apathetic disposition.

2.1.2. ALS–PPA

As already mentioned in Chapter One, many ALS patients present with prominent language dysfunction severe enough to warrant a diagnosis of ALS–PPA (Doran et al., 1995; Mitsuyama, 1984; Watanabe, 1893), even after accounting for motor speech difficulties (Bak et al., 2001). Neuropsychological studies of aphasia in ALS have revealed distinguishable profiles of language impairment for patients with ALS–PNFA and ALS–SD, which have been described as more severe than those seen in the corresponding aphasic syndromes of FTD (Bak & Chandran, 2012).

Both ALS–PNFA and ALS–SD patients show impairments in confrontation naming. ALS–PNFA patients show semantic and phonemic paraphasias, alongside word–retrieval difficulty (Bak et al., 2001; Rakowicz & Hodges, 1998). In ALS–SD, object naming deficits are prominent (Kim et al., 2009; Yokota et al., 2006), reflecting the break–down of semantic knowledge associated with SD (Boxer & Miller, 2005).

Figure 2.1.: Behavioural subtypes of FTD (Snowden et al, 2001)
<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Neuropsychological tests indicating impairments</th>
<th>Neuropsychological tests indicating preserved performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neary et al.</td>
<td>4</td>
<td>BNT; Verbal Fluency; WCST; WAIS; Paired Associate Learning; Weigl’s Block Task; Proverbs interpretation test</td>
<td>Money Road Map; Warrington Memory Test; Delayed Verbal Recall; Koh’s Block Figures</td>
</tr>
<tr>
<td>(1990)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peavy et al.</td>
<td>2</td>
<td>BNT; Verbal Fluency; WAIS; Stroop Test; Go–Nogo task; Mattis Dementia Rating Scale</td>
<td>WMS; Parietal Lobe Battery; Cancellation Test; JLO</td>
</tr>
<tr>
<td>(1992)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentileschi et al (1999)</td>
<td>1</td>
<td>BNT; Semantic Fluency; Stroop Test; MMSE; Verbal Judgments; Silly Sentences; Paired Word Learning, Corsi Supra–Span Spatial Learning; Autobiographical Memory Questionnaire; Semantic Questionnaire; Digit Cancellation; Token Test; Facial Recognition Test</td>
<td>JLO; Verbal Forward Span†; Forward Spatial Span, Raven’s Coloured Matrices; Arithmetic Judgements; Street’s Completion Test; Perceptual Maze Test; Overlapping Figures Test; Dual Task; Long Story Recall; Associative Matching Task ; Weigel’s Block Test†; Famous Faces†; Famous Faces†</td>
</tr>
<tr>
<td>Vercelletto et al (1999)</td>
<td>5</td>
<td>Verbal Fluency; WCST; Stroop; Aphasia Test, MMSE</td>
<td>WMS; Rey Words</td>
</tr>
<tr>
<td>Moretti et al</td>
<td>4</td>
<td>Phonemic Fluency; WCST; Stroop; PASAT; Proverbs interpretation test; Aphasia Test; MMSE; NPI</td>
<td>WAIS–R Similarities; Digit Span; Raven’s Progressive Matrices; JLO; Koh’s Block Figures; Story Retrieval; Past Events Retrieval</td>
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<tr>
<td>(2002)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2009)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† impaired at follow–up; * borderline impairment. BNT: Boston Naming Test; D–KEFS: Delis–Kaplan Executive Function Scale; JLO: Judgement of Line Orientation, MMSE: Mini Mental State Examination, NPI: Neuropsychiatric Inventory, PASAT: Paced Auditory Serial Addition Task; VOSP: Visual Object and Space Perception Battery; WAIS: Weschler Adult Intelligence Scale, WCST: Wisconsin Card Sort Task, WMS: Weschler Memory Scale.
Dissociative impairment patterns between the two syndromes are observed. In ALS–PNFA, although the comprehension of single–words remains intact, patients show agrammatism in production and difficulties with syntactic comprehension (Bak et al., 2001; Caselli et al., 1993; Catani et al., 2004; Tsuchiya et al., 2000). Conversely, patients with ALS–SD show preserved syntactic comprehension, but impaired single–word comprehension (Yokota et al., 2006).

One of the hallmark features of ALS–PNFA is a selective deficit in the processing of verbs, both in production and comprehension tasks (Bak & Hodges, 2004; Bak et al., 2001; Hillis et al., 2006). In an investigation of two ALS patients and four ALS–PNFA patients with variable degrees of FTD, a similar profile of impaired verb processing was observed across patient groups. Imaging data revealed atrophy and hypofusion of the frontotemporal cortices in these patients, while a post–mortem study of four of the demented patients showed pathological changes in areas of the inferior frontal gyrus, including Broca’s area (Bak et al., 2001). This dissociation has been demonstrated in pure PPA patients (Hillis et al., 2006; Hillis et al., 2004; Hillis et al., 2002), but is opposite to the pattern shown in SD patients (Hillis et al., 2004). While SD patients have demonstrated a select deficit in the processing of nouns as opposed to verbs (Hillis et al., 2004), this is yet to be confirmed in ALS–SD patients. The verb processing deficit in ALS–PNFA is not restricted to words and includes abstract concepts of actions, as opposed to objects (Bak & Hodges, 2004).

Other cognitive domains in ALS–PNFA and ALS–SD patients remain relatively preserved. Visuoperception and non–verbal memory in both disorders are reportedly intact (Catani et al., 2004; Kim et al., 2009; Rakowicz & Hodges, 1998; Yokota et al., 2006). Topographagnosia (agnosia for landmarks) and prosopagnosia (agnosia for faces) have been noted in ALS–SD (Coon et al., 2012). Although language dysfunction dominates the clinical picture of ALS–PPA, dysfunction in attention and executive abilities have shown to progress with time (Catani et al., 2004).

The presentation of behavioural features alongside PNFA and SD syndromes in ALS provides further evidence that ALS–bvFTD and ALS–PPA may overlap (Caselli et al., 1993; Doran et al., 1995; Rakowicz & Hodges, 1998). Similar to PPA or bvFTD, the emergence of co–occurring syndromes might indicate a progression in disease stage (Gorno-Tempini et al., 2011; Marczinski et al., 2004). Changes in behaviour typical of ALS–bvFTD have been noted in ALS–SD patients, who show increased levels of
apathy, reduced empathy, insight and social disinhibition (Coon et al., 2012; Kim et al., 2009). Behaviour in SD is believed to show a more compulsive quality than in bvFTD (Snowden et al., 2001). No formal comparison of behaviour in ALS–bvFTD and ALS–SD patients has been made; as such the qualitative differences between these patients in undetermined. Patients with ALS–PNFA may also show behavioural change. Increased irritability and depressive symptoms are pronounced in the late stages of disease (Catani et al., 2004); a similar evolution of behaviour has been noted in PNFA patients (Marczinski et al., 2004; Snowden et al., 1992).

2.1.3. The putative ALS – FTD cognitive continuum

Recently, efforts from different disciplines have converged in an attempt to characterise the overlap between ALS, ALS–FTD and pure FTD. Debate surrounds whether the association between these disorders represents a continuum of clinical patterns of one single disease, reflects the co–occurrence of separate diseases or corresponds to distinct nosological entities (Bak, 2010; Gentileschi et al., 1999). Compelling support for the ‘continuum hypothesis’ is provided by studies documenting common molecular, genetic and neuropathological mechanisms between the disorders (Chang et al., 2005; DeJesus-Hernandez et al., 2011; Neumann et al., 2006; Snowden et al., 2013). Notably, subsets of ALS patients show milder symptoms of cognitive and behavioural change which are characteristic of ALS–FTD (see Section 2.2.). Conversely, FTD patients may develop motor symptoms of ALS, accompanied by ALS–typical degeneration of the anterior horn and spinal cord (Lomen-Hoerth et al., 2002; Neary et al., 1998).

The proposal of a unitary disease spectrum encounters some challenges. If the cognitive–behavioural profile of ALS patients mirrors that of ALS–FTD and FTD, it would follow that the FTD–like symptoms in ALS would progress with disease duration. However, several longitudinal studies have failed to detect significant cognitive change over time in these patients (see Section 2.2.1.7.), although longitudinal assessment of patients with progressive disease is difficult, and it may be that the decline in physical ability outpaces the initially subtle cognitive deterioration in ALS. Studies typically support comparable profiles of cognitive–behavioural dysfunction between the disorders; however, some dissimilarities have been noted. For example, ALS patients have demonstrated different patterns of affective decision–making (Girardi et al., 2011; Torralva et al., 2007) and differences between ALS–FTD and FTD patients in terms of the severity of language comprehension deficits exist (Bak & Chandran, 2012).
Nonetheless, the interpretation of similarities and differences between the three diseases is further complicated by the increasingly acknowledged genotypic and phenotypic heterogeneity within each disorder (Sabatelli et al., 2013; Snowden et al., 2013). Profiles of impairment similar to those associated with the three clinical syndromes of FTD, are indicated in ALS–FTD and ALS (see Sections 2.1. and 2.2.). However, changes in domains such as language and social cognition, which are consistently present in PPA and bvFTD respectively, have not been examined in great detail in ALS–FTD or ALS. It is unclear, for example, if the socio–emotional processing deficits reported in ALS (see Section 2.3.) correspond to those apparent in bvFTD; and if when present are attributable to similar cognitive or neural mechanisms. A more detailed characterisation of the extent of cognitive and behavioural change in ALS is required to build evidence in support of or against the continuum of the disease entities.

2.1.4. Summary

This section outlined the cognitive and behavioural profiles of patients with ALS–FTD. In brief, the separate syndromes of ALS–bvFTD and ALS–PPA are characterised by executive–behavioural or language dysfunction, respectively. These syndromes correspond qualitatively to those of bvFTD and PPA. Within ALS–PPA, distinct profiles of language impairment are evident. The presentation of executive or language dysfunction in ALS–FTD patients may present in isolation or co–occur. An emergence of overlapping deficits may be mediated by disease stage. Similar patterns of deficits in non–demented ALS, ALS–FTD and pure FTD suggest a cognitive continuum between the diseases, but this remains controversial.
2.2. Cognition and behaviour in non–demented ALS

Following on from the proposed cognitive continuum between ALS and FTD outlined in Section 2.1., the current section will provide a critical overview of the literature pertaining to cognitive and behavioural changes in non–demented ALS patients.

Studies investigating domains of cognition (Section 2.2.1.) behaviour (Section 2.2.2.), mood and personality (Section 2.2.3) are reviewed in turn. In addition, some researchers have extended the assessment of ALS cognitive impairment to include examinations of performance on emotion and social cognition tasks. Evidence for ALS–related impairments in these domains is reviewed separately (Section 2.3.), to reflect the overall focus of the thesis. Finally, the primary aims of the thesis are outlined (Section 2.4.).

2.2.1. Cognition in ALS

2.2.1.1. 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 (e.g. Alvarez & Emory, 2006; Simões-Franklin et al., 2010). Given the anatomical connectivity of the frontal lobes with non–frontal regions, some authors emphasise the involvement of ‘frontal–subcortical circuits’ in executive behaviour (Stuss, 2011). Throughout this thesis, the term ‘executive dysfunction’ will be used to refer to the presence of dysfunction in any one or a collection of these “higher–level” processes, while ‘dysexecutive behaviour’ will connote 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 supported by evidence (see Stuss & Alexander, 2007). The current thesis offers these terms and definitions for simplicity and acknowledges the controversy surrounding the conceptualisation of the
executive function construct, or impairment thereof (see Banich, 2009). Non-demented ALS patients have shown difficulty on various indicators of executive function; each which will be considered in turn.

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 several cognitive processes in order to initiate appropriate responses and engage retrieval strategies in quick succession while maintaining output to avoid repetition. The demands of the separate tests differ. Category fluency tests place less demand on executive processes and more demand on semantic knowledge 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 subserved 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 (see Table 2.2.) and semantic fluency deficits (e.g. Abe et al., 1997; Abrahams et al., 2000; Hanagasi et al., 2002; Rottig et al., 2006) have been found in ALS, suggesting an underlying vulnerability of the cognitive and neural processes associated with the tasks in ALS.

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:

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

Studies have varied in the adoption of this control measure, leading to a possible overestimation of fluency impairment in the disease. 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), which also suggests a true fluency impairment in ALS independent of physical impairment.

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 patient 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; 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. ALS patients without fluency impairments showed normal rCBF activation patterns in line with healthy controls. 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).

Widespread cortical involvement in fluency performance has been suggested in ALS using other neuroimaging techniques. 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. In addition, impaired activation in temporal regions and the supramarginal gyrus of the inferior parietal lobe was found. 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 WM changes in the frontotemporal regions of ALS patients are associated with fluency performance (Abrahams et al., 2005a). Twenty–three ALS patients were classified into two groups of cognitive status (impaired and unimpaired) on the basis of phonemic fluency performance. Relative to controls (n=12), cognitively impaired patients (n=11) showed WM reductions in regions encompassing the medial temporal lobe, as well as in regions surrounding association fibres within the superior and medial frontal lobes. These patients also showed impairments on naming and memory tasks, consistent with the pattern of structural abnormalities described. Compared to controls, patients without fluency impairment (n=12) showed WM changes in regions surrounding fibres that connect the frontal lobes to other cortical areas, demonstrating that structural abnormalities may precede noticeable cognitive impairment in ALS. Broadly consistent with these results, a DTI study found that longer
fluency index times for an oral phonemic fluency task were associated with reduced FA in WM in the inferior and superior frontal gyri, as well as the corpus callosum and CST in 30 ALS patients (Pettit et al., 2013). These results also corroborate the above fMRI data which showed a decreased BOLD response in patients in the anterior PFC and inferior frontal gyrus (which corresponds to Broca’s area) during a fluency task (Abrahams et al., 2004). Together, these studies propose that disruption to particular WM pathways in ALS may underlie the impaired verbal fluency performance observed in patients.

**Attention, inhibition and working memory**

Reports of 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 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.
### Table 2.2.: Phonemic verbal fluency impairment in ALS patients

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<td>10</td>
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<tr>
<td></td>
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<td>146</td>
<td>Normative Data</td>
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<td>56</td>
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*included control for motor impairment. COWA, Controlled Oral Word Association Test.
Table 2.2. continued.: Phonemic verbal fluency impairment in ALS

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<td>43</td>
<td>28</td>
<td>ALS with PSP (n=20) significantly impaired relative to ALS patients without PBP (n=23) and controls</td>
</tr>
<tr>
<td></td>
<td>Abrahams et al (2000)</td>
<td>22</td>
<td>15</td>
<td>yes (but not for oral VFI*)</td>
</tr>
<tr>
<td></td>
<td>Abrahams et al (2005)</td>
<td>20</td>
<td>18</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>Wicks et al (2009)</td>
<td>41</td>
<td>35</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>Taylor et al (2013)</td>
<td>53</td>
<td>35</td>
<td>25% ALS patients below 5th percentile of control group</td>
</tr>
</tbody>
</table>

*included control for motor impairment, PSP, Pseudobulbar Palsy
Studies which have incorporated non–verbal tasks 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. Performance of ALS patients on less complex visual attention tests was comparable to the healthy control group.

There is increasing evidence for eye movement (saccade) abnormalities in patients (see Donaghy et al., 2011 for review) which might offer an alternative explanation for ALS impairments on visually–based tasks. Saccades are rapid eye movements that bring stimuli to the fovea of the retina. Reflexive saccades require little cognitive control and occur automatically when participants look at external stimuli. Anti–saccades are voluntary movements made in the direction opposite to the side where the stimulus is presented. While the former saccades are associated with activation of parietal lobe regions, the latter are thought to be mediated by the frontal eye fields of the PFC (Mort et al., 2003) and the DLPFC (Ford et al., 2005).

Shaunak et al (1995) found that relative to controls, ALS patients showed longer latencies for correctly made anti–saccades and higher distractibility (greater error rates) on an anti–saccades task. More recently, higher distractibility in patients has been replicated, and this has correlated with performances on tasks of executive function, such as the Stroop and WCST, as well as dysarthria scores (Donaghy et al., 2010; Evdokimidis et al., 2002). Shaunak et al (1995) did not find evidence for abnormal reflexive saccades in their patient sample, but other studies have indicated these to be slower in ALS (Leveille et al., 1982; Ohki et al., 1994), particularly in patients with bulbar–onset disease (Donaghy et al., 2010). Other eye abnormalities, such as saccadic intrusions (involuntary saccades that disrupt fixation) and impaired smooth pursuit (eye movements involved in tracking moving stimuli) have also been noted in ALS patients; these have been interpreted as further evidence for frontal lobe involvement in ALS (Donaghy et al., 2011).

Event Related Potential (ERP) studies allow the examination of attention in ALS through the adoption of physiological data alongside neuropsychological tasks. An advantage of these studies is that ERP components elicited by these tasks do not always necessitate an overt motor response. The first ERP study in ALS used an oddball task, in which participants are required to identify infrequent ‘target’ stimuli in a sequence of
promptly presented ‘standard’ stimuli. ERP recordings revealed prolonged latencies of the attention–sensitive N200 and P300 components in 60% of their patient sample (n=20, Gil et al., 1995). This was followed by findings of ALS patients demonstrating significant impairment relative to controls in detecting target stimuli during a visual serial search task, but not during a simple parallel search task (Munte et al., 1999), in keeping with Chari et al’s (1996) findings of a graded effect of attention impairment. Slower performance was accompanied by longer latencies and reduced amplitudes of the P300 in the complex task. On the parallel search task, no differences in P300 amplitude were found between patient and control groups. However, the onset of the P3 latency was 120ms slower for patients than controls. These results suggest that search behaviour in ALS may be corrupted by an attention deficit independent from motor impairment.

Similarly, abnormal P300 subcomponents have been identified in auditory oddball tasks. Hanagasi et al (2002) found reduced amplitudes of P3a and P3b and longer P3a latencies in patients compared to controls using both active and passive versions of this paradigm. Abnormal P3a parameters are thought to indicate deficient novelty detection processes and are associated with frontal areas, such as the AC (Escera et al., 1998). The P3b component is evoked through effortful target detection and is thought to reflect memory storage mechanisms originating in the hippocampal formation (Polich & Criado, 2006). Patients in this study also showed impairments on neuropsychological tests of attention, working memory, inhibition and visuospatial processing. Together with the ERP data, these results were interpreted as evidence for underlying dysfunction of a frontally–mediated attentional network in the ALS group.

Attention, as measured by digit span tasks, has been reported as impaired (Gordon et al., 2010) and, conversely, 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,
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 (see 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. 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).

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.

Although Abrahams et al, (1997) failed to find group differences on the Stroop test, the study did find a strong trend (p=.051) for a group effect on a negative priming (NP) task, a derivation of the Stroop test. In this condition, participants were required to name the colour of the ink in which an incongruous colour word was presented; however, the colour of the ink was the same as the colour word on the previous trial. Thus in order to respond correctly the participant must inhibit the distractor response on
a trial and then produce the previously inhibited response on the subsequent trial. Reaction times in healthy adults are typically increased in this condition compared to control and Stroop conditions, indicating a higher cognitive load of the NP task (Steel et al., 2001). In the study, ALS patients did not show this typical pattern, suggesting that the patients showed difficulty with inhibiting a previously suppressed stimulus. However, the higher cognitive load associated with the NP task might itself have influenced ALS performance.

An fMRI study which compared 14 ALS patients and 8 controls on the Stroop and NP tasks failed to demonstrate differences between the groups for either the Stroop or NP effects (Goldstein et al., 2011). However, the direction of the difference and a large effect size ($d=0.809$) for the Stroop effect suggested that the ALS group did show greater interference on the Stroop test compared to controls, but that the small sample size may have prevented finding a statistically significant difference. Relative to controls, the ALS group showed increased activation in the left temporal and AC areas during this task, reflecting greater difficulty in suppressing the distractor response. For the NP task, decreased activation in the left cingulate precentral gyrus and the left medial PFC was found in patients compared to controls, despite the behavioural data indicating no group difference in NP effect. These cerebral regions are associated with the working memory and articulatory aspects of the NP task (Steel et al., 2001). Lower activation of these areas during the NP task may therefore correspond to a reactivation of the previously suppressed distractor which is more readily available to ALS patients because of inefficient inhibitory processes or wider working memory difficulties.

The Hayling Sentence Completion Test (see Chapter 4) has also been used in ALS to assess inhibition of prepotent responses. Participants are read aloud several sentences with the last word of the sentence missing. In the first condition, they are primed to complete the sentence with a sensible word as quickly as possible. In the second condition, they are asked to provide a word which is unconnected to the sentence in every way. Effective performance in the second condition requires cognitive inhibition as the participant must suppress a highly associated word. Errors in this condition have been associated with OFC dysfunction in lesion and dementia groups (Hornberger et al., 2010; Volle et al., 2012). A comparison of errors on this condition between ALS patients and controls revealed a non–significant trend in one study (Wicks et al., 2009). 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.

Further support for disturbed response inhibition in ALS is provided by ERP methods.
Thorns et al (2010) administered 13 ALS patients with the Stop–signal paradigm
(Logan & Cowan, 1984), in which participants were cued by a stimulus to respond to a
following target using either a left or right hand button press. On 25 % of the trials a
stop–signal followed the target stimulus requiring the participants to abort the initiated
motor response. The behavioural data indicated that compared to controls (n=13),
patients showed less efficient stopping movements and a lack of behavioural adjustment
(no reaction time adaption) after the stop–signal trials. These deficits were accompanied
by reduced amplitudes for ERPs that index motor preparation, inhibitory control and
error processing.

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
neuropsychological 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; it is difficult to discern the relative contributions of
these components (Levine et al., 1995). 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, a K–means cluster analysis 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 (see Section 2.2.1.2.). 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.

Ecologically–valid tests of executive function

Investigations of executive function in ALS labour under the covert assumption that the measures used to assess this construct tap into patients’ everyday problem–solving and planning behaviour. This has, however, not been established. Concerns regarding the real–world application of some executive function tasks have been raised in the neuropsychology literature (Burgess et al., 2006; Chan et al., 2008; Chaytor & Schmitter-Edgecombe, 2003). With these reservations in mind, Stukovnik et al (2010) used a novel task which simulated the reality of everyday medication management. Participants were required to assemble coloured cards, each representing different medications, according to rules relating to each ‘card/medication–pill’ (e.g. take two different times a day; do not take with other medication) in as few steps as possible. ALS patients’ (n=22) overall performance was significantly worse than controls (n=22). Specifically, they placed fewer pills correctly, made more errors and broke more rules. Moderate to large effect sizes for group differences were observed. These were larger than those observed from other standard cognitive tests included in the battery, suggesting that tasks which imitate realistic problem–solving situations may be more
sensitive to the extent of cognitive impairment in ALS. Equivalently, a difficulty in co–ordinating multiple rules to achieve a familiar objective (medication scheduling) in the patient group indicates that executive dysfunction in ALS may bear real relevance to patient care and daily living.

Decision–making under realistic conditions of increasing complexity has also been assessed in ALS using an adapted version of the Holiday Apartment Task (Fellows, 2006). In this task, participants are required to choose the best apartment out of a range of alternatives (with differing attributes) for the purpose of a hypothetical holiday stay. Meier et al (2010) administered this task to 17 ALS patients and 18 controls. They found that while controls adopted an attribute–based strategy for all trials, the patients’ search strategy shifted from an attribute–based approach in the first trial to an apartment–based approach in the third trial, the highest level of complexity (more apartment options). An attribute–based approach is posited to reflect a ‘maximizing strategy’ where the best choice is the objective. An apartment–based approach is considered to represent a ‘satisfying’ strategy where an acceptable but not optimal (i.e. ‘good enough’) alternative is chosen (Simon, 1956). This latter approach has been demonstrated by patients with OFC lesions on comparable decision–making tasks and possibly reflects a deficient representation of stimuli value (Fellows, 2006; Fellows & Farah, 2003). The study therefore provides indirect support for the presence of underlying OFC dysfunction in non–demented ALS patients, which might compare to the early OFC involvement present in bvFTD (Hornberger et al., 2010; Wittenberg et al., 2008).

Meier et al (2010) included other tasks, which they designated as being either primarily OFC– or DLPFC–sensitive. Individual case analysis, using the control sample as a reference, revealed that impaired performance on tasks sensitive to OFC and DLPFC functioning were dissociated within the ALS group. Some patients (n=6) performed worse and showed classical dissociations on tasks sensitive to OFC function. In other patients (n=3) this pattern was apparent for DLPFC tasks only. Another subset of patients (n=5) showed dissociations on both sets of tasks. While caveats regarding the suggested specificity of these individual tasks are acknowledged, these findings implicate a broader involvement of the PFC in ALS cognitive dysfunction and that different patterns of cognitive impairment in patients might be associated with separate regions within the PFC.
2.2.1.2. Language

*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 section 2.1.2.), have also been demonstrated in ALS patients on these tasks (Mantovan et al., 2003; Rakowicz & Hodges, 1998; Strong et al., 1999). Both fluency and naming tasks involve executive and word–retrieval processes, but the latter is considered to be less dependent on executive resources, due to the available prompts of external stimuli (pictures of objects). It is regarded as a more direct assessment of language function than verbal fluency. Performance on the two tasks is associated with common and divergent underlying neural substrates; only confrontation naming activates the temporo–occipital cortices (see Abrahams et al., 2003). However, fMRI data acquired during tasks of phonemic fluency and naming revealed reduced BOLD responses in the inferior frontal gyrus of patients relative to controls for both tasks (Abrahams et al., 2004).

*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.
Verb and noun processing

The selective deficit in verb processing shown in ALS–FTD (see Section 2.1.), has also been demonstrated in non–demented ALS patients. 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. Patients' verb processing impairments correlated with the degree of atrophy in the premotor regions, while non–motor regions (including the bilateral DLPFC and inferior frontal cortex) correlated with both verb and noun processing ability. Previous imaging studies have revealed an association of verb processing and the motor cortices in healthy individuals (Hauk et al., 2004; Tettamanti et al., 2005). Grossman et al’s findings thus suggest that verb processing deficits in ALS may be related to the degradation of action knowledge associated with compromised motor regions. However, verb, and not noun, processing ability also correlated with executive function indices, indicating that the select impairment might be due in part to increased recruitment of executive resources on the verb processing component of the task.

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 dementia or 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).
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 fewer self–corrected utterances relative to controls at baseline and again at a 6 month follow–up. Using the Cookie Theft task, a 24 month longitudinal study found that ALS patients produced significantly fewer correct information units (CIU), a measure of content relevance and accuracy, compared to controls at baseline. Moreover, individual analyses revealed that 10/16 ALS patients scored greater than one standard deviation (1 SD) below controls at baseline on the CIU measure, a pattern which remained consistent throughout the study duration. Also at baseline, ALS patients produced fewer content units, an indicator of participants’ ability to deduce information from the picture. At this time period, 8/16 patients exceeded the 1 SD cut–off; however, this pattern did not persist throughout the study (Roberts-South et al., 2012). Patient performance was found in the context of preserved expressive vocabulary, comprehension and action naming, suggesting greater sensitivity of discourse methods over standard language measures to more subtle language impairments in ALS. Alternatively, 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). Unfortunately, measures of executive function were absent in this study, so a similar relationship in this ALS sample could not be examined.

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).
Phukan et al (2012) showed that although executive dysfunction and language impairment tended to co–occur, the isolation of language impairment in some patients was also present. However, similar to previous studies, object naming served as the only measure of language function in the cohort. A relatively large clinic–based study (n=51 ALS; n=35 controls) which used a comprehensive assessment of language function found a similar pattern of results (Taylor et al., 2013). In this study separate composite scores based on executive and language items were constructed for each participant. Of the 51 patients assessed, 31% were classified as showing executive deficits and 43% qualified for language impairment, on the basis of performing at or below the 5th percentile of the control group. In addition, established criteria for cognitive impairment (Strong et al., 2009) and an extension of these criteria to explore language deficits was applied to individual domain items. Thirteen patients (25%) were classed as ‘cognitively impaired’ based on executive deficits and 20 (39%) based on extended criteria including language. These results suggest that language dysfunction might be as prevalent if not more prevalent than executive impairment in ALS. Independence of language disruption was again evident, as seven of the 20 language–impaired patients showed no executive dysfunction. Furthermore, within the ALS sample, regression analysis demonstrated that the Executive function composite scores accounted for only 44 % of the variance in the language composite scores. As neuropsychological testing was weighted more towards language than executive and non–executive function (i.e. memory), this may have produced a battery disproportionately sensitive to language impairment. Nonetheless, these findings challenge the opinion of exclusive or predominant executive dysfunction in ALS. Instead, they delineate a cognitive profile which could be characterised by either executive dysfunction, language impairment or both.

2.2.1.3. Memory

Recall 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).

Recognition Memory

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; 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.

Nature and mechanisms of memory impairment

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 (95% CI [0.16;0.86]) but not delayed (95% CI[-0.002; 0.97]) verbal memory domains. A significant mean effect size for visual memory impairment was also found (95% CI [0.01; 0.84]) (both immediate and delayed studies were amalgamated to represent one domain in order to circumvent the small number of studies available in the latter). 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. In Raaphorst and colleagues’ meta–analysis, the effect size for impairments in delayed verbal memory (n=371; d=0.47; p>.05, 95% CI [–0.002; 0.97]) was within the same range as that of the immediate verbal memory domain (n=497; d=0.51; p<.05, CI 95% [0.16; 0.86]). It is possible that delayed verbal memory did not meet statistical significance due to the smaller number of participants contributing to that domain (Raaphorst et al., 2010). Furthermore, Phukan et al’s (2012) recent population study compared memory performance between ALS patients with intact cognition; ALS patients with predominantly executive dysfunction (ALS–Ex) and patients with non–executive cognitive impairment (ALS–NEx). Compared to cognitively intact patients, the ALS–Ex group performed significantly worse on immediate and delayed recall trials, but not on the retention or recognition trials. Conversely, the ALS–NEx patients performed significantly worse on all four memory conditions. These results suggest a heterogeneous pattern of memory impairment in ALS which can occur alongside and independent of executive dysfunction.

2.2.1.4. Visuoperception and visuoconstructive skills

Visuoperceptual function refers to a set of processes that include attention, object identification and recognition (Phukan et al., 2007). 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.
2.2.1.5. 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. 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.

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. However, only a subsample of patients completed the symptom questionnaire. Physical functioning in these patients was significantly higher than those without these data. Therefore the 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;
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).

Associations between the neuropsychological profile of ALS and emotional lability (EL) have 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).

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 cognitive change 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.

2.2.1.7. 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 on 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 computerised 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. These
conclusions are substantiated by Gordon et al. (2010) who observed that only animal naming (semantic fluency) deteriorated in their six–month study of 50 ALS patients. At the first testing session, mild to moderately deteriorated performance for some patients (n=14) was shown on measures of executive function, memory and other language abilities (confrontation naming), but these did not show deterioration between time points. In this study, neuropsychological testing did not accommodate for motor disability, but neither bulbar–onset nor severity of bulbar signs predicted impairment at the initial testing session. Gordon et al. (2010) did not investigate whether these variables predicted the progression of animal naming deficits.

While previous investigations have found little evidence to suggest marked cognitive deterioration, the reliance of these studies on between–group analyses may have masked the potential heterogeneity of impairment progression within cohorts. Robinson et al. (2006) used single–case methodology to compare 19 recently diagnosed patients and eight caregivers. As before, testing assessed multiple cognitive domains including executive function, memory, language and visuoperception. At the group level, comparisons of ALS performance at inclusion and six months later found no significant deterioration within or between groups. However, individual analysis revealed that seven ALS patients showed deteriorated cognitive performance over the test period. Of these patients, one patient showed progression of impairment on seven of the eight neuropsychological tests, while the remaining six patients showed abnormal performance on up to three of the tests at the six–month follow–up. Only three bulbar–onset patients were recruited to the study, precluding informative comparisons of this subgroup with limb–onset patients or controls. However, of the seven patients showing cognitive deterioration, two were bulbar–onset; the third bulbar–onset patient showed cognitive stability. These findings underscore the potential of individual analysis in detecting subtle progression of ALS cognitive deficits over time in otherwise presumed homogenous samples. They also indicate that deterioration in cognitive function in ALS is not restricted to bulbar–onset patients.

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. multidomain 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.

In summary, the longitudinal effects of ALS on cognition remain a controversial topic. Small clinic–based studies suggest that ALS patients show modest, if any, cognitive deterioration along the disease course. Some studies indicate cognitive symptoms progress only in bulbar–onset patients (Schreiber et al., 2005; Strong et al., 1999), but evidence of progression in limb–onset patients exists (Robinson et al., 2006). Findings from a population–based study (Elamin et al., 2013) may reconcile inconsistencies in the foregoing literature, by suggesting separate cognitive phenotypes with distinct patterns of symptom progression. Previous studies, in which only group–level data are compared, may obscure this proposed heterogeneity inherent in ALS samples.
2.2.2. Behaviour in non–demented 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 (see Chapter 1, Section 1.5.2.). 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 (see Chapter 1, Section 1.5.3.). 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 in non–demented ALS.

2.2.2.1. 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 (see Section 2.2.3.). The study design did not allow for the examination of these alternatives, but indicates an interesting avenue of investigation.
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.

Temporal lobe–mediated behaviours have also been detected in ALS using the Frontal System Behaviour Scale (Kertesz, 1997). 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). Furthermore, these studies employed subjective report designs and thus 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., 2010b; 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).

2.2.2.2. Prevalence of 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.

2.2.2.3. 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, ‘asponaneity’ (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 symptomatology 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).

2.2.2.4. 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 subscore 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.

2.2.2.5. The relationship between 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 (2007a) 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–severely impaired 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 co–morbidity 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.

2.2.2.6. Insight and awareness

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.

Recent CT scanning evidence has revealed possible topographical correlates of anosognosia in a small cohort of ALS and ALS–FTD patients (n=8 in each group, Ichikawa et al., 2013). Anosognosia scores (as determined by patient–clinician discrepancies for functional and cognitive impairments) in the ALS group were significantly lower relative to the ALS–FTD group. Scores from both groups were positively correlated with anterior and inferior horns sizes, suggesting an association between loss of insight and frontotemporal atrophy in both diseases. Follow–up CT data available for non–demented patients only (n=7) showed a longitudinal increase in inferior horn size. Increases correlated with anosognosia scores, suggesting that mild anosognosia in non–demented ALS might predict inferior horn enlargement, a reflection of medial temporal atrophy.
2.2.3. Mood and personality in ALS

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 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.

Depression is suggested to be unrelated to disease severity in the majority of studies (Atassi et al., 2011; Clarke et al., 2001; Grehl et al., 2011; Lule et al., 2008; Montgomery & Erickson, 1987; Rabkin et al., 2000; Tedman et al., 1997), although two early studies did find statistically significant but weak associations with physical
impairment (Hogg et al., 1994; Hunter et al., 1993). Recently, depressive symptoms were found to correlate negatively with ALSFRS scores (Oh et al., 2012). However, patients in this study were quite physically progressed and several were severely depressed, as measured by the BDI. Another study of 41 ALS patients found a significant relationship between depressive symptoms and the breathing and swallowing items of the ALSFRS, but not the total ALSFRS score (Hillemacher et al., 2004). This might suggest an increased vulnerability to depression for patients with bulbar or respiratory symptoms. Depressive symptoms correlated negatively with disease duration, indicating that the depression present in the sample may represent a psychological reaction to the diagnosis communication for some patients. By comparison, increased depressive symptoms have also been associated with limb dysfunction, even in high functioning ALS patients (n=22, Jelsone-Swain et al., 2012).

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 which may improve identification of patients at risk of developing depression.

Anxiety

The presence of anxiety has received little study in ALS. 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., 2010a; Tedman et al., 1997).

**Personality**

Personality is a complex concept, the definition of which is problematic. Here, it will be defined as the habitual patterns of cognitive, emotional and social behavioural traits (Sollberger et al., 2009). Several models of personality have been proposed, one of
which, the Five Factor Model (Digman, 1990), has received wide acceptance due to its universal replicability (McCrae & Terracciano, 2005; Rossier et al., 2005). This model postulates that personality arises from the covariation of five broad dimensions or traits, namely Neuroticism (‘N’), Extroversion (‘E’), Openness to experience (‘O’), Agreeableness (‘A’), and Conscientiousness (‘C’). These traits are seen to remain approximately stable throughout the adult lifespan (Costa & McCrae, 1988), although their permanence in the context of neurodegenerative disease is debatable. Personality change is noted in several neurodegenerative disorders and may differ qualitatively and quantitatively between conditions (Rankin et al., 2005; Sollberger et al., 2011), corroborating suggestions of a brain–personality relationship. Compared to other neurodegenerative conditions, personality in ALS has not been extensively studied.

ALS studies have predominantly focussed on pre–existing traits rather than change after disease onset. This remains despite the growing support for a clinical overlap between ALS and FTD; the latter can include profound alterations in personality from disease onset (Neary et al., 2005). An early review of sixteen ALS case reports noted pre–morbid traits of extraversion and ‘universal cheerfulness’ (Veit, 1947), in line with contemporary observations of ALS patients as being ‘warm and pleasant’ (Borasio et al., 2001).

Studies that have directly assessed personality in ALS have drawn contradictory conclusions. An early report by Brown & Mueller (1970) described an autonomous, ‘hard–working’ and ‘emotionally–controlled’ behavioural style in their 10 patients, based on self–ratings of the Internal–External locus of control scale (Rotter, 1971). Locus of control (LoC) refers to an individual’s perception of the relative contribution of external and dispositional factors to the outcome of situation (Rotter, 1975). The 10 patients were characterised by high internal LoC and by the adoption of denial as a psychological defence mechanism against depressive thoughts. These findings were challenged by a larger study which found a low use of denial coping (30%) and depression (n=35%) in their sample (n=40). Instead, internal LoC was highest for patients in the mid–stage of disease (Houpt et al., 1977, n=38), suggesting internality may vary with length of illness. Another study found that male patients (n=21), but not female patients (n=17), demonstrated a tendency of increased neuroticism (Peters et al., 1978). Compared to the general medical population, male participants showed elevated scores on hypochondriasis, depression, hysteria and schizophrenia scales. However, the composite personality profile of ALS patients did not differ from the medical reference
group. Together, findings from these early studies failed to identify a distinct profile of personality in ALS and attention in this area diminished.

In recent years, interest in personality in ALS has returned. Grossman et al 2006 compared caregiver ratings of premorbid personality between 47 ALS patients and those of a progressive disease control group (n=47; comprising of 15 MS, 22 lung cancer and 10 brain glioma patients). The study used the NEO Personality Inventory (NEO-PI, Costa & McCrae, 1992), a measure which operates under the FFM (McCrae & John, 1992). No differences between ALS patients and the control group on dimensions of ‘N’, ‘E’, ‘A’ and ‘C’ were observed. However, ALS patients were rated significantly lower on the ‘O’ dimension, believed to assess attentiveness to various forms of experience, such as intellectual curiosity, fantasy and emotional sensation. People who score low on this trait typically feel emotion less intensely than others and exert a higher level of emotional control (McCrae & John, 1992). The results of this study therefore resonate with Brown & Mueller’s earlier findings surrounding LoC. They may also partially explain why some patients evaluate aversive stimuli as less arousing or negative than healthy controls (see Section 2.3.2.). Moreover, scores on ‘O’ have been positively related to scores of depression (Wolfestein & Trull, 1997), raising the possibility that the low prevalence of mood disorder reported in ALS might be attributed at least in part to pre-existing personality characteristics.

Some studies have suggested meaningful relationships between personality traits and cognitive and behavioural functioning in neurodegenerative disease. Premorbid neuroticism is associated with higher levels of memory impairment in AD (Wilson et al., 2004), while cognitive indices have predicted personality traits of warmth, extraversion and dominance in a large neurodegeneration sample (n=286), after controlling for demographic variables, diagnosis and premorbid trait scores (Sollberger et al., 2012). These associations suggest that personality traits in neurodegeneration may be subserved by specific neuropsychological functions; possibly mapping onto common neural networks. In ALS, the current study of personality factors alongside cognition and behaviour is insufficient to suggest parallel associations between these variables.
2.3. Emotional processing and social cognition

Social interaction is integral to human life. 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). Social cues are embedded in language, paralinguistic information (such as intonation or emphasis) and non–verbal indicators (such as 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.

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.

2.3.1. Neural basis of socio–emotional processing

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 recognising 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. Subdivisions of the PFC include the OFC, ventromedial (vMPFC) and DLPFC regions. 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), but 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).

2.3.2. Emotional processing and social cognition in ALS

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 presumably 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.
2.3.2.1. Emotional Processing

*Emotional responding*

Altered emotional response to emotive material is suggested in ALS. 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 (Lule *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 (data were not reported). 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).
Faces were rank ordered according to the control–group ratings of approachability. Ratings for the 10 most approachable faces did not differ between groups; however, ratings for the 10 least approachable faces were rated as more approachable by the patient group than controls. All participants were categorised into ‘Trusters’ or ‘Conventional’ responders based on their average rating of the 10 least approachable faces. There were significantly more ‘Trusters’ in the patient group than in the control group. Within the patient group, performance on the paradigm task was not associated with cognitive status. In fact, six of the 11 cognitively intact patients fell into the ‘Trusters’ category, while only two of the seven cognitively compromised patients, one mildly impaired patient and one ALS–FTD patient, also fell into this category. The authors suggest that the rating behaviour was therefore not associated with frontal dysfunction in patients, and that since similar rating behaviour is apparent in amygdala–damaged patients (Adolphs et al., 1998), these results could likely be due to amygdala involvement. However, only vague descriptions of cognitive testing and diagnostic criteria were provided for 18 of the 26 patients, questioning the exclusion of frontal dysfunction involvement.

*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. 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.

In keeping with Papps et al’s findings, an fMRI study which incorporated an emotional decision task and a subsequent recognition memory test also found a failure of ALS individuals to display the normative pattern of enhanced memory for emotional words (Palmieri et al., 2010). Both the decision task and the memory test were associated with reduced right hemispheric activation and increased left hemispheric activation for unpleasant words versus neutral words in ALS patients compared to controls. No positively–valenced words were presented in the study, so it is not clear if a similar atypical lateralisation in ALS individuals would have occurred for pleasant words. The abnormal functioning of the right hemisphere in these ALS patients may have led to difficulties in the processing of the unpleasant words, possibly leading to their poorer recognition. Notably, during the recognition memory task, ALS patients showed reduced activation compared to controls in the right posterior cingulate gyrus. This area has been implicated in the interaction of emotional and memory–related processes as well as the reception of inputs from frontal cortical regions pertinent to the regulation of emotional and social behaviour (Maddock et al., 2003). However, since the neuropsychological battery did not include behavioural inventories, an examination of a relationship between the apparent dysfunction and behaviour could not be conducted. Nonetheless, these results do complement other findings of right hemisphere dysfunction in ALS patients with FTD and mild cognitive and/or behavioural symptoms (Murphy et al., 2007b). Structural MRI showed significantly reduced right hemisphere grey matter volume for patients with cognitive and behavioural symptoms in comparison to those patients without such symptoms. The structural distinctions between the ALS groups led the authors to suggest that right hemisphere atrophy in ALS patients might represent a biomarker for cognitive and behavioural change in the disease.
**Emotional 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 (see Table 2.3.). 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). 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.

**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 et al., 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.

2.3.2.2. Social Cognition

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 (see Table 2.4.). 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 (see Section 2.2.1.5.).
Table 2.3.: ALS impairments in basic emotion recognition from faces

<table>
<thead>
<tr>
<th>Author</th>
<th>Measure</th>
<th>Group</th>
<th>ALS</th>
<th>HC</th>
<th>ALS impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girardi et al (2011)</td>
<td>FEEST</td>
<td></td>
<td>14</td>
<td>20</td>
<td>Lower mean accuracy scores for all basic emotions† Two patients performed within the abnormal range of controls</td>
</tr>
<tr>
<td>Lillo et al (2012b)</td>
<td>Modified Ekman Faces Test</td>
<td></td>
<td>20</td>
<td>20</td>
<td>Lower mean total accuracy score than controls</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 bvFTD Higher mean total accuracy score than bvFTD patients</td>
<td></td>
</tr>
<tr>
<td>Staios et al (2013)*</td>
<td>TASIT EEA</td>
<td></td>
<td>35</td>
<td>30</td>
<td>No differences between positive and negative emotions</td>
</tr>
<tr>
<td>Savage et al (2013)*</td>
<td>TASIT EEA</td>
<td></td>
<td>13</td>
<td>30</td>
<td>No impairment in non-demented ALS patients relative to controls.</td>
</tr>
</tbody>
</table>

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. This profile of performance might indicate a general impairment in inferential ability related to executive dysfunction, rather than a specific ToM deficit. Support for this suggestion is provided by the finding that both total accuracy scores and the proportion of errors correlated significantly with measures of executive functioning, in particular with tests of mental set–shifting and abstraction (i.e. the WCST).

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. Two patients showed impairment (at or below 5th percentile of controls performance) on this aspect of the task. Of these patients, one was cognitively and behaviourally intact, based on established criteria (Strong et al., 2009). Furthermore, performance on all the task conditions showed no relationship to measures of executive function. A subset of 14 patients and 20 controls underwent whole brain VBM imaging procedures. In ALS patients, emotion attribution scores correlated positively with grey matter density in the
right fronto–insular cortex and the AC. Relative to controls, patients also showed reduced grey matter density in the ventromedial PFC, although these did not show a statistical association with experimental scores. All three regions have been implicated in empathic ability in healthy and neurological populations (for review, see Bernhardt & Singer, 2012). The results align with those from previous studies noting socio–emotional processing impairments which are isolated from executive dysfunction in patients. This selectivity corroborates suggestions of a variable vulnerability to cognitive change within the disease. Previous investigations which have used ToM measures that do not formally distinguish between emotional and cognitive aspects of ToM may contribute to the apparent discrepancies in patient performance across these studies. Performance differences may be explained by the heterogeneous quality of ALS ToM impairment, which itself may correspond to variation in neural damage.

**Empathy**

While some behavioural inventories include items which assess empathic responding (*e.g.* NPI), 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.
Table 2.4.: Studies of ALS ToM ability using static cartoons and social stories

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of measure</th>
<th>Conditions</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibbons et al (2007)</td>
<td>Happé Task</td>
<td>‘mental’ (inferences regarding character’s beliefs, feelings and intentions)</td>
<td>Absence of select ToM deficit in ALS patients. Patients showed heterogeneous impairment relative to controls, ranging from normal to significantly impaired.</td>
</tr>
<tr>
<td>16 ALS</td>
<td></td>
<td>‘control’ (inferences regarding physical causation or logical consequence)</td>
<td></td>
</tr>
<tr>
<td>Meier et al (2010)</td>
<td>Social Faux Pas Task</td>
<td>‘faux pas’ (character says or does something socially inappropriate)</td>
<td>Presence of select ToM deficit in ALS patients. Relative to controls, ALS patients tended to misidentify the faux pas and showed an inability to explain a correctly identified faux pas in the experimental condition.</td>
</tr>
<tr>
<td>18 ALS</td>
<td></td>
<td>‘control’ (no faux pas)</td>
<td></td>
</tr>
<tr>
<td>Cavallo et al (2011a)</td>
<td>Cartoon task</td>
<td>‘social contexts’ (actions for social goal)</td>
<td>Presence of select ToM deficit in ALS patients. Relative to controls, ALS patients performed worse on the social cartoon stories than the non–social items.</td>
</tr>
<tr>
<td>15 ALS</td>
<td></td>
<td>‘non–social contexts’ (actions for private goals)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>‘control’ (inferences regarding physical causation)</td>
<td></td>
</tr>
<tr>
<td>Cerami et al (2013)</td>
<td>Cartoon task</td>
<td>‘emotional’ (attribution about feelings)</td>
<td>Presence of select ToM deficit in ALS patients. ALS patients performed worse on the emotional attribution condition. No group differences were observed for cognitive attribution or control conditions.</td>
</tr>
<tr>
<td>20 ALS</td>
<td></td>
<td>‘cognitive’ (attribution about intentions)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>‘control’ (inference regarding physical properties of objects)</td>
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</tbody>
</table>
2.3.2.3. Ecologically–valid measures of socio–emotional processing

A limitation of previous socio–emotional studies in ALS is the reliance on static faces or unanimated social scenarios to assess processing impairments. These measures may fail to capture the complexity of everyday social interaction. Emotion recognition in the “real–world” typically includes the processing of transient facial expressions, alongside other contextual information, such as prosody of speech. Equally, drawing accurate inferences about the intentions and beliefs of a speaker requires the appreciation of the actual and subliminal content of what is being said. The inclusion of more realistic measures of social cognition might determine the extent of processing deficits reported in ALS and whether they are likely to represent everyday patient difficulties with interpreting social exchanges.

Only two ALS studies have incorporated realistic measures of emotion recognition in ALS (Savage et al., 2013; Staios et al., 2013). Both have used the dynamic emotion recognition subtest of The Awareness of Social Inference Test (TASIT, McDonald et al., 2002, see Chapter 4). On this task, participants are asked to identify an emotion portrayed by an actor in a scene, from a possibility of seven basic emotions. In the first study, performance for individual emotions were combined into positive (happy, surprised, neutral) or negative (sad, angry, anxious, revolted) emotions and compared between non–demented ALS patients (n=35) and controls (n=30). No significant differences were found between the groups for these combined scores. The inspection of group means for individual emotions revealed that controls outperformed patients on all emotion categories, except for the neutral and anxious items; but these differences were too small to contribute to a statistical effect (Staios et al., 2013). Savage et al (2013) found similar results for their non–demented ALS patient group. This study compared emotion recognition performance between groups of ALS, ALS–FTD, FTD and control participants using the TASIT subtest and a static emotion recognition task. Initially, the non–demented ALS patients (n=13) and the ALS–FTD patients (n=16) were combined to form one group (ALS/ALS–FTD). Both the ALS/ALS–FTD (n=29) and the bvFTD (n=25) patient groups recognised significantly fewer emotions on the separate tasks relative to healthy controls (n=30). However, when the ALS group was divided into those with and without FTD, only the ALS–FTD patients showed impairment on these tasks. Non–demented ALS patients, by contrast, showed preserved emotion processing relative to controls. These results indicate that deficits in this domain may be specific to ALS patients with comorbid FTD. They might also reconcile
the inconsistent findings across previous studies of emotion recognition in non–demented ALS, since these studies have included ALS and ALS–FTD patients in the same sample (e.g. Zimmerman et al, 2007) or possibly recruited patients with undiagnosed dementia.

Staios et al (2013) also compared non–demented ALS patients with control participants on a second subtask of the TASIT which comprises enacted social situations. Participants watched vignettes in which actors made sincere, simple sarcastic or paradoxically sarcastic statements. Under the sarcastic statement conditions, one of the actors means the opposite of what he is saying and intends for his interlocutor to accurately interpret his true meaning. On the simple sarcasm items, it is only through reading the paralinguistic cues of the actors that the participant is able to discern the sarcasm. On the paradoxical sarcasm items, the dialogue between the two actors makes no literal sense, unless it is assumed one of the actors is being sarcastic. Following these scenes, participants were asked a series of questions which assessed their interpretation of the actors’ meaning, intentions and feelings.

Staios et al found no difference between groups for sincere items, but patients were significantly impaired relative to controls on both sarcastic conditions. This implies that patients have a relative difficulty in discerning more socially complex exchanges in which the literal meaning of a conversation is superseded by covert paralinguistic cues that convey the intended meaning. That is to say, patients show impairment for high–order social cognitive abilities. Patients also performed worse than controls on a test of cognitive flexibility. When the effects of performance on this task were co–varied out statistically, patients remained significantly impaired on the sarcastic items. This suggests that patients’ social cognition deficits were not related to their apparent executive dysfunction. However, because only one measure of cognitive flexibility was administered, the relationships between patients’ executive functioning and their apparent social processing deficits may have been obscured. A broader battery of executive function might have uncovered a role of executive impairment in the results obtained. Furthermore, no behavioural measures were included in the study. As a result, it lacks sufficient evidence to conclude that patients’ performance on these measures correlate with their real–life social behaviour, such as a tendency to respond compassionately towards others or perceive others’ perspectives. Nonetheless, the study is novel in its adoption of more ecologically–valid tasks which provides greater insight into the scope of the apparent social cognition deficits in ALS.
2.3.2.4. Executive dysfunction, behaviour and socio–emotional processing in ALS

While there is evidence to suggest that deficits in emotional processing and social cognition are less marked than those observed in FTD patients, it is uncertain if, when present, these deficits are associated with cognitive or behavioural change. Moderate to strong correlations between behavioural scores and social–emotional tasks are reported (Girardi et al., 2011); but in general, behaviour is not commonly assessed alongside these measures. Performance has been correlated with executive function indices (Cavallo et al., 2011a; Gibbons et al., 2007; Girardi et al., 2011; Meier et al., 2010; Staios et al., 2013), suggesting that executive dysfunction may partially underlie the observed impairments. Although, studies adopting individual–case analysis have revealed some patients may be exclusively impaired on cognitive or socio–emotional tasks, while others show an overlap of dysfunction on these measures (Cavallo et al., 2011a; Cerami et al., 2013; Girardi et al., 2011; Meier et al., 2010). In both the Giradi et al (2011) and Cavallo et al (2011a) studies, patients’ aggregate performance was within the normal range on several executive function tasks, but was significantly impaired on tests of socio–emotional processing (Cavallo et al., 2011a; Girardi et al., 2011). Cerami et al (2013) also found no association between executive dysfunction and impaired emotion attribution.

In bvFTD, traditional cognitive tests may fail to detect frontal dysfunction in the early stages of disease (Gregory et al., 1999), while socio–emotional processing impairments can be profound and easily identified (Adenzato et al., 2010). Some authors have argued for the inclusion of social and emotion measures to consolidate a prediction of bvFTD diagnosis (Sarazin et al., 2012; Schroeter, 2012). In ALS the mechanisms underlying socio–emotional processing deficits are unclear. It is possible that these impairments reflect executive dysfunction, secondary to DLPC pathology, which in turn leads to impaired inferential ability (Bechara, 2002; Gibbons et al., 2007). Alternatively, they may reflect an isolated impairment similar to early bvFTD, implicating early OFC pathology. Should these findings in ALS patients prove robust, it may imply that socio–emotional tests serve as a more sensitive indicator of ALS frontal dysfunction than traditional executive function measures. This could hold implications for neuropsychological assessment of ALS patients, and more broadly, for the established criteria for cognitive impairment in ALS.
2.3.2.5. 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.

2.4. Primary aims of the thesis

As the current review has emphasised, there is growing evidence for cognitive and behavioural change in non-demented ALS patients, which may correspond to the milder changes apparent in ALS–FTD and FTD patients. In particular, ALS patients have demonstrated impairments in the ability to recognise emotion and interpret social information. The current study will incorporate a range of static and dynamic tasks of socio-emotional processing in order to assess the scope of these reported deficits in ALS. In addition, the study will examine the relative impact of patients’ executive (dys)function, mood, personality, empathy and behaviour on socio-emotional processing performance. Hypotheses relating to the second component of the thesis (caregivers of ALS patients) are outlined in Chapter Three.

2.4.1. Hypothesis One: Profile of executive impairment and changes in emotional processing and social cognition in ALS

The current study tests the hypothesis that patients with ALS will show impairments relative to controls in executive functioning and the processing of emotional and social information. To test this hypothesis, comparisons between patients and healthy controls on measures of executive function and an extended battery of social cognition were conducted.
2.4.2. **Hypothesis Two:** Profile of behavioural change in ALS

The current study tests the hypothesis that ALS patients will show higher levels of premorbid and current behavioural dysfunction on domains of apathy, dysexecutive behaviour and disinhibition.

2.4.3. **Exploratory Research Question One:** Mood, personality, empathy in ALS

The current study explores whether differences in ALS patients and healthy controls on measures of mood, personality and empathy exist.

2.4.4. **Hypothesis Three:** The contributions of executive function, behaviour, mood, personality and empathy to emotional processing and social cognition in ALS

The current study tests the hypothesis that executive (dys)function will be the main predictor of performance on tests of emotional processing and social cognition, with smaller contributions from behaviour, mood, personality and empathy (above and beyond patients’ demographic and disease symptoms).
3. Caregivers of ALS patients

The progressive and incapacitating nature of ALS means that patients require increased assistance as they progress towards the end–stage of the disease. Day–to–day disease management is more often than not undertaken in the patient’s home and provided by a family member (Chio, 2010; Mockford et al., 2006). The majority of psychosocial studies in ALS have investigated the patient’s experience of their disease, in terms of their mood and quality of life. A growing area of research focuses on the impact ALS may have on the family caregiver. Initially, the effects of the patients’ physical status and mood on caregivers’ wellbeing dominated research in the area. Recently, the evidence for cognitive–behavioural change within the disease has shifted attention towards the additional challenges such changes might pose to caregivers of ALS patients (Merrilees et al., 2010). This chapter will present an overview of research findings of the psychological consequences of ALS on the primary caregiver. A primary caregiver is defined here as the person most involved in the patient’s care on an informal basis.

A challenge in interpreting the caregiver literature comes from the multiple domains used to characterise the caregiver experience. Furthermore, debate surrounds the boundaries of its constituting constructs (see Hunt, 2003). In ALS, the topic of caregiver experience is broad and encompasses several factors, such as general health (Jenkinson et al., 2000), quality of life (Gelinas et al., 1998; Lo Coco et al., 2005; Trail et al., 2003) and religiosity (Bremer et al., 2004; Calvo et al., 2011) among others. This chapter will limit the discussion to three indices of caregiver experience, namely mood, perceived strain or burden and marital satisfaction, as these outcomes are examined within the current thesis. The constructs underlying these indices are generally poorly defined in ALS studies (Aoun et al., 2013). Here, definitions and studies of each construct will be discussed in turn; however, this arrangement does not mean to imply that these concepts are unrelated or isolated in their contribution to caregivers’ experiences. Particular emphasis will be placed on the effects of mild–moderate cognitive–behavioural change on caregivers of non–demented ALS patients. Furthermore, the impact of ALS on spousal (or partner) caregivers will be of focus. This is in keeping with the secondary objectives of the thesis, which is to understand the relative impact of executive function, socio–emotional processing, and behaviour in the patient with ALS on their spousal caregivers.
3.1. Caregiver outcomes

3.1.1. Mood

Mood is defined here as anxiety and/or depression. Estimates of depressive symptoms in ALS caregivers vary between 10% – 61% across studies (Chio et al., 2005; Chio et al., 2010; Goldstein et al., 2006a; Lillo et al., 2012a; Rabkin et al., 2009; Rabkin et al., 2000; Trail et al., 2003). However, using DSM–IV criteria, Rabkin et al (2009) found only 13% of 71 ALS caregivers satisfied criteria for major depressive disorder at their study baseline. This is lower than a previous study using the same criteria (18%, n=31, Rabkin et al., 2000). Studies of ALS caregivers show similar methodological discrepancies to those apparent in the patient literature, such as inconsistent assessment methods, which might account for the variable mood estimates reported between studies. Gender of the informant may also be important, as higher rates of depression have been reported in female compared to male ALS caregivers (Chio et al., 2010), but not consistently (Goldstein et al., 2006a). Women are typically over–represented in spousal ALS caregiver samples due to the disproportionate disease incidence rates between genders. As a result, gender comparisons in ALS caregiving are restricted by unequal group sizes.

There is evidence to suggest lower levels of depression in caregivers than patients (Gauthier et al., 2007; Goldstein et al., 2000; Goldstein et al., 1998; Rabkin et al., 2000); however, it is not certain if this is an artefact of the somatic items found in several depression inventories, inflating patient scores (see Chapter 2, Section 2.2.3.). Nonetheless, caregiver scores are higher than that of control participants (Pagnini et al., 2012; Tedman et al., 1997; Trail et al., 2003), suggesting a greater prevalence of depression in caregivers than the general population.

Some cross–sectional studies have reported positive correlations between caregivers’ and patients’ levels of depression (Chio et al., 2005; Rabkin et al., 2000). In a longitudinal study of 31 ALS couples, scores for the severity of patients’ and caregivers’ depressive symptoms were positively related at the study’s baseline; however, this association disappeared at a nine–month follow–up assessment of the same couples (Gauthier et al., 2007). Instead, the data indicated that while the caregivers’ depression scores significantly increased over time, the patients’ depression scores remained stable. Nonetheless, absolute scores for the caregiver group remained lower than that of patients throughout the study duration.
The relationship between caregiver depression and patient physical status is also inconsistent. Higher depressive symptoms in caregivers has been associated with greater functional impairment in patients (Adelman et al., 2004; Gauthier et al., 2007; Pagnini et al., 2010), and in particular with greater limb severity (Chio et al., 2005; Goldstein et al., 1998). However, other studies have not found these relationships (Chio et al., 2005; Olsson et al., 2010b; Rabkin et al., 2009; Rabkin et al., 2000) and another indicates that caregivers’ depression may be less dependent on patients’ level of disability than caregivers’ perceptions of the effect ALS has on their partner’s life (Goldstein et al., 1998). The impact of cognitive–behavioural symptoms in ALS patients on caregiver mood has received little attention to date. Gordon et al (2007) observed that cognitive–behavioural changes in 49 ALS patients were associated with increased depressive symptoms in caregivers. However, the specific behaviours that contributed to caregiver depression were not reported and the study did not control for patients’ disease symptoms. A later study also found a positive relationship between caregivers’ depression and levels of patients’ apathy and dysexecutive behaviour but not disinhibition, as measured by the informant FrSBe. Stepwise regressions found that the FrSBe Executive Dysfunction domain was independently related to caregivers’ depression, after controlling for patient parameters, such as disease severity and site of onset (n=70 couples, Chio et al., 2010).

Compared to depression, anxiety in ALS caregivers has not been studied in detail. Like depression, the level of anxiety apparent in participants is often defined by cut–off criteria specific to the mood assessment used in a particular study. Using the HADS, medium or higher levels of anxiety (HADS A ≥ 8) have been shown in 42% of caregivers (n=19) of patients with variable disease duration (Goldstein et al., 1998). By comparison, a study which used the STAI to assess 46 caregivers after at least 1 month of their spouse’s diagnosis, found that 58.7% and 13% met criteria for medium (total score: 40 – 59) and high (total score: 60 – 80) levels of state anxiety, respectively (Vignola et al., 2008).

Comparable levels of anxiety have been noted between patients and their caregivers (Pagnini et al., 2012; Rabkin et al., 2000) and greater caregiver anxiety has been related to reduced physical functioning of the patient in some (Bolmsjö & Hermerén, 2003; Jenkinson et al., 2000; Pagnini et al., 2010), but not all studies (Pagnini et al., 2012). Greater anxiety has also been associated with shorter time since disease onset (Goldstein et al., 1998) and might be related to the caregiver’s acceptance of the
diagnosis. Longitudinal research found that anxiety rates in ALS caregivers showed a slight decrease from the diagnostic stage at a nine month follow–up (Vignola et al., 2008). Both studies indicate moderate caregiver anxiety early in the disease course, possibly reflecting the uncertainty of the disease trajectory.

3.1.2. Burden and strain

The concepts of burden and strain are used interchangeably in ALS research (Aoun et al., 2013; Chio, 2010; Mockford et al., 2006). In the general caregiving literature, separate, albeit similar, definitions are provided by some authors, suggesting conceptual specificity between the two terms. Burden has been stated as the oppressive or worrisome load arising from caring for the chronically ill, while strain has been referred to as the excessive physical or mental exertion required of, and the associated tension felt by, persons providing such care (Hunt, 2003). However, references to both concepts in established assessment scales, such as the Zarit Burden Interview (ZBI; Zarit & Zarit, 1987), suggest that these concepts are not generally interpreted as distinct (Goldstein et al., 1998). In this review, burden will be used to encompass both terms except where ‘strain’ is described in individual studies as distinct. Burden is defined here as the sum of the objective (physical; practical) and subjective (psychological; existential) strains caregivers encounter through caring for their relative (Chio, 2010).

Several studies of ALS caregivers have noted relationships between levels of caregiver burden and the severity and progression of the patient’s functional impairment (Adelman et al., 2004; Chio et al., 2005; Hecht et al., 2003; Pagnini et al., 2010). In addition, greater caregiver burden is associated with higher levels of depression and anxiety (Chio et al., 2005; Gauthier et al., 2007; Goldstein et al., 1998; Pagnini et al., 2010; Rabkin et al., 2000). In the general caregiving research, filial caregiving is topical due to the ageing population (Stuijbergen & Delden, 2011); however, in ALS, spousal caregivers still form the largest group of informal caregivers in Europe and the UK (Chio, 2010; Mockford et al., 2006). Despite this, caregiver samples in ALS studies often comprise both filial and spousal caregivers (e.g. Chio et al., 2010; Hecht et al., 2003; Lillo et al., 2012a). Since no comparative studies between ‘caregiver–types’ have been conducted, it is not known whether this might affect the generalizability of study findings to the wider ALS caregiver population. However, there are presumably differences between caregiver groups in terms of their relationship with or attachment to patients which may affect the level of burden or strain felt (e.g. Conde-Sala et al., 2010). Goldstein et al (1998) found that reduced marital satisfaction following disease
diagnosis correlated positively with perceived strain in 19 spousal caregivers. Studies which have recruited heterogeneous caregiver samples and neglected to include measures of perceived relationship quality with the patient might have overlooked an important contributor to caregiver strain.

Restriction of personal time due to caregiving duties is frequently associated with burden (Chio et al., 2005; Hecht et al., 2003; Pagnini et al., 2010). In particular, Hecht et al (2003) found that in their sample of 37 ALS caregivers, higher burden scores were associated with increased ALS disease severity and greater hours per day devoted to care provision. Personal and social restrictions, alongside perceived physical and emotional problems associated with providing care, were the main components of burden. For a subgroup of caregivers who endorsed substantial ‘problem behaviour’ in their respective partner (n=14), total burden scores were significantly higher than in the remaining respondents. This suggests that burden scores obtained from the group overall might have been influenced by a small frequency of ‘problem behaviour’ in some ALS patients. The nature of ‘problem behaviour’ was not explicitly stated, so it is not possible to determine if this referred to patients’ mood, personality and/or ALS–related cognitive–behavioural change.

Subsequent research has examined the relationship between patients’ frontally–mediated symptoms and burden. A study of 70 ALS caregivers found that greater behavioural impairment (higher FrSBe scores) were associated with higher scores (greater burden) on components of the Caregiver Burden Inventory (CBI, Novak & Guest, 1989), as well as worse caregiver mood and reduced quality of life (Chio et al., 2010). Caregiver burden was positively related to the total FrSBe score and the subscales of apathy and dysexecutive behaviour but not disinhibition. Of the CBI domains, emotional and developmental burden (feeling ‘out of step’ with one’s peers) correlated most strongly with patients’ behavioural symptoms. Lillo et al. (2012a) used a different set of measures to assess burden and patient behaviour in 140 caregivers and found a dissimilar pattern of results. The revised Cambridge Behaviour Inventory (Wear et al., 2008) was used to assess patients’ behaviour, while the Zarit Burden Interview (ZBI) was used to classify caregivers into two groups: those experiencing low burden and those showing high burden scores (n=67 with cut–off burden score ≥17). In contrast to Chio et al’s (2010) findings, logistic regression found that caregiver ratings of disinhibition and impulsivity, along with caregiver stress (measured on a separate scale), were the main predictors of caregiver group status. Apathy, although reported in
80% of the patients by caregivers, did not explain caregiver burden in the statistical model.

The discrepant findings between the studies might be explained by the different tools used to measure burden in caregivers. The CBI is a multidimensional scale that includes objective (physical health; time–dependence) and subjective (social relationships outside of caregiver–patient relationship; emotional health) components of burden. The ZBI is unidimensional, emphasising the caregiver’s subjective feelings towards their caregiving role and the care recipient. It is possible that distinct behaviours are more pertinent to certain aspects of caregiver burden than others. For example, increased apathy in patients might be more burdensome to caregivers who require greater caring time or effort for patients who are less motivated to do things for themselves (reflected in time–dependence score on the CBI). Disinhibited and impulsive behaviours may be more relevant to caregivers’ feelings towards the patient (reflected on the ZBI) than objective measures of the caregiver role, such as time and caregivers’ physical health. In addition, Chio et al (2010) found that compared to other domains, disinhibition was relatively lower, with fewer patients meeting criteria for clinical impairment on this domain; offering another possible explanation for the lack of relationship between disinhibition scores and the CBI scores in this study. Moreover, the use of different measures to assess patients’ behaviour and, more obviously, possible differences in the patient and/or caregiver characteristics between the studies’ samples might have contributed to the divergent results obtained.

Both studies found that caregivers’ burden scores were not associated with patients’ physical status following logistic (Lillo et al 2012a) or stepwise (Chio et al 2010) regression analyses. These results are a departure from previous studies without behavioural data (Chio et al, 2005; Pagnini et al, 2010), implying that the influence of behavioural change in patients may dominate their disease symptoms in the prediction of caregiver burden in ALS.

Cross–sectional research has indicated factors associated with burden in ALS caregivers; however, the determination of causal relationships for caregiver outcomes is only possible through successive assessment over the duration of care provision. Goldstein et al (2006a) assessed the longitudinal impact of ALS on 21 spousal caregivers over the course of 12 months at six month intervals. Psychological distress (a global outcome score which combined measures of caregiver’s mood, perceived strain and burden) increased significantly over this period. At baseline, the psychosocial
impact of their partner’s functional impairment, the number of other dependents and the extent to which caregiver’s perceived their partners as showing emotional lability (EL) best predicted the outcome score. ALS symptom severity was not related to the caregiver outcome score at this time-point, indicating that psychosocially–salient features of disease, such as EL, might be more pertinent to caregiver distress in the initial stages of disease. A patient’s EL may be a source of social embarrassment for the caregiver or a cause for alarm for caregivers who might interpret EL as evidence for overt mood or behavioural change. Subsequent assessments revealed that the perception of negative aspects of social support and satisfaction with social relationships best predicted psychological distress at the penultimate and final stages of the study, respectively. These findings suggest dynamic trajectories of caregivers’ mood, strain and burden with progression of their partner’s disease. They also corroborate a previous cross–sectional study which found that caregivers’ ratings of their ability to cope with future anticipated strain and distress was influenced positively by the number of social groups to which they belonged (Goldstein et al., 1998).

3.1.3. Marital satisfaction

A shift in the marital dynamic between ALS–affected couples is expected as the patient’s physical status deteriorates (Oh & Schepp, 2013). Issues relating to sexuality (Oh & Schepp, 2013; Wasner et al., 2004), verbal communication difficulties (Joubert et al., 2011) and shared decision–making regarding palliative care (Bolmsjö & Hermerén, 2003) are only a few examples of factors that may influence the patient–spouse relationship. Although marital intimacy has been found to correlate with caregivers’ psychological distress (Goldstein et al., 2006a), little ALS research has investigated predictors contributing to caregiver perceptions of their marital relationship.

Caregivers of ALS have reported a change in marital satisfaction following the onset of their spouses’ disease (Goldstein et al, 1998). Reduced satisfaction did not correlate with measures of caregiver mood but showed a strong relationship with levels of strain (r=.50, n=19, p<.005). Notably, caregivers’ ratings of their spouses’ behavioural and communication changes together accounted for approximately 40% of the variance in the change between premorbid and post–illness–onset scores of marital satisfaction. This finding resonates with caregiving studies of patients with dementia and mild cognitive impairment that indicate an association between reduced caregiver–ratings of marital quality and the cognitive–behavioural difficulties the diseases present (Ascher et
Despite similar implications for ALS caregivers, no research has since investigated caregiver perceptions of neuropsychological change on the marital relationship.

In a further study, Atkins et al. (2010) assessed patients’ and caregivers’ perceptions of their marital relationship over the course of 12 months (three interviews; six months apart). While the study’s attrition of ALS couples (n=50 dyads at baseline; n=33 dyads second interview; n=27 dyads at conclusion) might limit the interpretations of the results obtained, the study did highlight possible contributors to marital satisfaction in ALS. Ratings of marital satisfaction did not change over the duration of the study for ALS patients or their spouses. However, spouse–caregiver ratings of their marital relationship at each assessment were lower than their retrospective ratings of their relationship before the onset of their partner’s ALS. Further, after adjusting for the pre–illness relationship score, caregivers’ marital satisfaction scores at the first and second interview were predicted by their ratings of the patients’ psychosocial function. At the final interview feelings of burden additionally predicted current marital satisfaction. For patients, ratings of their own psychosocial function predicted their marital relationship at the first interview only. These results indicate that the early reduction in everyday interpersonal activities between patient and caregivers may contribute to caregiver perceptions of reduced marital quality. Whether a reduction in these interpersonal exchanges could be partly attributable to cognitive–behavioural changes in the patient is unknown. The inclusion of objective and/or subjective measures sensitive to ALS–related cognitive–behavioural impairment might have enabled an exploration of this question.

3.1.4. Directions for future research

The findings of the above studies underscore the importance of the non–physical aspects of ALS in understanding caregiver wellbeing. As this review has demonstrated, caregivers’ perceptions of behavioural and psychosocial changes in patients appear to play an integral role in caregivers’ experiences of the disease. However, little progress has been made in expanding the understanding of caregivers’ perceptions of patients’ cognitive–behavioural change and the impact these may have on them in terms of their mood, perceived burden and, in the case of spousal caregivers, marital satisfaction. Where these have been assessed, there have been no objective measures of patients’ neuropsychological performance to corroborate caregivers’ perceptions of cognitive–behavioural change. Objective measures of cognition have been shown to predict stress
and burden in FTD caregivers (Greve et al., 1994; McCade et al., 2013; Miller et al., 2013; Nelis et al., 2011). Considering the overlap of cognitive symptoms between ALS and FTD patients, it would be of interest to examine if milder cognitive changes in non-demented ALS patients are similarly able to predict caregivers’ experiences.

In FTD research, behavioural abnormalities, such as personality change, social inappropriateness, reduced empathy and emotional reactivity, are associated with caregiver burden, depression and compromised marital quality (Ascher et al., 2010; Ballard et al., 2000; Davis & Tremont, 2007). Social disinhibition and reduced empathic concern in patients have been noted by ALS caregivers. Moreover, studies have associated certain personality characteristics with ALS patients using caregiver reports (see Chapter 2). Studies of ALS caregivers have yet to explore if perceived changes in personality and behaviour are associated with caregivers’ wellbeing and/or marital satisfaction. In addition, studies of patients’ awareness of cognitive–behavioural changes in ALS are limited (see Chapter 2, Section 2.2.2.6.), with some studies assuming reduced awareness in ALS patients on the basis of discordant ratings between caregivers’ and patients’ reports (e.g. Chio et al., 2010). No ALS studies to date have examined dyadic discrepancies alongside caregivers’ self–ratings of their wellbeing. Exploration of possible relationships between perceived changes in the patient or discordant caregiver–patient perceptions with caregiver outcome variables might implicate other factors important to caregivers’ experiences in ALS. Alternatively, since dyadic discrepancies can also be influenced by caregiver mood and burden themselves (Pfeifer et al., 2013), such relationships might indicate potential confounds in caregiver reports of patients’ behaviour.

3.2. Secondary aims of the thesis

Following previous caregiving research in ALS and the limitations discussed in this review, the current study explores relationships between patients’ (objective) cognitive dysfunction, (caregiver–rated) behavioural impairment and caregivers’ wellbeing (mood, burden, strain) and marital satisfaction. Changes in personality and behaviour, as perceived by the caregiver, as well as discrepancies between caregivers’ and patients’ perceptions of patients’ personality and behaviour will be examined; their relationship with caregivers’ outcomes will also be explored.
3.2.1. Hypothesis Four: Predictors of caregiver wellbeing

The current study tests the hypothesis that objective measures of cognitive function and caregiver-perceived behavioural impairment in patients with ALS will contribute significantly to caregiver wellbeing (in terms of mood, perceived burden and strain), above and beyond patients’ disease status and symptoms.

3.2.2. Hypothesis Five: Predictors of caregiver marital satisfaction

The current study tests the hypothesis that objective measures of cognitive function and caregiver–perceived behavioural impairment in patients with ALS will contribute significantly to caregivers’ perception of marital satisfaction, above and beyond patients’ disease status and symptoms.

3.2.3. Exploratory Question Two: Comparisons between patients’ and caregivers’ perceptions of patients’ behaviour, empathy and personality

This study explores differences between patients’ and caregivers’ perceptions of patients’ behaviour, empathy and personality and whether such differences are associated with caregiver outcomes (in terms of caregiver mood, perceived burden, strain and marital satisfaction). The study will also explore if caregivers’ perceived changes in patients’ personality and behaviour are associated with caregiver outcomes.
4. Methodology

4.1. Design

A between–group cross–sectional design was used to investigate emotional processing and social cognition in patients with ALS compared to healthy control participants. A within–subjects design was employed to investigate predictors of emotional processing, social cognition and behavioural change in patients with ALS. See Section 4.6.3 for details of statistical procedures.

4.2. Participants

4.2.1. Ethical approval

Ethical approval was obtained from the National Research Ethics (NRES) South East London Research Ethics Committee (REC) 4 (formerly The Joint South London and Maudsley and Institute of Psychiatry Research Ethics Committee) on 22 March 2011 (11/H0807/1). A substantial amendment to the study protocol (see below) received ethical approval from the NRES Committee London – Camberwell St Giles (formerly known as The Joint South London and Maudsley and Institute of Psychiatry Research Ethics Committee) on the 2 August 2011. A minor amendment was granted by the same committee on 17 May 2012. Please see Appendix I for copies of respective approval letters. R&D approval was obtained from the following sites: King’s College Hospital NHS Trust, East Kent University NHS Foundation Trust; NHS Medway Community Healthcare; Cambridge University Hospitals NHS Foundation Trust; and The National Hospital for Neurology and Neurosurgery, University College London NHS Trust.

A. Substantial amendment

Under the original study Protocol (version 2.0, dated 06.12.10); patients who possessed a Forced Vital Capacity (FVC), a measure of respiratory function, of less than 70% were excluded from invitation to the study. In practice, it was found that this measure was not consistently available or updated in patients’ medical notes at the various research sites. The use of a proxy measure the, Epworth Sleepiness Scale (ESS; Johns, 1991, 1992), was submitted as an amendment to replace FVC, under the revised study Protocol (version 3.0, dated 13.07.11). This alternative scale allowed the researcher to screen patients for respiratory symptoms in a non–invasive manner prior to the consent procedure.
B. Minor amendment

The application for a second amendment was in two parts. First, the study applied for approval to modify a criterion concerning patients’ psychoactive medication use. Originally participants receiving psychoactive medication were excluded from the study. In practice, many patients at the research sites were being prescribed such medication for the treatment of disease symptoms and not mood disorder per se. This measure was preventing otherwise eligible and suitable participants from taking part in the study. The amendment only allowed the recruitment of those patients prescribed psychoactive medication for palliative treatment (i.e. not for mood disorder). Control participants remained ineligible for psychoactive medication use.

Second with respect to this amendment, the study applied for approval to modify the recruitment process. A revised study Protocol (version 4.0, dated 27.04.12) was submitted alongside this amendment. This modification would allow one patient, who fell outside of the care of the NHS sites from which the study operated, but who had contacted the researcher directly to enquire about potential participation, to take part in the study. This patient received the same treatment and ethical protection as stipulated in the approved ethical opinion letter. This patient was screened with the same criteria as patients recruited via the research sites (See Section 4.2.3.) and received the same consent procedure. Access to the patient’s medical information was arranged, following the patient’s formal written consent and with the co–operation of the patient’s GP.

4.2.2. Recruitment and obtaining consent

4.2.2.1. Patients & caregivers

Patients were recruited from the MND clinics or teams at the following sites: King’s College Hospital and The National Hospital for Neurology and Neurosurgery, both in London; William Harvey Hospital, Ashford, East Kent; Addenbrooke’s Hospital, Cambridge and the Wisdom Hospice, Rochester, Kent. Clinical notes of patients attending the clinics or teams were screened regularly for eligibility (See section 4.2.3.). This process was facilitated by the principal investigator and clinical teams at each site. The Dementia and Neurodegenerative Diseases Research Network (DeNDRoN) research co–ordinators, based at MND centres at King’s College and Addenbrooke’s Hospitals, also assisted with screening at the respective sites.
The recruitment procedure was the same at each site, except at Addenbrooke’s Hospital. Here, patients who were identified as eligible by the DeNDRoN research nurse or MND clinic co–ordinators were posted a letter from the clinic staff informing them about the research study at the centre (see Appendix I.2.). The letter informed the recipient to make contact with the clinic team to indicate their consent for their address details to be released to the researcher. This enabled a formal recruitment pack (an invitation letter signed by the principal investigator at the relevant site, an information sheet, a consent form and a proposed schedule of the testing sessions, see Appendix I.3.a.) to be posted to patient who indicated an interest in the study. Once the patient had received the recruitment pack, the same recruitment process established at the other research sites ensued.

At all other research sites the recruitment procedure was the same. Patients who met the inclusion criteria (see Section 4.2.3.1.) were posted a recruitment pack on behalf of the principal investigator at the relevant site. Patients were instructed to return a signed consent form to the researcher or her academic supervisors if they did want to participate. If they did not want to participate, they were instructed to notify either the principal investigator or the research team. In this instance, the patient’s details were subsequently removed from the contact list and their personal information confidentially destroyed. Participants were also offered the researcher’s telephone contact number should they wish to discuss the study before consent. If no response was received within two weeks of the invitation, the researcher telephoned the participant to gauge interest in participation and answer any outstanding queries regarding the research. If a patient expressed willingness to participate they were contacted via telephone or email to arrange appointments for the testing sessions. At this time and if possible, a final screening measure was administered to ensure eligibility (see Section 4.4.1.2.). They were also asked if they would agree to the researcher contacting their partner or spouse to invite them to participate in the study. If the participant agreed, a caregiver recruitment pack (an invitation letter signed by the researcher, an information sheet, a consent form and a summary of interview content, see Appendix I.3.b.) was sent to the participant’s relative. Spouses or partners were not invited to participate if the patient declined participation. Patients who accepted an invitation to participate were still recruited to the study even if their relative declined invitation. Again, the spouse or partner was requested to return a signed consent form to the researcher or her academic supervisors if they did want to participate. They were also invited to
telephone or email the researchers should they wish to discuss the study before giving their consent. The spouse interview was arranged once the spouse expressed willingness to participate. Written consent was obtained prior to the interview in all cases.

Ninety-one ALS patients were invited to participate. Sixty-one patients consented to participate in the study, giving a recruitment rate of 67%. Of the 61 patients, two failed final screening criteria at the phone interview (see Section 4.4.1.2.), one consented to the study but later withdrew from participation prior to testing, two became ineligible due to suspected dementia and one became ineligible due to diagnostic uncertainty. This left a total of 55 ALS patients in the study.

Of the 55 ALS patients, seven were either widowed, divorced or single and thus no spouse or partner was available for interview; one patient declined to give their consent to allow their spouse to be invited to take part; one spouse was ineligible due to a dementia diagnosis and two partners were ineligible as they had not known the patient for at least two years prior to the ALS diagnosis (see Section 4.2.3.1.). This left 44 spouses or partners available for invitation to the study. Of the invited 44 spouses or partners, 35 consented to take part in the study, giving a recruitment rate of 79.5%.

4.2.2.2. Control group

Healthy control participants were recruited via the ‘Mindsearch’ database (http://www.mindsearch.iop.kcl.ac.uk) at the Institute of Psychiatry, King’s College London. Participants were selected at random from the database on the basis of specified criteria (see Section 4.2.3). Eligible participants were sent a control recruitment pack (an invitation letter, an information sheet and a consent form, see Appendix I.3.a.).

Control participants were also recruited via recruitment posters (see Appendix I.5.) placed in an around the region of Camberwell, Dulwich and Streatham. In addition, advertisements were placed on the online classifieds website, ‘Gumtree’ (http://www.gumtree.com/), as well as local online forum websites: ‘East Dulwich Forum’ (http://www.eastdulwichforum.co.uk/) and ‘West Dulwich Forum’ (http://www.westdulwichforum.co.uk/). All advertisements provided the researcher’s contact details and basic eligibility criteria. Potential control participants who contacted the researcher were assessed for eligibility before a formal invitation letter and an
information sheet were sent to them. Written consent was obtained at the time of the initial assessment session for all control participants.

4.2.3. Inclusion/exclusion criteria

4.2.3.1. Inclusion criteria

ALS Patients were only included if they fulfilled Revised El Escorial Criteria (ALSFRS-R; Brooks et al., 2000) for clinically definite, probable or laboratory–supported probable ALS. Patients had to have received a diagnosis at least 3 months prior to being contacted in order to remain sensitive to, and mitigate possible confounding effects of, immediate emotional reactions to the diagnosis. Patients with cognitive impairment were included, provided the impairment did not interfere with their capacity for informed consent (i.e. they did not have a formal diagnosis of dementia).

All patients and controls had to be under the age of 75 years. An upper age limit reduced the likelihood of recruiting patients with age–related illnesses associated with cognitive decline. All participants’ first language was English, as several of the tests included to assess language and executive function assumed English as a first language. Only patients and controls with an estimated IQ greater than 70 were included since a lower IQ may make the detection of focal cognitive deficits difficult.

Inclusion criteria specific for caregiver participants were as follows: caregiver participants were required to be identified by the patient as the 'primary caregiver' and were required to be the patient’s spouse or long–term partner as the study concerned the effects of behavioural change within the disease on marital relationships. Caregivers were required to have known the respective patient for at least 2 years prior to the diagnosis; this is because some of our questionnaires examined pre–morbid behaviours and personality.

4.2.3.2. Exclusion criteria

Exclusion criteria specific for patient participants included the following: patients with respiratory insufficiency (score >10 on the Epworth Sleepiness Scale, Johns, 1991; Johns, 1992; see Section 4.4.1.2.), since poor respiratory may exaggerate cognitive impairment (Newsom-Davis et al., 2001) and potentially confound the study’s findings. Patients were also excluded if they were in the advanced stage of the disease where a patient had lost the ability to communicate.
For all participants the following exclusion criteria applied: participants with a diagnosis of another neurological or a psychiatric condition (including drug or alcohol abuse) or diabetes that may affect cognition, affect and behaviour; participants with a formal diagnosis of dementia, since they would be unlikely to undertake our neuropsychology protocols and would not be able to give informed consent; participants whose first language was not English. Originally, participants who were receiving psychoactive medication were excluded, but this criterion was later withdrawn (see Section 4.2.1).

4.3. Test administration

Assessment of patients was carried out over two sessions of approximately 3½ hours each. Patient participants carried out these sessions over the course of at least two days, to mitigate possible fatigue. Controls participants were given the option of completing the two sessions in the course of one day with an extended break in between sessions. Participants were encouraged to take breaks as they required and were informed that they could suspend or end testing at any time without consequence. Tests were prioritised in order of importance to the objectives of this study. This allowed for at least the most important data to be recorded in cases where missing data was present. Due to the physical disability of ALS patients, a number of patient participants were unable to complete all tests of the neuropsychological battery. The number of participants with data missing on each test is outlined in Appendix II. Due to physical disability, some patients were either unable to use a pen or speak for long periods of time. In these instances, and where possible or appropriate, responses would be given verbally or by alternative communication methods (such as paper and pen or ‘tablet’) to prevent loss of data and participant fatigue; in these cases responses were recorded by the researcher. All participants received £30 gift vouchers for their participation.

4.4. Assessment of patient and control groups

4.4.1. Demographic and clinical variables

4.4.1.1. Clinical status

ALS participants’ clinical history and particular demographic details were ascertained from a brief interview prior to participation. The Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R; Cedarbaum et al., 1999) was administered in an
interview format to assess physical functioning. The ALSFRS–R is an ALS–specific clinical rating scale that measures patients’ activities of daily living and global functioning according to 12 items. It is a revision of the previous ALSFRS which underestimated the weight of respiratory dysfunction associated with the disease. The set of items relate to the following abilities: speech, salivation swallowing, handwriting, cutting food and handling utensils (for patients with and without gastrostomy), dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnea, orthopnea, and respiratory function. Participants evaluated these items on a 4–point likert scale; lower scores indicating a higher level of disability. The maximum score achievable upon completion is 48; reflecting no physical disability.

Good construct validity for this measure is demonstrated in one study (n=387) which showed strong correlations between the ALSFRS–R and other clinically relevant measures, namely an objective measure of FVC (\(r=.58\), \(p<.001\)) and the Sickness Impact Profile (SIP; Bergner et al., 1981) (\(\rho=-.58\), \(p<.001\)). Good inter–rater (ICC=0.93, 95% CI [0.84; 0.98]) and intra–rater reliability (ICC=0.95, 95% CI [0.92; 0.98]) and an acceptable level of internal validity were also reported (\(\alpha=.73\)) (Kaufmann et al., 2007). Furthermore, the measure has shown to predict survival time (Kaufmann et al., 2005; Kollewe et al., 2008) and a survey of ALS clinicians and researchers endorsed its efficacy in monitoring clinically meaningful changes to patient functional status over time (Castrillo-Viguera et al., 2010).

4.4.1.2. Daytime sleepiness

The Epworth Sleepiness Scale (ESS; Johns, 1991) was used as a proxy of respiratory function. The scale provides a measurement of participants’ general level of daytime sleepiness. Participants are asked to rate on a scale of 0 – 3 how likely they are to doze off or fall asleep in eight everyday situations, generating a maximum possible score of 24. A cut off score of 10 indicates abnormal sleepiness. For the purposes of screening, participants were administered this study via telephone or by post prior to the final recruitment stage. Patients who exceeded the cut–off score were not invited to participate.

The ESS was shown to successfully distinguish healthy individuals (n=30) from sleep–disordered patient groups (n=150), such as obstructive sleep apnoea syndrome (OASA), narcolepsy and idiopathic hypersomnia in an initial development study (Johns, 1991). Moreover, ESS scores were significantly correlated with sleep latency as measured by
overnight polysomnography. Within the OSAS group, ESS scores were significantly correlated with the respiratory disturbance index, calculated as the number of apnoeas and hypopnoeas which caused a decline of greater than 3% in arterial oxygenation saturation per hour of sleep. High and satisfactory internal consistency for sleep–disordered patients (Cronbach’s α=.88) and healthy controls (Cronbach’s α=.73) has been shown for the measure (Johns, 1992).

4.4.1.3. Estimated premorbid and current Intelligence Quotient (IQ)

Premorbid and current levels of IQ were estimated by means of the Wechsler Test of Adult Reading (WTAR; Holdnack, 2001) and the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), respectively.

The WTAR is a reading test that provides an indication of crystallized intelligence; stored knowledge and skills, such as vocabulary acquirement and reading pronunciation ability. The test was used as an estimate of premorbid function (Green et al., 2008; McGurn et al., 2004; Paque & Warrington, 1995). The test is based on a reading–recognition paradigm, whereby the stimuli words have anomalous grapheme-to-phoneme translations. This reduces the likelihood of superior test performance being a result of the application of learned pronunciation rules. Participants were presented with a page of 50 written words and asked to read them aloud. Accuracy of pronunciation was recorded. The test is untimed.

A high degree of consistency within and across assessments is shown for this measure. Internal consistency coefficients ranging from .87 – .95 in a British standardization sample and stable test–retest correlations ranging from .90 – .94 in a healthy population are reported in the test manual (Holdnack, 2001). Further, stable test performance has been shown for patients recovering from traumatic brain injury (Green et al., 2008). The WTAR was designed in keeping with the format and task demands of the National Adult Reading Test (NART; Nelson, 1982), another well accepted instrument for predicting premorbid intelligence. Correlations with other measures of reading recognition, including the NART, are high, indicating good convergent validity (Holdnack, 2001). It was co–developed and co–normed with the Wechsler Adult Intelligence Scale–Third Edition, (WAIS-III, Wechsler, 1997) making its selection suitable alongside the current IQ measure of this study.
Current IQ was measured using the WASI, which comprises four subtests: Vocabulary, Block Design, Similarities and Matrix Reasoning. Only two subtests of the WASI, namely ‘Vocabulary’ and ‘Matrix Reasoning’ were used, as they did not require limb motor function and could be completed relatively quickly. These subsets, one verbal and one non–verbal, combine to yield a two–subset estimate of full–scale IQ score (FSIQ–2).

The use of the WASI is advantageous due to its relative concision compared to other IQ measures. It has demonstrated exemplary internal consistency (WASI FSIQ-2 r=.96; Axelrod, 2002) and test–retest reliabilities (WASI FSIQ-2 r=.88; Wechsler, 1999). It also correlates highly with other IQ tests: a correlation coefficient between WAIS–III FSIQ and WASI FSIQ–2 of .87 has been observed (Wechlser, 1999). In addition, good construct validity of the WASI is suggested by an exploratory factor analysis of adult standardisation and clinical samples (Ryan et al., 2003).

4.4.2. Emotional processing and social cognition

4.4.2.1. Emotion recognition and social inference: dynamic vignettes

The Awareness of Social Inference Test (TASIT; McDonald et al., 2002) was used to examine the ability to perceive basic emotions in dynamic facial displays, as well as the ability to determine a speaker’s intention, meaning and attitude in everyday social scenarios. The TASIT comprises video vignettes, lasting between 15 – 60 seconds, in which professionally trained actors portray a variety of emotional and social exchanges. The test includes two versions, Form A and Form B, which each comprise three subtests (Emotion Evaluation; Social Inference – Minimal; Social Inference – Enriched) presented in consecutive order. Forms A and its three subtests were adopted for this study.

A. The Emotion Evaluation Test (EET)

This task comprises 28 video vignettes, in which actors portray positive (happiness, surprise), neutral and negative (anger, disgust, fear and sadness) emotions. Prior to testing, each participant was questioned about the definition of each emotion to ensure accurate understanding of emotion labels. Participants were instructed to indicate which emotion they believed was most strongly portrayed by the targeted actor in each scene by selecting one emotion from a response card presented alongside the vignette. The targeted actor was announced prior to each item. Answers were recorded on the record
sheet out of view from the participant. There was an initial practice item with a practice response card to familiarise the participant with the task format. Thereafter, participants made their selections from a possibility of four response cards, all displaying the same emotions in a multiple-choice array but in different order. These response cards were presented in a consecutive cycle from the first test item. Responses were scored as either correct or incorrect (1/0), yielding a maximal overall score of 28 and maximal subscores of 4 for each emotion.

B. The Social Inference – Minimal task (SI–M)

This subtest comprises 15 vignettes which included sincere, simple sarcastic and paradoxical sarcastic exchanges between two actors. In the sincere exchanges the dialogue and paralinguistic cues are consistent (the speaker’s thoughts and feelings are congruent with what he is saying). In the sarcastic exchanges, the targeted speaker means the opposite of what he is saying but intends his/her interlocutor to understand the real meaning. There are two types of sarcastic exchanges. In the simple sarcastic exchanges, one of the actors is being sarcastic, but only through successful interpretation of the paralinguistic cues, can the participant discern the sarcasm. In the paradoxical sarcastic exchanges, the dialogue between two actors is paradoxical and does not make sense unless it is understood that one actor in the scene is being deliberately sarcastic.

After viewing each item, participants were required to answer four questions relating to the scene. Each question required a ‘Yes’, ‘No’ or ‘Don’t Know’ answer, which was recorded on the record sheet. The four questions were designed to assess understanding of four different elements of the exchange, for example:

a) the first question asks what one of the actors was doing to the other actor – i.e. what he/she was trying to make another person do, think or feel (second order Theory of Mind, ToM).

b) the second question asks what a targeted actor was trying to say to the other person – i.e. what is the message he/she is trying to get across (meaning).

c) the third question asked what a targeted actor was thinking – i.e. what was his/her underlying belief which may have differed from what he/she was actually saying (first order ToM).

d) the fourth question ask what a targeted actor was feeling – i.e. what is the emotion
he/she was feeling or how did he/she feel towards the other actor or situation (emotion).

Examples of question types are provided in Appendix III.a.

Each probe question was scored as correct or incorrect or omission (1/0/0). This yielded a maximum score of 60 for the subtask, a maximal score of 20 for each exchange type (Sincere, Simple sarcasm, Paradoxical sarcasm) and a maximal score of 15 for each element (Do, Say, Think, Feel).

C. The Social Inference – Enriched task (SI–E)

This subtest comprises 16 vignettes. In each of the scenes one of the actors is saying something contrary to his/her thoughts or feelings. Eight vignettes depicted actors attempting to conceal his/her true thoughts and feelings by telling either a “white” or “sympathetic” lie. A further eight of the vignettes depicted an actor deliberately using sarcasm to highlight the contradiction between his speech and thoughts and feelings.

Of the 16 scenes, eight scenes made use of visual cues (such as a physical object) to reveal the true state of affairs, while the remaining eight scenes used verbal cues (a prologue or epilogue) to provide this information. In four of the ‘visual cue’ scenes, the actor is telling a lie but the visual evidence is only apparent to the speaker and not his/her interlocutor. The participant has to attend to the physical object to which the speaker refers and observe which character can directly perceive that object. In the other four ‘visual cue’ scenes, the visible evidence of one actor’s obvious sarcasm is available to both parties in the scene. In four of the scenes which provided either an epilogue or prologue, the actor is telling a lie; whilst in the remaining four scenes an actor is being sarcastic. However, in these eight scenes only the speaker is aware of the true state of affairs. This is revealed in the prologue or epilogue.

After viewing each item, participants were required to answer four questions relating to the scene. The four questions were designed to assess understanding of four different elements of the exchange, as above in the second subtest. Examples of these question types are also provided in Appendix III.a.

Each question required a ‘Yes’, ‘No’ or ‘Don’t Know’ answer, which was recorded on the record sheet. As before, each probe question was scored as correct or incorrect or don’t know (1/0/0). This yielded a maximum score of 64; maximal scores of 32 for each
exchange type (Lie or Sarcastic); maximal scores of 16 for each of the elements (Do, Say, Think, Feel) and maximal total scores of 32 for each cue type (visual, verbal).

Ecological validity for the TASIT has been indicated in a study of 21 patients with Traumatic Brain Injury that related performance on the TASIT with measures of social behaviour (McDonald & Flanagan, 2004). Patients’ use of humour in spontaneous conversations with a study confederate correlated positively with the EET ($r=.46$), the SI-M ($r=.58$) and the SI-E ($r=.67$) of the TASIT. Social manners (politeness, interruptions), egocentric behaviour and ‘partner involvement behaviour’ (e.g. encouraging the interlocutor to talk about himself) also correlated positively with the SI-E of the TASIT ($r=.57$; $r=.77$; $r=.49$, respectively). Convergent validity for the TASIT is supported by another study of adult brain injury in which TASIT performance was compared with specific tests of social perception (McDonald et al., 2006). Significant correlations ranging between $.37 < r < .69$ were revealed for all parts of the TASIT and emotion identification performance on the Ekman and Friesen series (Ekman & Friesen, 1976). The SI-M of the TASIT was also associated ($r=.68$) with second–order ToM stories (Bibby & McDonald, 2005), but not simple first–order ToM stories or control stories requiring only physical inference. Performance of the TASIT has been shown to discriminate bvFTD patients with and without pronounced neuropathology in an fMRI study. Poor performance, particularly in interpreting sarcastic items and emotions, was associated with damage to the lateral orbitofrontal cortex, insular and the temporal poles (Kipps et al., 2009).

Most social cognition studies that have used the TASIT have compared participants’ performance on the Sarcasm or Lie conditions with their performance on the Sincere condition. Little research has investigated dissociations in performance between the ‘Do’, ‘Say’, ‘Think’ or ‘Feel’ domains of the TASIT subtasks. One study used the SI-E subtask to compare performance across these domains between 77 healthy controls and 102 neurodegenerative patients ($n=39$ bvFTD; $n=32$ AD; $n=16$ progressive supranuclear palsy; $n=15$ cerebrovascular disease) (Shany-Ur et al, 2012). Patients with AD and cerebrovascular disease performed similarly to controls across all domains under the three conditions of the task (Sincere; Lie; Sarcasm). Relative to controls, patients with bvFTD were impaired on all four domains for both the Lie and Sarcasm conditions, suggesting a generalised mentalising deficit contributing to the bvFTD group’s impaired overall performance on these conditions. Notably, patients with progressive supranuclear palsy performed similarly to controls on all domains with the exception of
the ‘Think’ domain under the Lie condition. The results indicated that the impaired overall performance on the Lie condition demonstrated by these patients was driven by an isolated impairment in making inferences regarding characters’ true beliefs in exchanges involving deception. These findings highlight possible advantages in comparing performance across the domains of the TASIT scenarios (e.g. ‘Do’; ‘Say’, ‘Think’, ‘Feel’) to reveal specific difficulties underlying overall performance deficits on the TASIT conditions (e.g. Sincere, Sarcasm, Lie). Nonetheless, the specific reliability and validity of using these domains have, as yet, not been examined.

4.4.2.2. Mental state attribution: static facial images

The ability to identify feelings and thoughts of others was also assessed using the Reading the Mind in the Eyes Test – Revised version (RME; Baron-Cohen et al., 2001). The RME consists of 36 facial images depicting only the eye region. Each image is surrounded by 4 words; one target word and three distracters (foils), all similar in valence. The words describe complex mental states which require the attribution of a belief or intention to the pictured person. Word examples are as follows: annoyed, cautious, hostile, tentative. Participants were asked to select which word they believed best described the mental or emotional state of the person in the picture, either orally or by pointing to the word. In the control condition, participants were asked to judge the gender of the target person. The researcher recorded each answer on the record sheet, out of view of the participant. A glossary of terms for the word items was provided for participants to refer to throughout the test if they were unsure of the word definitions.

The RME was originally developed for the detection and measurement of subtle impairments in mentalising ability of adults with autistic spectrum disorders. The current test is a revision of an earlier version (Baron-Cohen et al., 1997). Normative data for this test is based on typical data from a study in which performance of healthy participants was compared to participants with Asperger’s syndrome (AS) or High-functioning Autism (HFA). In this study, the test demonstrated successful discrimination between the three participants groups; the AS and HFA groups showing impaired performance. The test has also demonstrated impaired performance in patient groups with bilateral lesions of the orbitofrontal region (Stone et al., 1998) and amygdala (Stone et al., 2003).

The RME was selected on the basis of its widespread use as a ToM measure and brevity of administration. We also wished to replicate previous findings of impairment on this
measure in an ALS sample (Girardi et al., 2011) within the context of the present investigation of social cognition in ALS.

4.4.2.3. Mental state attribution: static cartoons

The Happé Cartoons and Written Scenarios task (Happé et al., 1999) was adopted to investigate mental state attribution for characters in humorous illustrations. These materials were the same as those described in Gibbons et al (2007) and Snowden et al (2003). The task comprises two separate subtasks with separate materials: a cartoon interpretation exercise and a forced-choice task. Both subtasks compare comprehension of two types of cartoons: ‘mental’ and ‘physical’. Both cartoon types require the integration of visual information and the drawing of inferences. However, only the ‘mental’ cartoon type requires the attribution of mental states. The ‘physical’ cartoon set therefore constitutes the control condition in which mental state attribution is not required. In the ‘mental’ cartoon set, the humour related to a character’s ignorance, false belief, intention or act of deception, while in the ‘physical’ cartoon set, the humour was based on physical absurdity or impossibility. Illustrative examples of cartoons are shown in Appendix III.b.

Scoring and classification of responses for each subtest were undertaken by two raters for 30 items of each subtest (15 patient items; 15 control items). One of the raters was blinded to the participant’s group status. Inter–rater reliability for the ratings are described in the Results sections (Chapter 5; Section 5.2.2.4.) and shown in Appendix VI.2.

A. Cartoon Inference subtask

Participants were shown 12 single–frame cartoons, which were presented in random order. Cartoons were presented consecutively with the instruction to describe what was funny about each one. Six of the cartoons (three ‘mental’ and three ‘physical’) included captions, which the participant was required to read aloud. The cartoon remained in view until the participant had finished responding. Time taken to respond (the time from presentation of the cartoon to the first offer of a response) was recorded. Responses were recorded verbatim. Participants who gave vague answers were prompted with “anything else?” to encourage a more explicit answer.
Scoring of the responses was in accordance with the scheme used by Gibbons et al (2007) and Snowden et al (2003). Performance accuracy of responses was rated on a three–point system, as follows:

a) 3 points = full and explicit explanations  
b) 2 points = partial or implicit responses  
c) 1 point = reference to relevant parts of the cartoon but without further explanation  
d) 0 points = omissions and responses that provided irrelevant or inaccurate detail

Responses awarded less than a perfect score of three, were classified under the following error categories:

a) Omissions (‘don’t know’ responses)  
b) Concrete responses (itemisation of elements of cartoon without integration)  
c) Descriptions (description of relevant parts of cartoon or involving integration of elements but without inferences outside of the cartoon content)  
d) Misconstructions (responses that provide inferences outside of the cartoon’s content but that which are faulty or inaccurate)  
e) Partial responses (responses that involve accurate inferences but are incomplete and not explicitly stated)

B. Cartoon Forced–Choice task (Cartoon Pairs)

In this subtask, participants were presented with 10 cartoon pairs, both identical except for one cartoon having had the humorous element removed. Cartoon pairs were presented juxtaposed with the position of left and right cartoon being counterbalanced across items. Participants were instructed to select which cartoon they believed to be the humorous one of the pair. Accuracy of selection and time to respond (time from cartoon presentation to the first offer of a response) were recorded. Participants were also asked to explain what was humorous about the cartoon they had selected. Responses were recorded verbatim. Vague responses were, as above, prompted with “anything else?” to encourage an explicit answer. Cartoons remained in view of the participant until they indicated completion of their response.

The response scoring and error classification schemes were identical to that of the Cartoon Inference task.
4.4.2.4. Mental State Attribution: written scenarios

Sixteen written scenarios (adapted from Happé et al., 1999) were used to assess mental state attribution of characters in prose. The passages were the same as those used by Gibbons et al (2007) and Snowden et al (2003). Sixteen passages, depicting characters in everyday situations, were presented on cards to participants, followed by a question. The passages comprised two types of scenarios, eight cards in each set type, which constituted two separate conditions. The ‘mental’ condition involved stories which depicted double bluffs, mistakes, persuasion and white lies on the part of a character in the passage. These stories required an inference about the characters thoughts, feelings, desires and intentions in order to respond to the passage question. The ‘physical’ condition, involved stories also depicting characters within a scenario but were followed by questions relevant to inferences of physical causation or logical sequence. This set of scenarios thus constituted the control condition. Examples of these scenarios are shown in Appendix III.c.

Participants were instructed to read each passage silently and indicate reading completion by turning over the card. The respective item question was revealed on the other side of the card and was read aloud by the experimenter. This question remained in full view of the participant until they moved on to the next item. Participants were informed beforehand that once the card was turned over they could not refer to the content again. ‘Mental’ and ‘physical’ items were completed in blocks; blocks were presented in counter–balanced order. Reading time (from the receipt of card to turning over of the card) was recorded. Responses were recorded verbatim.

Scoring and classification of responses for each subtest were undertaken by two raters for 30 items for this subtest (15 patient items; 15 control items). One of the raters was blinded to the participant’s group status. Inter–rater reliability for the ratings are described in the Results sections (Chapter 5; Section 5.2.2.4) and shown in Appendix VI.2.

The scoring scheme adopted by Gibbons et al (2007) and Snowden et al (2003) was used. Performance accuracy of responses was rated on a two–point system, as follows:

a) 2 points = explicit and full responses
b) 1 point = partial or implicit responses
c) 0 points = omissions or inaccurate responses
In addition, responses receiving a less than perfect score of two were classified under the following error categories:

a) Omissions (‘don’t know’ responses)

b) Concrete responses (reiterations of parts of the passage without integration)

c) Descriptions (identification of relevant parts of the story or integration of elements but without drawing inferences)

d) Misconstructions (inaccurate inferences)

e) Partially correct (inferences which are not explicitly stated or are implied incompletely)

4.4.2.5. Empathy

The Interpersonal Reactivity Index (IRI; Davis, 1980) was selected to determine empathic behaviour of patients as perceived by themselves, through self–report, and their caregivers, through informant report. The IRI is a 28–item questionnaire in which respondents endorse statements with regards to themselves or another according to a 5–point Likert scale (0: Does not describe me/him/her very well; 5: Describes me/him/her very well). It comprises four scales (each containing seven items) namely, Perspective taking (PT); Empathic Concern (EC); Fantasy (F) and Personal Distress (PD). The PT scale measures the tendency to spontaneously assume the psychological perspective of others; F assesses the tendency to identify oneself with the feelings and behaviour of fictitious characters from novels or film; EC assesses sympathetic feelings towards others; and finally, the PD scale evaluates feelings of anxiety in emotionally–tense interpersonal situations. This latter scale has been suggested as a measure of emotional self–control rather than a facet of empathy (see Baron-Cohen & Wheelwright, 2004). Each subscale has a maximum total score of 28.

Empathy is defined as a multidimensional construct, comprising of both cognitive and emotional aspects. The cognitive component reflects the comprehension of another’s point of view without necessarily simulating that person’s emotion. The emotional component, on the other hand, refers to the recognition of another’s emotional experience as a result of congruent emotional reactions induced by witnessing their experience (Davis, 1980).
This scale was adopted for its comprehensive measurement of both cognitive (PT) and emotional (EC) components of empathy. The IRI subscales have shown good internal consistency (.71<α<.77) and acceptable test–retest reliability (test–retest correlation coefficients ranged from .62 to .71) (Davis, 1980). A validation study also showed that the IRI subscales correlated strongly in magnitude and in the anticipated direction with measures of social functioning, self–esteem, emotionality, and sensitivity towards others (Davis, 1983).

4.4.3. Executive functioning

4.4.3.1. Fluency

The modified version of Thurstone’s written fluency test was used as a measure of orthographic fluency (Abrahams et al., 1997). Thurstone’s written fluency test has been shown to have good test–retest (.79) and inter–rater reliability (.98) (Cohen & Stanczak, 2000). Impairment in this domain is a widely reported in MND (see Chapter 2, Section 2.2.1.1.) and this test has been shown to be effective in detecting executive dysfunction whilst mitigating confounds of physical disability in MND patients (Abrahams et al., 1997; Abrahams et al., 2004; Abrahams et al., 2005a; Abrahams et al., 2005b; Abrahams et al., 2000). The test comprised two parts. The first part, the ‘generation condition’, required participants to write down as many words as possible in a given time limit and under conditions in which the response was specified by a particular restriction, such as a letter. The first restriction required participants to produce words beginning with “S” in five minutes; the second restriction required four–letter words beginning with the letter “C” in four minutes. Participants were instructed against the production of suffixes, proper nouns or plurals. In the second part, the ‘copy condition’, participants were timed as they copied out the words that they had previously provided. A Verbal Fluency Index (VFI) was then 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:

$$ VFI = \frac{\text{time for generation condition} - \text{time for copy condition}}{\text{Total number of words generated}} $$
If participants were unable to write they were asked to give responses verbally while the examiner wrote down the answers in front of them. In the ‘copy condition’, these participants were given the list they had generated and asked to read it aloud. The time taken to read the list was recorded and a VFI was subsequently calculated.

4.4.3.2. Response inhibition

Response inhibition was examined by means of the Hayling Sentence Completion Test (Burgess & Shallice, 1997). The task is also believed to provide a measure of response initiation and strategic thinking (Burgess & Shallice, 1996).

The test comprised two sections. The first section, the Sensible Completion (SC) condition, required participants to complete 15 statements with an appropriate missing word as quickly as possible. For example, “He scraped the cold food from his …” (acceptable response: ‘plate’). Latency of the response was recorded as a measure of response initiation. The second section of the test, the Unconnected Sentences (US) condition, required participants to replace the missing word with an inappropriate word that was unrelated to the sentence meaning in every way. As in the first section, there were 15 statements. For example, “The dog chased our cat up the …” (an acceptable inappropriate response: ‘spoon’). This component of the test required participants to inhibit an appropriate and easily accessible response (‘tree’) in favour of the generation of a novel unrelated one (‘spoon’), thereby acting as a measure of cognitive inhibition. Error scores were also recorded. Category A errors constituted sensible and appropriate responses, while category B errors were recorded as responses which are indirectly related to the sentence. Normal performance on SC but impaired performance on US (longer latencies and more errors), may indicate anterior frontal lobe damage (Burgess & Shallice, 1996). However, since scores are calculated from summing the timed responses in each condition, dysarthria in some of the patients might exaggerate impairment. Therefore, the current study calculated the difference in total latency between the two sections of the task (US total time – SC total time), allowing for an index of cognitive inhibition that controls for motor disability (i.e. slowed speech).

Acceptable split–half reliability (SC=.63; US=.78) has been reported in a study of response suppression and initiation abilities in patients with frontal lesions (Burgess & Shallice, 1996), suggesting the measure is sensitive to frontal dysfunction. Further, the US condition has shown to correlate significantly with the informant version of the Dysexecutive Questionnaire from the Behavioural Assessment of Dysexecutive
Syndrome (Wilson et al., 1996), supporting the ecological validity of the measure (Wood & Liossi, 2006). The Hayling error score has also been correlated with initiation time on the Tower of London test \((r=.40, p<.001;\) Andrés & Van der Linden, 2000), suggesting convergent validity of this measure of executive function.

4.4.3.3. Rule detection & concept formation

A visuospatial rule attainment task was used to examine rule detection, concept formation and cognitive flexibility. The Brixton Spatial Anticipation Test (Burgess & Shallice, 1997) constitutes a 56–page stimulus booklet. Each page presents an arrangement of 10 circles divided equally into two rows and which are numbered 1 – 10. On each page, one circle is coloured blue. The position of the blue circle alters from page to page, according to a set of rules that change abruptly. Participants were presented with each page in sequence and asked, on the basis of the rule learned in previous pages, to indicate where they anticipated the position of the coloured circle to be on the following page. The total number of errors provided the outcome measure, with higher scores indicating worse performance. The test does not require a limb motor response, as participants can call out their predictions.

Split–half reliability and test–retest reliability for this test were originally reported as .62 and .71, respectively (Burgess & Shallice, 1997). A more modest test–retest reliability of .61 has since been cited; however, these coefficients are comparable with those reported for other accepted executive function measures, such as the Wisconsin Card Sorting Test (WCST) and the Behavioural Assessment of Dysexecutive Syndrome. Further, an investigation of the applicability and validity of the measure in a clinical sample revealed adequate sensitivity and specificity for executive function when comparing Korsakoff’s syndrome and healthy controls (AUC=.74, 95% CI [.66; .82]). Stroke and psychiatric disorder samples also performed in the “below average” range more frequently, suggesting the measure is sensitive to subtle cognitive deficits (Van den Berg et al., 2009).

Category formation was examined by means of The Card Sorting Test, one of nine subtests of the Delis–Kaplan Executive Functioning Test (D-KEFS; Delis et al., 2000). The task requires participants to sort cards into mutually exclusive categories based on the verbal or visual information of the cards; it recruits mental operations that rely on working memory and mental search ability (Libon et al., 2012), as well as conceptual flexibility and monitoring capacity (Latzman & Markon, 2010). This test is endorsed by
sufficient validity and reliability data of the D–KEFS (Delis et al., 2004) and good test–retest ability (Homack et al., 2005).

Prior to test administration, all participants underwent a screening pre–test. This entailed the presentation of a list of stimulus words. Participants were required to read aloud each word and inform the researcher of any word for which they did not know the meaning. Participants were also asked if they had any difficulties in perceiving shapes and/or colours. Finally, an orientation set was conducted using practice cards in which the researcher demonstrated the rules of the task and the targeted arrangement and description of sorts.

The test was administered and scored according to the standard protocol described in the task manual. This comprises a Free Sort condition, followed by a Recognition Sort condition. In the first condition participants were instructed to sort six cards into two groups, three cards per group, according to as many different concepts or rules they could identify. There are a maximum of eight sorting rules for each of the two card sets. Three of these rules are determined by verbal–semantic information from words printed on each card. The five other rules are determined by visuospatial patterns on the cards. Participants were required to provide the sorting rule that they used to group the cards. The manual stipulates that a maximum free sorting time of 4 minutes should be allotted for each card set. Due to the physical impairment of the patient participants, this restriction was not observed. Instead, the administration of each card set was discontinued when either the participant had completed 10 attempted sorts, attained all target 8 sorts, or indicated that he or she could not generate any sorts for the second time (i.e. after one prompt from the researcher). Cumulative sorting times were recorded by the researcher but not used in analyses. Participants were encouraged to work as quickly as possible. Where the participant was unable to sort the card by hand due to limb disability, he or she would instruct the researcher to place the card into groups.

In the recognition condition, cards were sorted into groups by the researcher and participants were asked to identify or describe the rule that the researcher used. The discontinuation of each trial occurred when 45 seconds elapsed from the sort presentation or when the participant provided a response (correct or incorrect).
In the first condition, cards sorts were awarded a score of 1 if they were correctly made. A score of 0 was awarded for incorrect sorts, repeated sorts and sorts which were unconfirmed by the description response (i.e. a correct sort but incorrect description).

Description responses for both conditions were scored according to a 2–point system:

a) 2–points were awarded when a target or appropriate general concept was identified (e.g. “they are all animals”).

b) 1–point was awarded when a specific feature of the stimuli (e.g. “they all have legs”) or a correct description was provided for only one of the card groups.

c) 0–point was awarded for omissions (e.g. “don’t know”), a repetition of a previously correct description, an incorrect response (e.g. “these are happy” for animal groups) or an overly inclusive description which applied to both groups (e.g. “they are things found in a planet” for animal and transport group).

The current study calculated a sorting score (maximum possible sorting score – score obtained) and a description score (maximum possible free sorting description score – description score obtained) to be used in the computation of a composite score of executive functioning.

4.4.4. Language

The Graded Naming Test (GNT; McKenna & Warrington, 1983) was used to assess object naming ability, as an indication of language function.

Pictures of 30 objects were presented consecutively and in ascending difficulty to participants (i.e. items are ordered in terms of progressively lower frequency, such as ‘kangaroo’ to ‘retort’). Participants were required to name the object on each page before proceeding. Where a participant was unable to produce an intelligible response (due to dysarthria), they were allowed to indicate a response through written communication. All answers were recorded verbatim. Items were scored “1” if the object was named correctly, and “0” if otherwise. In some cases, participants misperceived an item altogether (e.g. ‘broom’ for ‘tassel’) or gave a generic response (e.g. ‘animal’ for ‘boar’). In these cases, the researcher prompted the participant with “What is another name?” or “What else could it be?” The raw score served as a measure of the participant’s current naming vocabulary.
The GNT was first standardised in a group of 100 subjects in the late 1970s (McKenna & Warrington, 1980). A subsequent restandardisation study (n=710) provides revised norming data. The test has shown excellent test–retest reliability study in healthy and patient samples (Bird & Cipolotti, 2007; Bird et al., 2004).

4.4.5. Memory

The short form of the Californian Verbal Learning Test 2nd Edition (CVLT-SF; Delis et al., 2000) was used to assess verbal memory. This is an abbreviated version of the original test battery with a shortened wordlist (9 words instead of 16), only one list to remember (instead of two) and fewer recall trials. Participants were required to recall a list of nine words under different conditions. These conditions included free recall, cued recall and recognition. Responses were recorded verbatim throughout the trials.

In the immediate free recall condition, the researcher read the list of nine words to the participant, who was then asked to recall as many of the listed words as possible (in any order). This process was repeated three times, creating four trials. After the fourth trial, a 30–second distractor task occurred, in which participants counted backwards from 100 until the researcher asked them to stop. After this distractor task, a short–delay free recall condition followed. Here, participants were asked to name as many words from the list that the researcher had read in the preceding trials. Upon completion of this condition a 10–minute delay interval followed during which the researcher administered a non–verbal task to the participant. Following this interval, the long–delay free recall condition occurred. Participants were asked again to name as many words as possible from the original list. Following this condition, a long–delay cued recall condition was administered, in which the researcher asked the participant to name all the words from the list pertaining to separate categories (‘Fruits’, ‘Clothing’, ‘Fruits’). Following this condition, a long–delay yes/no recognition condition followed. The researcher read aloud a list of 27 words, nine of which were items from the preceding trials. After each word was read aloud by the researcher, the participant indicated if the word was from the original word list.

The CVLT–II and its predecessor, the CVLT, have been widely adopted in memory research in both clinical and non–clinical populations. Criticisms of the original CVLT, which were directed mainly at its norming procedure (see Elwood, 1995; Randolph et al., 1994; Wiens et al., 1994), led to the restandardisation and development of the
revised edition, using a larger (n=1087) and more representative reference sample. Reliability data are provided in the test manual for the normative sample and a small mixed neuropsychiatric sample (n=124), for which internal consistency estimates range from .78 – .89 and .80 – .96 respectively. Further, a non–clinical sample (n=62) which was administered both editions in a counterbalanced order, showed comparable performance and satisfactory correlations between the tests. The authors argue the validity of the CVLT–II on the basis of its close association with its well validated predecessor. The short version of the test was developed for quick administration and to identify memory problems without overly taxing participants. We chose this measure with our patient participants in mind. Normative data for the ‘short version’ is provided in the manual, however, how this data was derived is not specified.

Previous research has shown that CVLT–SF recall data contributed effectively in discriminating between the memory profiles of patients with AD, bvFTD and SD following discriminant analysis (Kramer et al., 2003)

4.4.6. Mood and personality

4.4.6.1. Anxiety and depression

The revised version of the Hospital Anxiety and Depression Scale (HADS; Gibbons et al., 2011) was used to determine depression and anxiety. This modified version is a 12–item questionnaire, subdivided equally into two separate scales of anxiety (HADS–A) and depression (HADS–D). Items are scored 0 – 3; with a higher score indicating greater levels of anxiety or depression. The original version of the HADS (Zigmond & Snaith, 1983), which included seven items on each subscale, shows satisfactory internal validity (Dagnan et al., 2000), reliability and discriminant validity (Cameron et al., 2008). However, Rasch analysis of the original version in 298 ALS patients, found that the removal of two items, one from each subscale, improved the fit of each remaining 6–item subscale to the Rasch model. The items removed from each subscale were: “I feel restless as I have to be on the move” (HADS–A) and “I feel slowed down” (HADS–D).

The authors suggest that the modified version is suitable for MND patients in clinic and research, following satisfactory reliability. Both subscales showed good internal construct validity, as Person Separation Indices (PSI) for HADS–A=.84 and HADS–D=.79 were obtained. The modified subscales possessed no gender– or age– related item bias (Gibbons et al., 2011).
New cut–off criteria for the modified version, which accounts for the reduced number of items of the scale, have been provided (Gibbons et al., 2011). These criteria are as follows:

i) HADS–D ≥ 8; case level of depression  
ii) 5 ≥ HADS–D ≤ 7; borderline level of depression  
iii) HADS–D ≤ 4; normal / non–case level of depression  
iv) HADS–A ≥ 9; case level of anxiety  
v) 7 ≤ HADS–A ≤ 8; borderline level of anxiety  
vi) HADS–A ≤ 6; normal / non–case level of anxiety  

Although these revised criteria have not been validated against clinical diagnostic interview, the suggested prevalence of case–level depression in the Gibbon’s et al (2011) sample (11.1%) was similar to the pooled prevalence estimate of three other MND studies (9.7 %; range 9 % – 11%) which used DSM–IV criteria to diagnose the presence of major depression in MND patients (Ganzini et al., 1998; Rabkin et al., 2005; Rabkin et al., 2000).

4.4.6.2. Personality  
The NEO–Five Factor Inventory (NEO–FFI, Costa & McCrae, 1992) self–report adult version was used to assess current personality in patient and control participants. This scale is an abridged version of the NEO Personality Inventory (NEO–PI) instrument and was developed to provide a comprehensive measure of personality for greater convenience and concise completion.  

Participants were required to read a series of statements and to endorse these statements along a five–point scale. The scale response options included Strongly Agree; Agree, Neutral, Disagree of Strongly Disagree. Participants made their selection by highlighting one option on the record sheet or calling out their selection to the researcher who recorded it on their behalf. The gender–specific norms reported in the manual to derive $T$–scores for each domain were used.

All NEO–PI versions are based on the Five–Factor Model (FFM; Digman, 1990; McCrae & Costa, 1987), an established dimensional model of personality structure. The model describes five domains of personality, namely Neuroticism (N), Agreeableness
(A), Conscientiousness (C), Extraversion (E) and Openness (O), identified from factor analysis of adjectives or ‘traits’ used in common English language.

The NEO–FFI comprises 60 items from the 180 items of the NEO–PI, which were selected upon identifying those items which most strongly contributed to the five domains, using principal component analysis and a varimax rotation procedure. These items received minor substitutions in order to vary item content, eliminate items with joint loadings and safeguard against potential acquiesce response bias, by including forward and reverse scored items (Costa & McCrae, 1992). The short version provides a single domain score for each factor only, whilst the longer version comprises six facet scores within each of the domains. The NEO–FFI was therefore not designed to provide a complete measurement of the five personality factors, but reasonable estimates of each domain (McCrae & Costa Jr, 2004).

Correlations between the NEO–FFI scales and the NEO–PI validimax factors reportedly range from .75 to .89. Correlations with the revised NEO–PI (NEO–PI–R) scales are reported as ranging from .77 to .92 (Costa & McCrae, 1992). Test–retest reliability for the five scales is high and internal consistency is adequate (ranging from .68 - .86; Costa & McCrae, 1992).

4.4.7. Behaviour

4.4.7.1. Executive / Frontal system mediated behaviour

The Frontal Systems Behavioural Scale (FrSBe; Grace & Malloy, 2001) was selected to assess frontal–lobe mediated behaviours. The questionnaire contains 46–items which may be rated on a scale of 1 (almost never) to 5 (almost always); with respect to behaviour both before (premorbid baseline) and after the onset of illness. The questionnaire yields a Total score and three subscale scores, which correspond to three behavioural syndromes, namely ‘Apathy’, ‘Executive Dysfunction’ and ‘Disinhibition’. It may be administered as either a self–rating scale or in an informant–rating format. Both ALS participants and controls were asked to complete this measure on the basis of current behaviour. In addition, ALS participants were instructed to rate their behaviour two years prior to their disease diagnosis; control participants were asked to rate their behaviour two years prior to the testing session. Raw scores for each subscale and a Total score were calculated for both before and after response scales. These were then converted into standardized scores (T–scores) using normative data presented in the manual. The normative data provided in the manual is derived from a sample (n=436)
of men and women ranging in age (18 – 95 years) and educational attainment (10 years to doctoral level). The normative tables are stratified for gender, age and education; providing T–scores for self–rating and family–rating versions.

As described in the manual, scores above 65 were considered to indicate clinically significant impairment; scores between 60 – 64 were considered to show borderline clinical impairment and scores below 60 were considered to indicate no behavioural impairment at all. An index of behavioural change was calculated by comparing the T–scores based on the normative data of ratings for current and premorbid behaviour.

High internal consistency of the self–report version of this scale is reported with adequate α coefficients for ‘Total’ (.88), ‘Apathy’ (.72), ‘Disinhibition’ (.75) and ‘Executive Dysfunction’ (.79) in normative samples (Grace & Malloy, 2001). Similarly impressive α coefficients have been demonstrated in a large (n=324) neurological sample, 63% of which were neurodegenerative disease patients (Stout et al., 2003). In this study, a factor analysis supported a factor structure corresponding to the three subscales representing frontally–mediated behaviour. Good construct validity has also been shown in a study comparing patients with frontal lobe damage (n=24) to those without frontal lesions (n=15) as well as healthy controls (n=48). Scores for the frontal lesion group were significantly higher than those of the comparative groups. A significant behaviour change for the lesioned group was shown when comparing premorbid and post lesion behaviour (Grace et al., 1999).

Convergent validity of this measure has been shown in a study comparing the FrSBe with another well validated measure, the Neuropsychiatric Inventory (NPI; Cummings et al., 1994). Significant correlations between the NPI Total and FrSBe Total score; the NPI and FrSBe Apathy subscales; and the NPI and FrSBe disinhibition subscales in 30 dementia patients and their caregivers were found. Furthermore, the FrSBe Executive Dysfunction and Apathy subscales were associated with deterioration in instrumental activities of daily living, suggesting ecological validity for the measure (Norton et al., 2001).

4.4.7.2. Emotional lability

Emotional lability (EL), was measured by the Emotional Lability Questionnaire (ELQ; Newsom-Davis et al., 1999) Both the self–rated and informant–rated versions of this scale were used. This measure comprises 33 items encompassing three subscales
measuring ‘Laughter’, ‘Crying’ and ‘Smiling’ on a 4-point Likert scale. Higher scores indicate higher levels of perceived EL. Participants were asked to consider their ‘emotional and behavioural condition’ over the four weeks preceding the interview. Each subscale was preceded by a screening question, in which the participant was asked to respond if, and how often, the patient experienced any sudden episodes of laughing/crying/smiling in the past four weeks. If the participant responded “never”, the subsequent subscale was excluded, otherwise the participant responded to the subscale questions.

The ELQ was developed as a modification of the Pathological Laughter and Crying Scale (Robinson et al., 1993) for the specific assessment of EL in MND populations. A validation study, using a sample of ALS patients and matched healthy controls (n=43 in each group) showed both patient and informant versions of the questionnaire to have good internal validity as good concordance between total scores and the separate subscales scores was found for each. Construct validity was corroborated by good agreement between patients and their caregivers for total score ($r=.37$, $p=.02$), crying ($r=.44$, $p=.006$) and laughing subscales ($r=.34$, $p=.04$). There was a greater number of significant correlations within and between ELQ versions for the patients as compared to the controls, indicating high sensitivity to EL pathology (Newsom-Davis et al., 1999).

4.5. Assessment of spouses or partners

4.5.1. Caregiver mood

In keeping with the patient and control participant assessments, the modified HADS (Gibbons et al., 2011) was used to determine depression and anxiety in spousal caregivers. The modified version was used instead of the original HADS version (Zigmond & Snaith, 1983) because the study sought to compare patients’ and caregivers’ depression and anxiety scores.

4.5.2. Perceived strain & burden

The Morris Strain Scale (MSS, Morris et al., 1988) was administered to assess the perceived strain felt by the spouse or partner in relation to their relative’s illness. Numerous issues which potentially may represent a source of strain for the caregiver are assessed, such as the amount of control they feel they possess over their reactions to their partner’s disease and their expectations regarding their ability to cope with the
future. Caregivers indicated the level of strain they felt on a seven-point bipolar rating scale (a minimum score of 1 representing no strain; a maximum score of 7 representing severe strain) following each of the six items. A total range of scores for the scale was 6 – 42, with higher scores reflecting greater perceived strain.

At present no published data regarding the validity or reliability of the scale is available. However, the scale has been used in previous research investigating the psychological impact of ALS on patients and their caregivers (Goldstein et al., 1998; Goldstein et al., 2006a)

The Zarit Burden Inventory (ZBI, Zarit et al., 1980; Zarit & Zarit, 1987) was administered to caregivers in order to measure the perceived burden associated with their partner’s illness and the negative consequences of their caregiving role. The inventory comprises 22 items reflecting themes such as health, finances, interpersonal relations and social functioning. Spouses or partners were asked to respond to each item according to a five-point scale of “Never” (0); “Rarely” (1); “Sometimes” (2); “Quite Frequently” (3) and “Nearly Always” (4). A global score was obtained by summing all the items; a higher score indicating greater perceived burden.

The ZBI has been validated across different cultural and ethnic populations (Hébert et al., 2000; Taub et al., 2004). High internal consistency (α=.91) and test–retest reliability (α=.71) are reported (Hébert et al., 2000; Vitaliano et al., 1991). Predictive ability for caregiver QOL has also been shown in a sample of dementia caregivers (Schreiner et al., 2006).

4.5.3. Perceived marital satisfaction

Marital satisfaction, from the perspective of the caregiver, was measured using the Marital Intimacy Scale (MIS; Morris et al., 1988). This measure was based on the operational definition of ‘intimacy’ produced from research by Warring and colleagues (Waring & Patton, 1984; Waring et al., 1980). The scale consists of 25 statements and is designed to measure 8 dimensions of the marital relationship, namely: affection, cohesion, expressiveness, compatibility, conflict resolution, sexuality, autonomy and identity. Caregivers were asked to indicate their level of agreement with each statement along the following scale: 0=‘strongly agree’, 1=‘agree’, 2=‘undecided’, 3=‘disagree’ or 4=‘strongly disagree’. Alternate items are reverse scored. Of the 25 items, one item is a global measure of marital satisfaction and is not included in the calculation of the total
MIS score. The remaining 24 items constitute the marital satisfaction subscale; a higher total score indicating greater marital satisfaction (a maximum of 96).

Caregiver participants were required to complete this measure over two time scales: at the time of the interview and approximately two years before the onset of their spouse’s ALS symptoms. This provided a measure of ‘present’ and ‘past’ intimacy, respectively.

As with the MIS, the validity and reliability of this measure remains unreported. This measure was adopted for this study on the basis of its use in previous studies of caregiving in ALS (Atkins et al., 2010; Goldstein et al., 1998; Goldstein et al., 2006a).

4.5.4. Perceptions of behaviour in their spouse with ALS

The informant version of the FrSBe was used to assess spousal caregivers’ perceptions of frontal–lobe mediated behaviour in the respective patient. Caregiver participants were asked to complete the form with respect to their spouse's behaviour at the time of testing and two years preceding their disease diagnosis. Scoring of this version involved a similar procedure to the self–rating version, as described above. An estimate of the change in perceived executive function following the ALS symptoms was obtained from subtracting present scale scores from the past scale scores. Normative data for the family–rated version are also provided in the manual. Estimates of perceived behaviour change in patients following their ALS symptoms were obtained from subtracting caregivers’ present behaviour $T$–scores from their past behaviour $T$–scores. In addition, patient–caregiver discrepancy scores for patients’ behaviour for each time point (premorbid or current) were also calculated by subtracting the patients’ premorbid/current $T$–scores from the caregivers’ premorbid/current $T$–scores.

Internal consistency for the informant–rating format has shown to be high; with adequate $\alpha$ coefficients for ‘Total’ (.92), ‘Apathy’ (.78), ‘Disinhibition’ (.80) and Executive Dysfunction’ (.87) in normative samples (Grace & Malloy, 2001).

4.5.5. Perceptions of emotional lability

An informant–version of the ELQ was administered to caregiver participants. This measure was identical to the patient and control questionnaire, except that the responses were presented from the perspective of a third party. Good internal validity of both scale versions has been found, as described in Section 4.4.7.2. (Newsom-Davis et al., 1999).
4.5.6. Caregiver perceptions’ of patients’ current empathy

The IRI was modified so that responses were presented from the perspective of a third party. Scoring remained the same as the patient version. This modified IRI version has previously been adopted for caregivers of FTD and AD patients (Hsieh et al., 2013). Patient–caregiver discrepancy scores for patients’ current levels of empathy were calculated for each domain by subtracting the patients’ current ratings from the caregivers’ current ratings.

4.5.7. Caregiver perceptions’ of patient personality

Informant–versions of the NEO–FFI were administered to the spouse or partner of the patient. Caregivers were asked to endorse statements about their partner’s personality over two time–frames: at the time of testing and approximately two years before the onset of their spouse’s symptoms. This provided measures of ‘past’ and ‘present’ perceived personality on the part of the caregiver. Estimates of perceived personality change in patients following their ALS symptoms were obtained from subtracting caregivers’ present personality T–scores from their past personality T–scores. In addition, patient–caregiver discrepancy scores for patients’ current personality were also calculated by subtracting the patients’ current T–scores from the caregivers’ current T–scores.

Data from spouse ratings (n=91) suggest that the informant NEO–FFI scales correlate well with the domain scales from the full revised version, as correlations ranging from .88 to .94 have been found (Costa & McCrae, 1992). The five domains of the retrospective informant version of the NEO–FFI has shown good to excellent inter–rater reliability (average ICC 95% CI [.68; .78]), excellent intra–informant reliability (average ICC 95% CI [.84; .96]) and good internal consistency (.68<α<.91) in a sample of AD caregivers, indicating that it is a reliable measure of premorbid personality (Archer et al., 2006).

4.6. Data Handling and statistics

Collected data were analysed using The IBM Statistical Package for the Social Sciences (SPSS) Version 21.0.; the R Statistical Programme Version 3.0.1 and STATA Version 11.0.
4.6.1. Data protection and confidentiality

Demographic sheets and consent forms, as well as letters of correspondence to participants, were separated from record forms or performance data and locked in a separate filling cabinet. Copies of consent forms for patient and spouse participants were sent to the respective research sites for inclusion in the site–file or the patients’ medical files (as determined by the specific R&D protocols at each site). Hard copies of performance data were anonymised and stored in a locked filing cabinet at the Institute of Psychiatry. Data were inputted into password–protected databases which were stored on security–controlled computer networks.

4.6.2. Power analysis

Gpower® was used to conduct power analyses. Sample size was estimated on the basis of a between group (ALS, Controls) comparison of scores on the TASIT. To detect a medium effect size $f=0.25$ ($GPower$ 3.0.8), for a 2x2 ANOVA [group (ALS, controls)] x task; [(e.g. lies, sarcasm)] with 80.76 % power and $\alpha=0.05$, a sample size of 49 participants per group would be required.

Based on this sample size for ALS patients, the study set out to recruit a similar size for caregivers. For a linear regression with three predictor variables, this would have had >85% power with $\alpha=0.05$ to detect a medium effect size of $f^2=0.25$ ($R^2=0.20$, $GPower$ 3.0.8).

4.6.3. Statistical protocol and procedures

4.6.3.1. Outliers and normality

Parametric and non–parametric analyses were used to analyse the data. Univariate normality was assessed using the D’Agostino–Pearson Omnibus Test (D’Agostino et al., 1990), histograms, Q–Q plots, and the examination of skew and kurtosis values. Where multivariate normality was required for multivariate analyses (e.g. MANOVA), this was assessed using Shapiro–Wilk multivariate normality test (Royston, 1983).

Since parametric data are sensitive to the presence of outliers, all outliers were detected using, histograms, box–plots and the robust Median Absolute Deviation (MAD) method (Hampel, 1974; Leys et al., 2013). Multivariate outliers were assessed using the Mahalanobis $D^2$ statistic (Mahalanobis, 1936). Each outlying value was re–coded with a score one unit higher than the next highest non–outlying score in the distribution.
(Tabachnick & Fidell, 2013). After outliers were re-coded, normality was re-assessed. When recoded distributions showed skewness values $\geq|2|$, they were submitted to Naperian log transformation. As some distributions contained values that were negative or less than one, a constant was added to each score before the transformation. The constant was equal to the absolute value of the minimum score within the distribution plus one unit (Field, 2009), leaving the distribution’s minimum value at 1.00 before the transformation.

4.6.3.2. Assumptions

A. Parametric analyses

In addition to the assumptions of normality, other assumptions specific to the parametric tests used were assessed. For $t$–tests and ANOVAs, homogeneity of variance (HOV) was assessed for grouped distributions using the Levene’s HOV test (Levene, 1960). For ANOVA with repeated measures, the sphericity assumption was assessed using Mauchley’s test (Mauchly, 1940) and the covariance–variance matrix was consulted to determine the degree of compound symmetry. Where sphericity was not upheld, the Greenhouse–Geisser correction (Greenhouse & Geisser, 1959) was applied. For MANOVA, the linearity assumption was examined using scatterplots. Box’s M (Box, 1954) was used to assess the homogeneity of covariance assumption; an adjusted significance level of $p<.001$ was applied (Tabachnick & Fidell, 2013). A comparison of the covariance matrix for the variables across the groups was also conducted. When covariates were included in any of the above analyses, the homogeneity of regression slopes assumption was assessed using scatterplots and the interaction term method (SPSS>Univariate>Model>Custom).

For the Multiple Regression (MR) analyses, multicollinearity was assessed by consulting the respective correlation matrix (ideally $r<.80$); Variable Inflation Factor (VIF) scores (ideally VIF$<10.0$) and the inverse Tolerance scores (ideally Tolerance$>0.10$) (Field, 2009). Cook’s Distance (CD) was used to screen for influential cases (ideally CD$<1.0$) (Cook, 1977). Linearity and homoscedasticity of residuals were assessed using scatterplots.

B. Non–parametric analyses

Certain non–parametric tests (e.g. Mann–Whitney $U$ test) assume HOV (Sheskin, 2003); this was assessed using the non–parametric Levene’s HOV test (Nordstokke &
Zumbo, 2010). Where HOV was not upheld, the Moods’ Medians test (Mood, 1954) was used. Group differences for nominal and ordinal variables were assessed using the Pearson’s Chi–Square test (see Agresti, 2002) or McNemar test (McNemar, 1947). Where the expected count was less than 5 (20%) in 2x2 designs, the Fisher–Boschloo exact test (Lydersen et al., 2009) was used.

4.6.3.3. Treatment of missing data

Due to the physical disability and fatigue of the ALS participants, a number of patients were unable to carry out tasks that involved handwriting and prolonged speech. The number of participants with data missing on each test is delineated in Appendix II and noted throughout the Results section. For group comparisons, missing data were excluded from individual analyses but cases remained in the dataset. For the within–group multiple regressions, only participants with data for all the relevant variables were included in the analyses.

4.6.3.4. Correcting for multiple testing

Composite scores combining several related variables were calculated for between–group and multiple regression analyses. This was undertaken with the objective of reducing the likelihood of making Type I errors through conducting multiple comparisons using individual neuropsychological test or questionnaire scores. Where exploratory between–group comparisons for individual tests were conducted, Bonferroni corrections (see Abdi, 2007) were applied to account for the number of comparisons and inflated risk of Type I errors. For correlational analyses, a $p$–value of $p<.01$ was adopted to correct for multiple correlations. Where these corrections are not applied, this is noted in the text.

4.6.3.5. Effect sizes and confidence intervals

Where possible, tables in the Results section provide effect size estimates and confidence intervals (CI). Formulas for effect size estimates are shown in Appendix IV. For parametric group comparisons, such as the $t$–test, Cohens’d and the 95% CI for the mean difference are reported. For ANOVA and MANOVA analyses, partial–eta squared, $\eta^2_p$, is used to represent the proportion of variance in the outcome variable that is attributable to the predictor variable in question (excluding the variance explained by other predictor variables, if appropriate). Multiple regression analyses are accompanied
by adjusted $R^2$, Beta coefficients (B), standardised Beta coefficients ($\beta$) and the 95% CI for B.

For non-parametric analyses and where medians are compared, Pearson’s $r$ correlation coefficient is used as a measure of association for the Mann–Whitney $U$ test. For Mood’s Median test, Pearson’s Chi–Square Test and Fisher–Boschloo tests, Cramer’s V ($\phi_c$) represents the strength of association between variables. The Hodges–Lehmann 95% CI (Hodges & Lehmann, 1963) is reported as an estimate of the difference in population medians (both independent and paired group analyses). The Newcombe–Wilson hybrid 95% CI (Newcombe, 1998) is reported for an estimate of differences in proportions (both independent and paired group analyses).
5. Executive function, emotional processing and social cognition in ALS

Overview

The current chapter reports a detailed study of neuropsychological change in patients with non-demented ALS. A primary focus of this chapter is the investigation of the profile and prevalence of executive impairment and changes in emotional processing and social cognition in patients. Performance on measures of memory and language is also examined. As a secondary focus, this chapter will explore profiles of behavioural change, mood, personality and empathy in ALS. Finally, the chapter will describe the relative contributions of executive function, mood, personality, empathy and behaviour to emotional processing and social cognition in ALS patients.

5.1. Introduction and hypotheses

Chapter Two outlined studies reporting the presence of mild to moderate cognitive change in patients with non-demented ALS. Executive dysfunction is the most consistently reported cognitive impairment, although changes in other domains, such as attention, memory and language, are reported. More recently, attention has shifted to patient performance on tasks assessing the processing of emotional and social information. Although some studies suggest impairments in emotion recognition and Theory of Mind (ToM) in non-demented patients, findings are neither consistent nor conclusive. In addition, the study of social cognition in ALS has so far not included empathy. The presence of a relationship between these changes and ALS-related executive dysfunction is contentious. It is possible that these impairments reflect a primary deficit in executive function or, alternatively, are independent of patients’ executive abilities. Furthermore, little is known about the contributions of additional factors such as mood, personality traits and behaviour to these reported deficits.

5.1.1. Hypothesis One: Profile of executive impairment and changes in emotional processing and social cognition in ALS

The current study tests the hypothesis that patients with ALS will show impairments relative to controls in executive functioning and the processing of emotional and social information. To test this hypothesis, comparisons between patients and healthy controls on measures of executive function and an extended battery of social cognition were conducted. The relevant findings are reported in Section 5.2.2.
5.1.2. **Hypothesis Two:** Profile of behavioural change in ALS

The current study tests the hypothesis that ALS patients will show higher levels of premorbid and current behavioural dysfunction on domains of apathy, dysexecutive behaviour and disinhibition. A comparison of behaviour between patients and healthy controls is reported in Section 5.2.3

5.1.3. **Exploratory Research Question One:** Mood, personality, empathy in ALS

The current study explores whether differences in ALS patients and healthy controls on measures of mood, personality and empathy exist. The relevant findings are reported in Sections 5.2.4 – 5.2.7.

5.1.4. **Hypothesis Three:** The contributions of executive function, behaviour, mood, personality and empathy to emotional processing and social cognition in ALS

The current study tests the hypothesis that executive (dys)function will be the main predictor of performance on tests of emotional processing and social cognition, with smaller contributions from behaviour, mood, personality and empathy (above and beyond patients’ demographic variables and disease symptoms). Findings from this investigation are reported in Section 5.2.9.

5.2. **Results**

5.2.1. **Participant characteristics**

A. **Sample Size**

Testing took place between April 2011 and June 2013. In total, 57 ALS patients and 50 control participants were recruited to the study. Of these, two ALS participants were excluded due to suspicion of co–morbid FTD which only became apparent during the initial assessment. A further ALS patient was excluded due to diagnostic uncertainty which only became apparent after the testing sessions. One control participant was excluded on the basis of a recent diagnosis of depression and neurological illness which was withheld from the researcher at screening and disclosed only after testing. Therefore data is reported on 55 ALS patients and 49 control participants. These final group numbers exceed, in the case of patients, and meet, in the case of controls, the
numbers required per group, as determined by the *a priori* power analysis (see Chapter 4, Section 4.6.2.).

**B. Clinical variables**

Table 5.1 summarises the disease profile of the ALS patients. Patients had an average disease duration (months since symptom onset) of less than three years. The average diagnostic delay (months between symptom onset and diagnosis date) was approximately 16 months. The average age at time of symptom onset was approximately 58 years. Disease progression rate was estimated using the decline in the patient’s ALSFRS–R total score since symptom onset (48 minus ALSFRS–R score divided by time from symptom onset to date of assessment). Approximately 76% of patients had limb–onset, which is similar to population estimates (Haverkamp *et al.*, 1995). The majority of patients were receiving Riluzole, while 15 patients were receiving medication with psychoactive properties. These included antidepressants, benzodiazepines and analgesics for the management of disease symptoms, such as sialorrhea, emotional liability, spasticity and pain (*i.e.* not for mood disturbance). Please refer to Appendix V.a. for details of participant medication (patients and controls) and Appendix V.b. for details specific to participants using psychoactive medication. A comparison of medicated and non–medicated patient subgroups is conducted in Section 5.2.8.

**C. Epworth Sleepiness Scale scores**

Both patients and controls completed the above questionnaire as a screening measure before testing (see Chapter 4, Section 4.4.1.2.). A cut–off score of ≤10 was used to indicate respiratory sufficiency and thereby ensure eligibility. Some control participants (n=15) did not complete this measure as it was introduced into the neuropsychological battery after initial testing had commenced. There were no differences between patient (\(M=3.5, \text{SD}=3\)) and control (\(M=4.2, \text{SD}=3\)) scores on this measure as revealed by a two–tailed *t*–test, \(t(87)=1.12, p=.27, d=0.25, 95\% \text{ CI [-0.6; 2.0]}\).
Table 5.1.: Clinical profile of disease for ALS patients

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since symptom onset</td>
<td>31.8</td>
<td>(18.5)</td>
</tr>
<tr>
<td>Months since diagnosis</td>
<td>16.3</td>
<td>(16.4)</td>
</tr>
<tr>
<td>Age at symptom onset (years)</td>
<td>57.8</td>
<td>(8.8)</td>
</tr>
<tr>
<td>ALFSFRS–R total score (max 48)∞</td>
<td>34.1</td>
<td>(7.8)</td>
</tr>
<tr>
<td>ALSFRS–R bulbar severity score</td>
<td>9.0</td>
<td>(3.0)</td>
</tr>
<tr>
<td>ALSFRS–R Limb severity score</td>
<td>14.2</td>
<td>(6.5)</td>
</tr>
<tr>
<td>ALSFRS–R Respiratory severity score</td>
<td>10.8</td>
<td>(1.8)</td>
</tr>
<tr>
<td>Median Disease progression rate†</td>
<td>0.48</td>
<td>(0.0/0.3)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region of onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limb</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Bulbar</td>
<td>13</td>
</tr>
<tr>
<td>Currently receiving Riluzole</td>
<td>43</td>
<td>(78.2)</td>
</tr>
<tr>
<td>Currently receiving psychoactive medication</td>
<td>15</td>
<td>(27.3)</td>
</tr>
</tbody>
</table>

∞ ALFSRS–R: bulbar=items 1–3; Limb=items 4–9; respiratory=items 10–12. † Disease progression rate = (48–ALFSRS–R total) / months since symptom onset. * median absolute deviation (MAD)/Interquartile range (IQR)
D. Demographic variables

Table 5.2 summarises participants’ demographic characteristics. The two groups were matched with regard to age and years of education; two–tailed $t$–tests revealed no significant differences between groups on these variables. Similarly, non–parametric Mann–Whitney $U$ tests revealed no between group differences on the revised HADS Depression and HADS Anxiety scores (Gibbons et al., 2011). A two–tailed Pearson’s Chi–squared analysis revealed that the ratio of males to females was not significantly different across groups. In addition, the number of participants who had had previous contact with a GP or psychiatrist was not significantly different across groups. There was a significant association between group and marital status. Inspection of the standardised residuals revealed that single status contributed to this significance; more controls than patients were single. The ratio of single and non–single participants between groups was not considered to be clinically relevant. All participants were white Caucasian, except for two participants (one control and one patient) who were of African descent, as determined by the researcher.

E. Estimated premorbid IQ and current IQ

Between group comparisons of IQ measures are shown in Table 5.3. Four ALS patients did not receive premorbid IQ estimates as they were unable to complete the WTAR due to dysarthria. Full–scale IQ estimates were not calculated for seven ALS patients as they did not complete both subtests of the WASI. Six patients were unable to complete the Vocabulary subtest due to dysarthria and/or fatigue. One patient participant did not complete the Matrix Reasoning subtest due to lack of time. Non–parametric Mann–Whitney $U$ tests showed no between–group differences for the obtained estimates of premorbid and current IQ. The median premorbid and current IQ estimates were within the High Average range for both patients and controls.

F. Treatment of demographic covariates

No group differences on demographic or IQ variables were found between groups. However, correlations between these variables and the neuropsychological test scores were assessed for the overall data and within groups (adjusted $p<.01$ for multiple correlations). Identified covariates were entered into the analyses either alone or in combination to examine the effect on the outcome of significance testing. Instances whereby this procedure changed the outcome of the results are noted in the text; otherwise results are presented without the inclusion of the covariate(s).
Table 5.2.: Demographic characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>t( df )</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALS (n=55)</strong></td>
<td><strong>HC (n=49)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (yrs.)</strong></td>
<td>60.3 (8.5)</td>
<td>60 (9.7)</td>
<td>-0.14 (102.00)</td>
</tr>
<tr>
<td><strong>Education (yrs.)</strong></td>
<td>14.5 (3.5)</td>
<td>14.5 (2.7)</td>
<td>-0.00 (100.13)</td>
</tr>
<tr>
<td><strong>Median (MAD/IQR)</strong></td>
<td></td>
<td><strong>U(z)</strong></td>
<td><strong>p</strong></td>
</tr>
<tr>
<td><strong>ALS (n=55)</strong></td>
<td><strong>HC (n=49)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HADS Depression†</strong></td>
<td>2 (1/3)</td>
<td>1 (1/4)</td>
<td>1109.5 (-1.58)</td>
</tr>
<tr>
<td><strong>HADS Anxiety†</strong></td>
<td>4 (2/4)</td>
<td>3 (2/4)</td>
<td>1307.0 (-0.27)</td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
<td></td>
<td><strong>χ² (df)</strong></td>
<td><strong>p</strong></td>
</tr>
<tr>
<td><strong>ALS (n=55)</strong></td>
<td><strong>HC (n=49)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>Gender</em> Men</em>*</td>
<td>40 (72.7%)</td>
<td>34 (69.4%)</td>
<td>0.14 (1)</td>
</tr>
<tr>
<td></td>
<td>15 (27.4%)</td>
<td>15 (30.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td>17.55 (3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Single</strong></td>
<td>1 (1.8%)</td>
<td>13 (26.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Married</strong></td>
<td>47 (85.5%)</td>
<td>30 (61.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Divorced</strong></td>
<td>1 (1.8%)</td>
<td>4 (8.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Widowed</strong></td>
<td>6 (10.9%)</td>
<td>2 (4.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Mental Health</strong></td>
<td>11 (20%)</td>
<td>8 (16.3%)</td>
<td>0.53 (1)</td>
</tr>
</tbody>
</table>

*p*–values from two–tailed *t*–tests except † Mann–Whitney *U* test; * Pearson’s Chi–square test. Significant results are shown in **bold**–*p*<.05. **Mental health=previous contact with a GP or psychiatrist regarding mental health.
Table 5.3.: Premorbid and current IQ measures

<table>
<thead>
<tr>
<th>IQ Measures</th>
<th>Median (MAD/IQR)</th>
<th>U(z)</th>
<th>p</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS (n=51)</td>
<td>HC (n=49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted premorbid FSIQ†</td>
<td>112 (4/9)</td>
<td>114 (4/11)</td>
<td>1111.5 (-0.95)</td>
<td>.34</td>
</tr>
<tr>
<td></td>
<td>ALS (n=48)</td>
<td>HC (n=49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WASI Full Scale IQ</td>
<td>117 (7.5/14)</td>
<td>119 (6/13)</td>
<td>1004.00 (-1.24)</td>
<td>.21</td>
</tr>
</tbody>
</table>

*p*–values from Mann–Whitney *U* tests. *r*, Pearson’s correlation coefficient. †WTAR and demographic predicted premorbid FSIQ.

5.2.2. Executive function and emotional processing and social cognition

5.2.2.1. Group comparisons on composite scores

To compare executive and socio–emotional functioning between ALS patients and healthy controls, composite scores for each domain were created. This was carried out with the objective of reducing the likelihood of making Type 1 errors through multiple comparisons of test scores. Composite scores were created as follows: test scores were standardised by subtracting the mean score of the control group from each participant’s score on an individual test and then dividing the difference by the corresponding standard deviation of the control group. The resulting standardised scores were then summed according to theorized function and divided by the number of component tests constituting the composite. All scores shared the same direction; a higher score represented poorer performance. If scores did not share this direction, they were reflected (maximum possible score – obtained score). When participants did not complete all measures in the composite, the measures that were completed were standardised and averaged as above. Missing data for each task are shown in Appendix II. Since language and memory assessment included only one test, composite scores were not computed for these domains. Performance on these measures is explored in Section 5.2.2.4.
The measures included in the composite scores\(^1\) were:

- Executive function score: D–KEFS free sorting; D–KEFS free sorting description; Phonemic VFI–S words; Phonemic VFI–C words; Brixton errors (5 measures)

- Emotion Processing and Social Cognition (EMOSOC) score: TASIT EET errors; TASIT SIM errors; TASIT SIE errors; Happé Cartoon Inference (C–Inference); Happé Cartoon Pairs Forced choice (C–Pairs); Happé Written Scenarios (Scenarios); RME errors (7 measures)

Verbal fluency involves both language and executive components (see Chapter 2, Section 2.2.1.1.). However, both phonemic fluency indices showed stronger total–item correlations when included within the Executive function composite than within a language score (\textit{i.e.} with the GNT score) (see Table 5.4.). Both measures therefore remained in the Executive function composite score.

<table>
<thead>
<tr>
<th>(r) values</th>
<th>Executive function</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>VFI–S words</td>
<td>.58</td>
<td>.45</td>
</tr>
<tr>
<td>VFI–C words</td>
<td>.68</td>
<td>.31</td>
</tr>
</tbody>
</table>

A. *Internal consistency of composite scores*

Table 5.5. summarises the results of the analysis of the internal consistency of composite scores. Both composite scores demonstrated satisfactory internal consistency with Cronbach’s alpha coefficients of greater than .7 (DeVellis, 2003; Nunnally, 1978). The inter–item correlations for each composite were above the recommended threshold of .20 (Briggs & Cheek, 1986), except for Brixton errors which showed only a small correlation with verbal fluency–S words ($r=.14$) within the Executive function composite. However, the corrected inter–item correlation of the Brixton error component reached the acceptable benchmark level ($r=.30$) (DeVellis, 2003). Furthermore, removal of this component from the composite did not substantially improve Cronbach’s alpha (from .78 to .80). Therefore, the component remained in the composite. Initially, the Hayling latency and error scores were considered as components for the Executive function composite; however, these items correlated poorly with the total score of the respective composite ($r<.30$), despite contributing to a near sufficient level of internal consistency ($\alpha=.69$). These components were subsequently dropped from the model, leaving five items making up the final composite. Performance on the Hayling Test is examined separately in Section 5.2.2.4.

<table>
<thead>
<tr>
<th>Composite</th>
<th>Number of items</th>
<th>Cronbach’s Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive function</td>
<td>5</td>
<td>.78</td>
</tr>
<tr>
<td>Emotional Processing and Social Cognition (EMOSOC)</td>
<td>7</td>
<td>.83</td>
</tr>
</tbody>
</table>
B. Group differences on composite scores

A one–way MANOVA revealed a statistically significant difference between patients and controls on the combined dependent variables (composite scores) \( F(2,101)=4.68, p=.01, \text{Wilks' Lambda}=0.92, \eta^2=.09 \). Univariate contrasts revealed that the patient mean scores were significantly higher (more impaired) for the executive function composite \( F(1,102)=8.6, p=.004, \eta^2=.08 \) and the EMOSOC composite \( F(1,102)=5.53, p=.02, \eta^2=.05 \). As advised by Harris (1975), a Bonferroni correction was applied; results remained significant (adjusted \( p=.025 \)).

A one–way MANOVA was also conducted on the untransformed data and detected significant differences \( F(1,102)=4.036, p=.02, \text{Wilks' Lambda}=0.93, \eta^2=.07 \). However, between–group differences on the EMOSOC composite did not remain significant, following a Bonferroni correction. These results are compared in Table 5.6, which presents original means and standard deviations (SD) alongside back transformed means with corresponding confidence intervals (CI).

For exploratory purposes and to help interpret the statistically significant MANOVA effect, the standardised discriminant function coefficients were consulted. These coefficients were derived from the untransformed data for ease of interpretation, and are therefore interpreted cautiously. One canonical variate was extracted from the MANOVA. As can be seen in Table 5.7 the standardised discriminant function coefficients suggest that group membership was maximally differentiated by the Executive function composite, which showed a greater weighting than the EMOSOC composite. However, the correlation between the EMOSOC composite and the canonical variate was of appreciable magnitude \( r=.77 \). The Executive function composite loaded highest on the canonical variate \( r=.97 \).
Table 5.6.: Composite scores untransformed and transformed data

<table>
<thead>
<tr>
<th>Composite</th>
<th>ALS (n=55)</th>
<th>HC (n=49)</th>
<th>$F(df)$</th>
<th>$p$</th>
<th>$\eta^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive†</td>
<td>0.5 (1)</td>
<td>0.0 (0.7)</td>
<td>4.95 (1,102)</td>
<td>.007*</td>
<td>.07</td>
</tr>
<tr>
<td>EMOSOC†</td>
<td>0.4 (0.1)</td>
<td>0.0 (0.1)</td>
<td>2.66 (1,102)</td>
<td>.03</td>
<td>.05</td>
</tr>
<tr>
<td>Composite</td>
<td>Back transformed Mean (CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive††</td>
<td>0.80 (0.74; 0.88)</td>
<td>0.67 (0.61; 0.73)</td>
<td>8.60 (1,102)</td>
<td>.004*</td>
<td>.08</td>
</tr>
<tr>
<td>EMOSOC††</td>
<td>0.30 (0.28; 0.33)</td>
<td>0.26 (0.24; 0.29)</td>
<td>5.53 (1,102)</td>
<td>.02*</td>
<td>.05</td>
</tr>
</tbody>
</table>

$p$-values are from ANOVAs. Uncorrected significant results shown in **bold** $p<.05$. Results significant following Bonferroni correction are shown in **bold**$^*$ $p<.025$. † Untransformed original data. ††Back transformed data. EMOSOC, Emotional Processing and Social cognition; $\eta^2$, partial-eta squared. Note: higher scores indicate worse performance.

Table 5.7.: Discriminant function coefficients associated with MANOVA†

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>B</th>
<th>Standardised $\beta$</th>
<th>Structure $\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive function composite</td>
<td>.98</td>
<td>.79</td>
<td>.97</td>
</tr>
<tr>
<td>EMOSOC composite</td>
<td>.41</td>
<td>.31</td>
<td>.77</td>
</tr>
</tbody>
</table>

N=104; † untransformed composites as dependent variables. B=unstandardized coefficients; Standardised $\beta$=standardised coefficients; Structure $\beta$=structure coefficients/ Pearson’s $r$ correlations between dependent variables and canonical variate.
5.2.2.2. Group differences on component scores

Following the identification of group differences on the composite scores, performance on individual tests constituting these composites was explored in more detail. Once outliers were identified they were re-coded according to the procedure specified in Chapter 4, Section 4.6.3.1. Not all distributions met this assumption according to the statistical normality test; transformations did not improve distributional characteristics. However, these distributions did not show strong skew or kurtosis values (Skew<|2|, Kurtosis<|4|) and inspection with histograms confirmed this. Furthermore, the means, 5% trimmed means and medians within each group were similar, suggesting approximate symmetry. Under these conditions, distributions were deemed reasonably normal and parametric tests were used.

A. Executive function measures

Results are shown in Table 5.8. Two–tailed t–tests revealed significant group differences on the D–KEFS sorting; D–KEFS description and Phonemic VFI–C words tests. A trend was found for the Phonemic VFI–S word task. When a Bonferroni correction (adjusted $p<.01$) was applied, only group differences on the D–KEFS sorting and description tasks remained.

Sensitivity analyses using non–parametric tests on the data distributions with outliers revealed between group differences for D–KEFS sorting and D–KEFS description tests. Results remained significant following a Bonferroni adjustment (adjusted $p<.017$) for these measures. No between groups difference was found for the Phonemic VFI–C test. Results are shown in Table 5.9.

Eleven ALS patients completed the VFI measures orally to accommodate motor disability. Index scores were compared between these patients and those who completed the written version of the task using Mann–Whitney $U$ tests on non–recoded raw data. No significant differences between patients in the oral version group ($Mdn=4.6$) and written version group ($Mdn=4.2$) were found for the VFI–S words task, $U=199.5$, $z=-0.89$, $p=.37$, $r=-.12$. Furthermore, no significant differences between patients in the oral version group ($Mdn=9.5$) and the written version group ($Mdn=11.3$) were found for the VFI–C words task, $U=205$, $z=-0.78$, $p=.44$, $r=-.12$. These results justify the combination of administration subgroups in the previous VFI analyses.
Table 5.8.: Measures of executive function

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean (SD)</th>
<th>t(df)</th>
<th>p</th>
<th>d</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS</td>
<td>HC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D–KEFS sorting</td>
<td>6.1 (2.1)</td>
<td>4.9 (2.3)</td>
<td>-2.7 (100)</td>
<td><strong>.009</strong></td>
<td>0.55</td>
</tr>
<tr>
<td>D–KEFS desc.</td>
<td>26.6 (10.6)</td>
<td>20.5 (8.4)</td>
<td>-3.2 (100)</td>
<td><strong>.002</strong></td>
<td>0.63</td>
</tr>
<tr>
<td>VFI–S words</td>
<td>5.2 (3.3)</td>
<td>4.2 (2.1)</td>
<td>-1.8 (93.5)</td>
<td>0.08</td>
<td>0.35</td>
</tr>
<tr>
<td>VFI–C words</td>
<td>16.0 (11.7)</td>
<td>12.1 (6.6)</td>
<td>-2.2 (86.9)</td>
<td><strong>.03</strong></td>
<td>0.42</td>
</tr>
<tr>
<td>Brixton errors</td>
<td>18.3 (5.8)</td>
<td>16.3 (6.4)</td>
<td>-1.7 (102)</td>
<td>.10</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*p*–values from *t*-tests. Uncorrected significant results shown in **bold**–*p*<.05. Results significant following Bonferroni correction are shown as **bold***–*p*<.01. desc., description; *d*, Cohen’s *d*; 95% CI, confidence interval for difference between means. *Note*: higher scores indicate worse performance.

Table 5.9.: Non–parametric sensitivity analysis

<table>
<thead>
<tr>
<th>Measure</th>
<th>Median (MAD/IQR)</th>
<th>U(z)</th>
<th>p</th>
<th>r</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS</td>
<td>HC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D–KEFS sort.</td>
<td>6 (1/3)</td>
<td>5 (1/2)</td>
<td>900.00 (-2.7)</td>
<td><strong>.007</strong></td>
<td>-.27</td>
</tr>
<tr>
<td>D–KEFS desc.</td>
<td>24 (7/15)</td>
<td>20 (4/8)</td>
<td>874.5 (-2.85)</td>
<td><strong>.004</strong></td>
<td>-.28</td>
</tr>
<tr>
<td>VFI–C Words</td>
<td>11 (4.1/12.8)</td>
<td>11.5 (3.7/7.03)</td>
<td>1182 (-1.08)</td>
<td>.28</td>
<td>-.12</td>
</tr>
</tbody>
</table>

*p*–values from Mann–Whitney *U* tests. Results significant following Bonferroni correction are shown as **bold***–*p*<.017. desc., description. *r*, Pearson’s correlation coefficient; 95% CI, Hodges–Lehmann confidence interval for difference between medians. *Note*: higher scores indicate worse performance.
B. Emotional processing and social cognition measures

Results are shown in Table 5.10. Two–tailed $t$–tests revealed significant group differences on the Happé Cartoon Inference test (C–Inference), Happé Cartoon Pairs test (C–Pairs) and the Happé Written Scenarios test (Scenarios). These differences remained significant following a Bonferroni correction (adjusted $p<.007$). No group differences were found for any of the TASIT subtest scores or the RME errors score.

Sensitivity analyses using non–parametric tests on the non–normal data distributions with outliers revealed between group differences for C–Inference, C–Pairs test and Scenarios Test. Results remained significant following a Bonferroni adjustment (adjusted $p<.017$) for all tests except the Happé Cartoon Pairs test. Results of these analyses are displayed in Table 5.11.

Table 5.10.: Measures of emotional processing and social cognition

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean (SD)</th>
<th>$t(df)$</th>
<th>$p$</th>
<th>$d$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS</td>
<td>HC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RME</td>
<td>10.5 (4.8)</td>
<td>9.9 (4)</td>
<td>-.64 (101)</td>
<td>.52</td>
<td>0.13; -2.3; 1.2</td>
</tr>
<tr>
<td>TASIT EET</td>
<td>5.9 (2.5)</td>
<td>5.3 (2.7)</td>
<td>-1.21 (102)</td>
<td>.23</td>
<td>0.24; -1.6; 0.6</td>
</tr>
<tr>
<td>TASIT SIM</td>
<td>10.6 (6.7)</td>
<td>8.8 (5.6)</td>
<td>-1.44 (102)</td>
<td>.15</td>
<td>0.28; -4.2; 0.7</td>
</tr>
<tr>
<td>TASIT SIE</td>
<td>12.7 (6.6)</td>
<td>12.7 (6.1)</td>
<td>-0.03 (102)</td>
<td>.98</td>
<td>0.01; -2.5; 2.4</td>
</tr>
<tr>
<td>C–Inference</td>
<td>12 (5.2)</td>
<td>7.0 (4.7)</td>
<td>-4.87 (91)</td>
<td>$&lt;.001^*$</td>
<td>1.01; -7.0; -3.0</td>
</tr>
<tr>
<td>C–Pairs</td>
<td>11.6 (4.6)</td>
<td>8.3 (5.1)</td>
<td>-3.2 (91)</td>
<td>$.002^*$</td>
<td>0.67; -5.3; -1.2</td>
</tr>
<tr>
<td>Scenarios</td>
<td>9.6 (4)</td>
<td>7.0 (4.2)</td>
<td>-2.82 (81)</td>
<td>$.006^*$</td>
<td>0.62; -4.4; -0.8</td>
</tr>
</tbody>
</table>

$p$–values from $t$–tests. Results significant following Bonferroni correction are shown as **bold**–$p<.007$. $d$, Cohen’s $d$; 95% CI, confidence interval for difference between means. Note: higher scores indicate worse performance.
Table 5.11.: Non–parametric sensitivity analysis

<table>
<thead>
<tr>
<th>Measure</th>
<th>Median (MAD/IQR)</th>
<th>$U(z)/X^2 (df)$</th>
<th>$p$</th>
<th>$r / \phi_C$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS</td>
<td>HC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C–Inference</td>
<td>11 (3/5)</td>
<td>6 (3/6)</td>
<td>502 (-4.45)</td>
<td>$&lt;.001^*$</td>
<td>-.46</td>
</tr>
<tr>
<td>C–Pairs†</td>
<td>11 (3/7)</td>
<td>7 (4/8)</td>
<td>5.6 (1)</td>
<td>.018</td>
<td>.25</td>
</tr>
<tr>
<td>Scenarios</td>
<td>9 (3/5)</td>
<td>6 (2.5/6)</td>
<td>534 (-2.95)</td>
<td>.003*</td>
<td>-.32</td>
</tr>
</tbody>
</table>

$p$–values from Mann–Whitney $U$ tests except † Medians test. Uncorrected significant results shown in **bold**–$p<.05$. Results significant following Bonferroni correction are shown as **bold**–$p<.017$. $r$, Pearson’s correlation coefficient; $\phi_C$, Cramer’s V; 95% CI, Hodges–Lehmann confidence interval for difference between medians, $\infty$ CI interpreted with caution due to asymmetrically skewed distributions.

*Note*: higher scores indicate worse performance

5.2.2.3. Single–case analysis: deficits and dissociations

As suggested by previous research, group level analysis may mask the heterogeneity of cognitive performance that exists within ALS samples (Bak & Hodges, 2004; Gibbons et al., 2007; Girardi et al., 2011; Rippon et al., 2006). For this reason, single–case methodology was applied to explore individual performance on the composite scores and their individual components. The Bayesian Tests for Deficits and Dissociations were used (Crawford et al., 2011). These methods are extensions of classical tests (Crawford & Garthwaite, 2002) which have already been adopted in ALS research (e.g. Gibbons et al., 2007; Meier et al, 2010), but which allow for the control of covariates. In common with the original methods, they test the null hypothesis that the case’s score is an observation from the scores in the control population, but the control population is redefined as controls having the same value(s) on the covariate(s) as the case (Crawford et al., 2011). Deficits and dissociations were operationalised as follows:
i) Deficit:
   a) The case’s score is significantly lower/higher\(^2\) than controls (controlling for covariates)

ii) Dissociation:
   a) The case’s score on Task X is significantly lower/higher\(^2\) than controls (controlling for covariates) \textit{and}
   b) The case’s score on Task Y is not significantly lower/higher\(^2\) than controls (controlling for covariates) \textit{and}
   c) The standardised difference between the case’s scores for Tasks X and Y are significantly different from the standardised difference for the same tasks in the control group (controlling for covariates)

Deficits and dissociations were inferred by consulting the effect size for the difference between case and controls (including the 95% Credible Interval, CI\(_b\)) and the point estimate of the abnormality of the case’s score(s) (again, including the 95% CI\(_b\) of the same quantity). The point estimate of the abnormality of a case’s score is the estimated proportion of controls, with the same values on the covariates, that will obtain a score lower than the case. In situations where error and reflected scores were entered, the point estimate of abnormality of the case’s score reflected the percentage of the control population, with the same values on the covariates, expected to obtain a higher score than the case. Participants were defined as meeting criteria for impairment on composite or component scores if the point estimate of abnormality was at or above 95% of the controls and the CI\(_b\) indicated confidence in this estimate (\textit{i.e. if 90\%} \(<\text{CI}\(_b\)< 100\%).\(^2\)

Criteria for dissociation included a point estimate of abnormality at or below 5% of the controls and if the CI\(_b\) indicated confidence in this estimate (\textit{i.e. if 0\%} \(<\text{CI}\(_b\)<10\% ). The proportions of participants meeting criteria for impairment or dissociation were compared between the groups using two–tailed Pearson’s Chi–square test or two–tailed Fisher–Boschloo’s exact tests (Lydersen et al., 2009), where appropriate.

\textit{A. Selection of covariates}

Three covariates were included in the analyses: age, gender and education (number of years in formal education). The selection of these covariates was primarily theory

\(^2\) For error or reflected scores, case’s score is significantly \textit{higher} than controls
driven. Age has shown robust relationships with executive function (MacPherson et al., 2002; Salthouse & Miles, 2002; Vaughan & Giovanello, 2010; Verhaeghen & Cerella, 2002; Wecker et al., 2000; West et al., 2010; Zelazo et al., 2004) and social cognitive abilities (Calder et al., 2003; Isaacowitz et al., 2007; Keightley et al., 2006; Maylor et al., 2002; Orgeta & Phillips, 2007; Seddon & Waller, 2000; Sullivan & Ruffman, 2004). Gender differences on performance of measures of emotional processing and social cognition are well documented (Bradley et al., 2001; Hall, 1978; Hall & Matsumoto, 2004; Hoffmann et al., 2010; Schulte-Rüther et al., 2008); and have been shown for some measures of executive function (Halpern et al., 2011; Lezak, 2004; Mathuranath et al., 2003; van Hooren et al., 2007). The effects of education, premorbid and current IQ on executive function and social cognition are also indicated (Lezak, 2004; Nisbett et al., 2012; Riggio et al., 1991; Shanley et al., 1971). In the current study, these three variables correlated moderately with the composites scores and several of the components; however they also correlated moderately to strongly with each other (.4< \rho<.7). Since not all patient participants were able to complete both IQ measures due to physical disability, years of formal education acted as a proxy for intellectual functioning for all participants.

B. Composites

Results for the relative proportion of impairment in each group for the composites are shown in Table 5.12. Proportionately more patient participants showed impairments on the Executive and EMOSOC composites. However, two–tailed Fisher–Boschloo exact tests revealed that the differences in these proportions were not significant for either composite. The number of patients and controls who showed isolated impairment on either the Executive or EMOSOC composite, as well concurrent impairment on both composites is shown in Table 5.13. Dissociations between performance on the separate composites (including the direction of the dissociation) were examined for cases in which isolated impairments on either composite was found (also in Table 5.13).

C. Individual component scores

Results for the relative proportion of impairment in each group on the components of the Executive function composite are shown in Table 5.14. Two–tailed Pearson’s Chi–squared analyses revealed significant between–group differences regarding proportion of participants impaired on the VFI–S words and VFI–C words tasks. Inspection of the percentages revealed that ALS patients were more likely to be impaired on these
measures than healthy control participants. When a Bonferroni correction was applied (adjusted \( p<.01 \)), only the between–group difference on the VFI–S words remained significant. Results for the relative proportion of impairment in each group on the components of the EMOSOC composite are shown in Table 5.15. A two–tailed Pearson’ Chi–squared test revealed a significant between–group difference regarding the proportion of participants impaired on the C–Inference task only. Inspection of the percentages revealed that ALS patients were more likely to be impaired on this task than healthy control participants. When a Bonferroni correction was applied (adjusted \( p<.007 \)), this difference remained significant.

Table 5.12.: Single–case analysis – composite scores

<table>
<thead>
<tr>
<th>Composite</th>
<th>N (%)</th>
<th>( P )</th>
<th>( \phi_c )</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS (n=55)</td>
<td>HC (n=49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive</td>
<td>7 (12.7)</td>
<td>3 (6.1)</td>
<td>.31</td>
<td>.11</td>
</tr>
<tr>
<td>EMOSOC</td>
<td>6 (10.9)</td>
<td>3 (6.1)</td>
<td>.45</td>
<td>.09</td>
</tr>
</tbody>
</table>

\( p \)-values from two–tailed Fisher–Boschloo test. \( \phi_c \), Cramer’s V; 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions.

Table 5.13.: Profile of impaired performance across composites

<table>
<thead>
<tr>
<th>N impaired</th>
<th>ALS (n=55)</th>
<th>HC (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive &amp; EMOSOC</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Executive only</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>EMOSOC only</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Dissociation</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Impaired on Executive; not impaired on EMOSOC</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Impaired on EMOSOC; not impaired on Executive</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>
### Table 5.14.: Single–case analysis: Executive function composite components

<table>
<thead>
<tr>
<th>Composite</th>
<th>N (%)</th>
<th>$\chi^2$ (df)</th>
<th>$P$</th>
<th>$\varphi_c$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS</td>
<td>HC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D–KEFS sorting †</td>
<td>4 (7.5)</td>
<td>4 (8.2)</td>
<td>—</td>
<td>&gt;.99</td>
<td>.01</td>
</tr>
<tr>
<td>D–KEFS desc.</td>
<td>10 (16.9)</td>
<td>4 (8.2)</td>
<td>2.46 (1)</td>
<td>.12</td>
<td>.16</td>
</tr>
<tr>
<td>VFI–S words</td>
<td>11 (20)</td>
<td>1 (2)</td>
<td>8.19 (1)</td>
<td>.004*</td>
<td>.28</td>
</tr>
<tr>
<td>VFI–C words</td>
<td>11 (20)</td>
<td>3 (6.1)</td>
<td>4.28 (1)</td>
<td>.04</td>
<td>.20</td>
</tr>
<tr>
<td>Brixton errors†</td>
<td>5 (9.1)</td>
<td>2 (4.1)</td>
<td>—</td>
<td>.43</td>
<td>.10</td>
</tr>
</tbody>
</table>

$p$–values from two–tailed Pearson’s Chi–square test except † two–tailed Fisher–Boschloo exact test. Uncorrected significant results shown in **bold–** $p<.05$. Results significant following Bonferroni correction are shown as bold*– $p<.01$. $\varphi_c$, Cramer’s V. 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions. desc., description.

### Table 5.15.: Single–case analysis: EMOSOC composite components

<table>
<thead>
<tr>
<th>Composite</th>
<th>N (%)</th>
<th>$\chi^2$ (df)</th>
<th>$P$</th>
<th>$\varphi_c$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS</td>
<td>HC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RME</td>
<td>6 (11.1)</td>
<td>1 (2)</td>
<td>—</td>
<td>.10</td>
<td>.18</td>
</tr>
<tr>
<td>TASIT EET</td>
<td>3 (5.5)</td>
<td>2 (4.1)</td>
<td>—</td>
<td>&gt;.99</td>
<td>.03</td>
</tr>
<tr>
<td>TASIT SIM</td>
<td>3 (5.5)</td>
<td>1 (2)</td>
<td>—</td>
<td>.56</td>
<td>.09</td>
</tr>
<tr>
<td>TASIT SIE</td>
<td>4 (7.3)</td>
<td>1 (2)</td>
<td>—</td>
<td>.32</td>
<td>.12</td>
</tr>
<tr>
<td>C–Inference†</td>
<td>14 (31.1)</td>
<td>3 (6.3)</td>
<td>13.04 (1)</td>
<td><strong>&lt;.001</strong></td>
<td>.38</td>
</tr>
<tr>
<td>C– Pairs</td>
<td>6 (13.3)</td>
<td>2 (4.2)</td>
<td>—</td>
<td>.15</td>
<td>.16</td>
</tr>
<tr>
<td>Scenarios</td>
<td>5 (13.2)</td>
<td>2 (4.4)</td>
<td>—</td>
<td>.19</td>
<td>.16</td>
</tr>
</tbody>
</table>

$p$–values from two–tailed Fisher–Boschloo exact test except † Pearson’s $\chi^2$ test. Results significant following Bonferroni correction are shown as **bold**– $p<0.007$. $\varphi_c$, Cramer’s V. 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions.
D. Number of components impaired

Figures 5.1. and 5.2. show the proportion of participants from each group that demonstrated impairments on the Executive function and EMOSOC components, respectively.

For the Executive function components: 30 (54.5%) patients were unimpaired on all components compared to 42 (85.7%) controls; 16 (29%) patients were impaired on one component compared to 2 (4.1%) controls; 4 (7.3%) were impaired on two components compared to 3 (6.1%) controls; 3 (5.5%) patients were impaired on three components compared to 2 (4.1%) controls; 2 (3.6%) patients were impaired on four components compared to no controls. No patients or controls were impaired on all five components. This means that, 45.4% of ALS patients and 14.3% of controls were impaired on at least one executive component.

For the EMOSOC components: 32 (58.2%) patients were unimpaired on all components compared to 43 (87.8%) controls; 15 (27.3%) patients were impaired on one component compared to 2 (4.1%) controls; 4 (7.3%) patients were impaired on two components compared to 3 (6.1%) controls; 1 (1.8%) patient and 1 (2.1%) control were impaired on three components; 2 (3.6%) patients were impaired on four components compared to no controls. No patients or controls were impaired on five or six components only; however, 1 (1.8%) patient was impaired on all seven components compared to no controls. This means that 41.8% of patients and 12.3% of controls were impaired on at least one EMOSOC component.
Figure 5.1.: Participants demonstrating impaired performance on the Executive function composite components by number of impaired components

HC, healthy controls (n=49), ALS, patients (n=55).

Figure 5.2.: Participants demonstrating impaired performance on the EMOSOC components by number of impaired components

HC, healthy controls (n=49), ALS, patients (n=55); EMOSOC, emotional processing and social cognition.
5.2.2.4. Performance on individual tests of neuropsychological function

5.2.2.4.1. Language

The Graded Naming Test (GNT) was used to ascertain naming ability. At the group level, a Medians test found no between–group differences for patients and controls. When the single–case methods were applied, ALS participants showed proportionally more impairments than the control participants. However, this difference did not reach statistical significance as revealed by a Fisher–Boschloo Exact test. Table 5.16. displays results for group and individual level analyses.

Table 5.16.: Graded naming test: group and single–case analysis

<table>
<thead>
<tr>
<th>Group–level analysis</th>
<th>Median (MAD/IQR)</th>
<th>$X^2$ (df)</th>
<th>$p$</th>
<th>$\phi_c$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS (n=55)</td>
<td>HC (n=49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GNT (max 30)</td>
<td>23 (2/3)</td>
<td>24 (2/4)</td>
<td>0.6 (1)</td>
<td>.44</td>
<td>.08</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Single–case analysis</th>
<th>N (%)</th>
<th>$X^2$ (df)</th>
<th>$p$</th>
<th>$\phi_c$</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS (n=55)</td>
<td>HC (n=49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GNT</td>
<td>4 (7.3)</td>
<td>1 (2)</td>
<td>.32</td>
<td>.12</td>
<td>-0.1; 0.2</td>
</tr>
</tbody>
</table>

$p$–values from Medians test (Group level analysis) and Fisher–Boschloo test (Single–case analysis). $\phi_c$, Cramer’s V; 95% CI, Hodges–Lehmann confidence interval for difference between medians except * 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions. Note: Higher score indicates better performance for group–level analysis.

5.2.2.4.2. Memory

The short form of the California Verbal Learning Test (CVLT) was used to examine immediate and delayed verbal recall. Results for this task are presented in Table 5.17. $T$–scores and standardized scores, normed for age and gender, from the CVLT manual, were used. At the group level, two–tailed $t$–tests and median tests revealed no significant between–group differences on any of the CVLT measures. Single–case analyses were also performed for the memory measures. Raw scores were used for both participant groups. Age, gender and education were entered as covariates, as before.
The proportion of impairments per group was not found to be statistically significant following two–tailed Fisher–Boschloo exact tests. These results are shown in Table 5.18.

### Table 5.17.: Group comparisons of CVLT performance

<table>
<thead>
<tr>
<th>Group–level analysis</th>
<th>Mean (SD)</th>
<th>t(df)</th>
<th>p</th>
<th>d</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standardized scores</strong> (min-5; max 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALS (n=51)</td>
<td>HC (n=49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate free recall **</td>
<td>50.1 (12.4)</td>
<td>53.6 (11.5)</td>
<td>1.5 (98)</td>
<td>.20</td>
<td>-0.29</td>
</tr>
<tr>
<td>Short delay free recall</td>
<td>0.1 (1.3)</td>
<td>0.1 (1.3)</td>
<td>2.5 (98)</td>
<td>.80</td>
<td>0.07</td>
</tr>
<tr>
<td>Long delay free recall†</td>
<td>1.8 (0.8)</td>
<td>1.7 (0.2)</td>
<td>-0.9 (98)</td>
<td>.38</td>
<td>0.17</td>
</tr>
<tr>
<td>Long delay cued Recall</td>
<td>-0.2 (1)</td>
<td>0.2 (1)</td>
<td>1.9 (98)</td>
<td>.07</td>
<td>-0.37</td>
</tr>
</tbody>
</table>

| Medians (MAD/IQR) | | | | | |
| ALS (n=51) | HC (n=49) | | | | |
| Total intrusions | 0.0 (0/1) | 0.0 (0/1) | 0.00 (1) | .95 | .01 | 0.0; 0.0 |
| Total repetitions | -0.5 (0.5/2) | 0.0 (0.5/2) | 0.16 (1) | .69 | .04 | 0.0; 0.5 |
| Delayed recognition hits | 0.0 (0.5/2) | 0.0 (0.5/1) | 2.53 (1) | .11 | .16 | 0.0; 0.5∞ |
| Recognition false–positives | -0.5 (0.5/1) | -0.5 (0.5/1) | 0.00 (1) | .95 | .01 | -0.5; 0.0 |

*p–values from two–tailed t–tests except p† Median tests. ** T–score (min 5; max 95); † Naperian log transformed data (original means and SDs). d, Cohen’s d; φc, Cramer’s V; 95% CI, confidence interval for difference between means except * 95% CI, Hodges–Lehmann confidence interval for difference between medians, ∞ ,CI interpreted with caution due to asymmetrically skewed distributions. Note: Higher score indicates better performance for recall trials.
Table 5.18.: Percentage of impaired performance on CVLT

<table>
<thead>
<tr>
<th>Single–case analysis</th>
<th>ALS (n=51)</th>
<th>HC (n=49)</th>
<th>p</th>
<th>φc</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate free recall</td>
<td>4 (7.8)</td>
<td>2 (4.1)</td>
<td>.65</td>
<td>.08</td>
<td>-0.1; 0.2</td>
</tr>
<tr>
<td>Short delay free recall</td>
<td>3 (5.9)</td>
<td>2 (4.1)</td>
<td>&gt;.99</td>
<td>.04</td>
<td>-0.1; 0.1</td>
</tr>
<tr>
<td>Long delay free recall</td>
<td>3 (5.8)</td>
<td>3 (6.1)</td>
<td>&gt;.99</td>
<td>.01</td>
<td>-0.1; 0.1</td>
</tr>
<tr>
<td>Long delay cued recall</td>
<td>5 (9.8)</td>
<td>3 (6.1)</td>
<td>.69</td>
<td>.07</td>
<td>-1; 0.2</td>
</tr>
<tr>
<td>Total intrusions</td>
<td>4 (7.8)</td>
<td>1 (2)</td>
<td>.31</td>
<td>.13</td>
<td>-0.1; 0.2</td>
</tr>
<tr>
<td>Total repetitions</td>
<td>2 (3.9)</td>
<td>2 (4.1)</td>
<td>&gt;.99</td>
<td>.00</td>
<td>-0.1; 0.1</td>
</tr>
<tr>
<td>Delayed recognition hits</td>
<td>4 (7.8)</td>
<td>3 (6.1)</td>
<td>&gt;.99</td>
<td>.03</td>
<td>-0.1; 0.1</td>
</tr>
<tr>
<td>Recognition false–positives</td>
<td>4 (7.8)</td>
<td>2 (4.1)</td>
<td>.65</td>
<td>.04</td>
<td>-0.1; 0.2</td>
</tr>
</tbody>
</table>

*p–values from two–tailed Fisher–Boschloo test. φc, Cramer’s V; 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions. HC, healthy controls.

5.2.2.4.3. Executive function: Hayling Sentence Completion Test

The following section compares participant groups on error scores from the Hayling Sentence Completion Test. Differences on the D–KEFS, the Phonemic VFI tasks and the Brixton test were previously compared in Sections 5.2.2.2 and 5.2.2.3.

Three measures of performance were obtained from the Hayling Test: a latency score; the number of Category A errors committed and the number of Category B errors committed. The latency score was calculated by subtracting the time taken for the Response Initiation trial (‘Sensible Sentence’) from the Response Suppression trial (‘Unconnected Sentence’). Since these three variables did not correlate positively and/or strongly with other items entered under the Executive function composite (see Section 5.2.2.1), they were not adopted as component measures within that score. Group–level and single–case analyses were conducted for these measures.
For the group–level analyses, correlations between demographic variables and the three measures were assessed. No significant correlations were present between performance and demographic variables for either the overall or grouped data; only analyses without covariates are reported. For the single–case analyses, variables age, education and gender were entered as covariates. Results for group and single–case analyses are shown in Table 5.19.

For the group–level analyses, two–tailed t–tests on Naperian log transformed data revealed significant between–group differences for the Category A and Category B errors only, with controls outperforming patients on both trials. When a Bonferroni correction was applied (adjusted \( p<.017 \)), group differences remained for the error conditions. No significant group differences were found for the Hayling Latency score.

Sensitivity analyses on the error scores using Mann–Whitney \( U \) tests with untransformed non–recoded data (non–normally distributed) revealed between group differences for both conditions. For the Category A condition, controls (\( Mdn=1.0 \)) committed significantly fewer errors than patients (\( Mdn=3.0 \)), \( U=826.00, z=-3.34, p=.001, r=-.33 \). For the Category B condition, controls (\( Mdn=1.0 \)) committed significantly fewer errors than patients (\( Mdn=3.5 \)), \( U=932.50, z=-2.61, p=.009, r=-.26 \).

For the single–case analyses, proportionally more patients met criteria for impairment than controls on all conditions of the task. These differences were significant as revealed by two–tailed Pearson’s Chi–squared test. However, when a Bonferroni correction was applied (adjusted \( p<.017 \)) these differences were no longer significant.
### Table 5.19: Hayling Test: group–level and single–case analysis

<table>
<thead>
<tr>
<th>Group–level analysis</th>
<th>Mean (SD)</th>
<th>t(df)</th>
<th>p</th>
<th>d</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS</td>
<td>HC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=54)</td>
<td>(n=49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hayling Latency</td>
<td>40.7 (34.9)</td>
<td>30 (29.5)</td>
<td>-1.7 (101)</td>
<td>.09</td>
<td>0.33</td>
</tr>
<tr>
<td>Category A ∞ (max 15)</td>
<td>1.2 (0.7)</td>
<td>0.7 (0.6)</td>
<td>-3.4 (101)</td>
<td>.001*</td>
<td>0.66</td>
</tr>
<tr>
<td>Category B ∞ (max 15)</td>
<td>1.3 (0.7)</td>
<td>0.9 (0.6)</td>
<td>-2.5 (101)</td>
<td>.013*</td>
<td>0.49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Single–case analysis</th>
<th>N (%)</th>
<th>$X^2$ (df)</th>
<th>$p^†$</th>
<th>$\phi_c$</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS</td>
<td>HC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=54)</td>
<td>(n=49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hayling Latency</td>
<td>30 (55.6)</td>
<td>17 (34.7)</td>
<td>4.5 (1)</td>
<td>.03</td>
<td>.21</td>
</tr>
<tr>
<td>Category A</td>
<td>12 (22.2)</td>
<td>3 (6.1)</td>
<td>5.4 (1)</td>
<td>.02</td>
<td>.23</td>
</tr>
<tr>
<td>Category B</td>
<td>12 (22.2)</td>
<td>3 (6.1)</td>
<td>5.4 (1)</td>
<td>.02</td>
<td>.23</td>
</tr>
</tbody>
</table>

*p*-values from two–tailed $t$–tests except $p^†$ two–tailed Pearson’s Chi–square test. Uncorrected significant results shown in **bold**–$p<.05$. Results significant following Bonferroni correction are shown as **bold***–$p<.017$; ∞ Naperian log transformed data. $d$, Cohen’s d; $\phi_c$, Cramer’s V; 95% CI, confidence interval for difference between means except 95% CI*, Newcombe–Wilson hybrid confidence interval for difference between proportions. **Note**: Higher scores indicate worse performance.

### 5.2.2.4.4. Emotional processing and social cognition

#### A. TASIT task

**i) The Emotion Evaluation Test (EET)**

Recognition scores for positive (happy, surprised) and negative (sad, angry, anxious, disgust) emotions were combined to form two superordinate variables: positive and negative. The scores of these new variables were normalised to a maximum score of 1 using the following formula:
Normalised \( (e_i) = \frac{e_i - E_{min}}{E_{max} - E_{min}} \) where \( e_i \) = score for case in the \( i^{th} \) row

\( E_{min} = \) the minimum value for variable E

\( E_{max} = \) the maximum value for variable E

Neutral items were not included in this analysis. A split–plot ANOVA, with Group as the between–subjects factor and Valence–type as the within–subjects factor was conducted. There was no interaction effect for the factors \([F(1,102)=0.32, p=.58, \eta^2=<.001]\), no main effect of Group \([F(1,102)=0.31, p=.58, \eta^2=<.001]\) and no main effect of Valence–type \([F(1,102)=0.03, p=.88, \eta^2=<.001]\).

Performance on separate emotions (including neutral) was compared between groups. A split–plot ANOVA, with Group as the between–subjects factor and Emotion–type as the within–subjects factor, was conducted. The was no interaction effect for the factors \([F(5.34,544.4)=0.92, p=.47, \eta^2=.01]\). There was no main effect for Group \([F(1,102)=2.08, p=.15, \eta^2=.02]\). There was a significant main effect for Emotion–type \([F(5.34,544.4)=41.1, p<.001, \eta^2=.30]\). Figure 5.3. displays group means for each emotion category.

Figure 5.3.: TASIT EET performance

ALS, patients (n=55); HC, healthy controls (n=49). Errors bars represent 95% CI for mean; max score for each emotion is 4.
ii.) The Awareness of Social Inference – Minimal (TASIT SIM)

Participant performance on items of sincere, simple sarcasm and paradoxical sarcasm was explored. A split-plot ANOVA, with Group as between-subjects factor and Statement-type (sincere; simple sarcasm; paradoxical sarcasm) as the within-subjects factor, was conducted. There was no evidence for an interaction between Group and Statement-type \([F(1.43,146)=1.76, \ p=.18, \ η_p^2=.02]\). Although there was a main effect for Statement-type \([F(1.43,146)=7.45, \ p=.003, \ η_p^2=.07]\), no main effect for Group was present \([F(1,102)=2.1, \ p=.15, \ η_p^2=.02]\). Figure 5.4. displays group means across the statement categories.

**Figure 5.4.: TASIT SIM Statement–type performance**

ALS, patient (n=55); HC, healthy controls (n=49). Error bars represent 95% CI for mean; max score for each statement condition is 20.
Participants’ interpretations of the four elements of the social exchanges were also assessed between groups. A split–plot ANOVA, with Group as the between–subjects factor and Element (Do, Say, Think, Feel) as the within–subjects factor, was also conducted. There was no interaction effect \( F(2.73,278.3)=0.66, \ p=.57, \ \eta^2=.01 \). Although there was a main effect for Element \( F(2.73,278.3)=4.52, \ p=.005, \ \eta^2=.04 \), there was no main effect of group \( F(2.73,278.3)=1.74, \ p=.19, \ \eta^2=.02 \). Figure 5.5. displays group means across element conditions.

**Figure 5.5.: TASIT SIM Element condition performance**

ALS, patients (n = 55); HC, healthy controls (n = 49); Error bars represent 95% CI for mean; max score for each statement condition is 15.
iii.) The Awareness of Social Inference – Enriched (TASIT SIE)

Performance on the lie and sarcastic items from the enriched subtask of the TASIT was compared between groups. A split–plot ANOVA, with Group as between–subject factor and Statement–type (Lie; Sarcasm) was conducted. There was no interaction effect $[F(1,102)=0.68, \ p=.41, \ \eta^2=.01]$. There was a main effect of statement–type $[F(1,102)=88.32, \ p<.001, \ \eta^2=.46]$ but not for group $[F(1,102)=0.009, \ p=.92, \ \eta^2<.001]$. Figure 5.6. displays group means for each statement category.

**Figure 5.6.: TASIT SIE Statement–type performance**

<table>
<thead>
<tr>
<th>Statement type</th>
<th>ALS</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lie</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Sarcasm</td>
<td>22</td>
<td>24</td>
</tr>
</tbody>
</table>

ALS, patients (n = 55); HC, healthy controls (n = 49). Error bars represent 95% CI for mean; max score for each statement condition is 32.
Participants’ interpretations of the four elements of the enriched social exchanges were also examined. A split-plot ANOVA with Group as between–subjects factor and Element (Do, Say, Think, Feel) was conducted. No interaction between factors was indicated \( F(2.4,246)=19.54, \ p=.17, \ \eta^2=.02 \]. Although there was a main effect of Element \( F(2.4,246)=19.45, \ p<.001, \ \eta^2=.16 \], there was no main effect of Group \( F(1,102)=0.004, \ p=.95, \ \eta^2<.001 \]. Figure 5.7. displays group means for each statement category.

**Figure 5.7.: TASIT SIE Element–type performance**

ALS, patients (n = 55); HC, healthy controls (n = 49). Error bars represent 95% CI for mean; max score for each statement condition is 16.
Performance on items which contained visual (physical objects) or verbal cues was assessed between groups. A split-plot ANOVA, with group as between–subjects factor and Cue–type (visual; verbal) as the within–subjects factor, was conducted. No interaction between factors was present \([F(1,102)=0.94, p=.34, \eta^2=.01]\). Although there was a main effect for inference–type \([F(1,102)=73.73, p<.001, \eta^2=.42]\), there was no main effect of group \([F(1,102)=0.004, p=.95, \eta^2<.001]\). Figure 5.8. displays group means for each inference condition.

**Figure 5.8.:** TASIT SIE Cue–type performance

ALS, patients (n=55); HC, healthy controls (n = 49). Error bars represent 95% CI for mean; max score for each cue condition is 32.
B. The Happé Cartoon Inference and Written Scenarios Task (Happé Task)

Sections 5.2.2.2 and 5.2.2.3 indicated that significant differences existed between patients and controls on the total scores for the three subtest of the above task. Here, each subtest will be analysed in more detail.

Several ALS patients (n=10, Cartoon Inference subtests; n=17, Scenarios subtest) and controls (n=1, Cartoon Inference subtests; n=3, Scenarios subtest) were unable to complete this task due to fatigue and/or time constraints (see Appendix II). The groups of participants that did complete these tasks were compared on demographic data (see Appendix VI.1). For the Cartoon Inference subtests, no group differences were found for any demographic variables. For the Scenarios subtest there was significant group difference for the WASI IQ measure only. Controls’ scores (Md=120, n=45) were significantly higher than patients’ scores (Md=116, n=35) on this scale (U=581.0, z=-2 p=.05, r=-.20). However, this difference did not remain significant following a Bonferroni correction (adjusted p<.03) and the effect size estimate (r=-.20) was small according to the Cohen (1988) conventions. Therefore the difference between the group median scores was considered insufficient to affect the between-group analyses conducted on the experimental tasks.

i.) Inter–rater reliability

The researcher trained a second rater in the scoring scheme for the cartoon and scenario subtasks, outlined in Chapter 4, Section 4.4.2. The second rater was unaware of the diagnostic status of participants throughout the rating period. Training included familiarisation, discussion and clarification of the classification schemes for accuracy and errors. The training also included a pilot inter–rater consultation of 10 responses from each subtest (5 patient items; 5 control items). These data were not used in the final inter–rater reliability analyses. Thirty participants’ responses (15 patient items, 15 control items) from each subtest, which were coded by both raters, were used to assess inter–rater reliability. Percent agreement scores were calculated for each item by dividing the number of agreements by the number of agreements plus disagreements. For the classification of the accuracy of responses, Cohen’s linear weighted Kappa coefficients values were calculated for each item. For the classification of error responses, Cohen’s unweighted Kappa coefficients were calculated for each item. Percent agreement and Kappa coefficients for items of each subtest are shown in Appendix VI.2. Interpretation of the strength of agreement was based on the system.
proposed by Landis & Koch (1977): <0, Poor agreement; .00 – .20, Slight agreement; .21 – .40, Fair agreement; .41 – .60, Moderate agreement; .61 – .80, Substantial agreement; >.81, Almost perfect agreement. The majority of the ratings (84.2%) demonstrated agreement of .70 or above and none had agreement values of less than .60.

ii.) Response times for subtests

Mean response times for each subtest were compared between groups. The patients and controls did not differ significantly in terms of time taken to respond to either mental or physical conditions for any of the subtests (see Appendix VI.3.).

iii). Cartoon Inference subtask

Accuracy scores for the above task were compared between groups using a Group x Cartoon-type (physical; mental) split-plot ANOVA. There was no Group by Cartoon-type interaction \[F(1,91)=1.36, \ p=.25, \ ηp^{2} =.02\]. However, there was a main effect of Group \[F(1,91)=21.61, \ p<.001, \ ηp^{2}=.19\] and a main effect of Cartoon-type (physical; mental) on performance accuracy \[F(1,91)=6.38, \ p=.01, \ ηp^{2}=.07\]. Figure 5.9. displays group means by cartoon condition.

Five types of errors were recorded for responses that did not meet criteria for full/explicit explanation (i.e. an accuracy score < 3). The error categories were: partial, misconstruction, description, concrete and omission. The number of total errors per error category was summed and compared between groups (see Table 5.20). For both groups, most errors constituted partial (or incomplete) inferences and descriptive responses. There was a significant difference between groups for the number of partial errors and descriptive responses given, with ALS patients committing more errors for both error categories. These differences remained significant following a Bonferroni correction (adjusted \(p<.01\)).

A break-down of errors over the conditions revealed that both groups made significantly more partial errors in the physical condition \[F(1,91)=10.32, \ p=.002, \ ηp^{2}=.10\]; both groups made significantly more misconstructions on the physical condition \[F(1,91)=5.47, \ p=.02, \ ηp^{2}=.06\]. While the ALS group made significantly more description errors on the mental condition compared to the physical condition, the reverse was true for the control group \[F(1,91)=6.51,p=.01, \ ηp^{2}=.07\]; the ALS group
showed significantly more description errors on the mental condition compared to controls \[F(1,91)=20.59, p<.001, \eta^2=.12\].

Figure 5.9.: Cartoon Inference subtask performance across cartoon conditions

ALS, patients (n=45); HC, healthy controls (n=48). Error bars represent 95% CI for mean. Max score for each cartoon condition is 18.
Table 5.20: Cartoon Inference subtask errors

<table>
<thead>
<tr>
<th>Error Type</th>
<th>ALS (n=45)</th>
<th>HC (n=48)</th>
<th>t(df)</th>
<th>p</th>
<th>d</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td>4.6 (1.7)</td>
<td>2.9 (1.7)</td>
<td>-4.9 (91)</td>
<td>&lt;.001*</td>
<td>1.0</td>
<td>-2.4; -1.0</td>
</tr>
<tr>
<td>Misconstruction</td>
<td>0.5 (0.8)</td>
<td>0.5 (1.1)</td>
<td>0.6 (91)</td>
<td>.96</td>
<td>0.0</td>
<td>-0.4; 0.4</td>
</tr>
<tr>
<td>Description</td>
<td>2 (1.5)</td>
<td>0.8 (1)</td>
<td>-4.5 (74.7)</td>
<td>&lt;.001*</td>
<td>0.9</td>
<td>-1.8; -0.7</td>
</tr>
<tr>
<td>Concrete</td>
<td>0.2 (0.8)</td>
<td>0.0 (0.2)</td>
<td>-1.5 (49.3)</td>
<td>.15</td>
<td>0.3</td>
<td>-0.4; 0.1</td>
</tr>
<tr>
<td>Omission</td>
<td>0.1 (0.4)</td>
<td>0.3 (0.7)</td>
<td>1.5 (72.9)</td>
<td>.15</td>
<td>-0.3</td>
<td>-0.6; 0.4</td>
</tr>
</tbody>
</table>

*p*-values from two-tailed *t*-test. Results significant following Bonferroni correction are shown in bold*.* *d*, Cohen’s d; 95% CI, confidence interval for difference between means. *Note*: higher score indicates worse performance.

iv.) Cartoon Pairs subtask

The number of correct choices made by patients and controls for physical and mental cartoons were compared using a split-plot ANOVA. There was no Group by Cartoon-type (physical; mental) interaction for choice accuracy \([F(1,91)=0.3, p=.93, \eta^2=.01]\). The two groups did not differ in their ability to select the ‘funny’ cartoon from the two alternatives \([F(1,91)=0.008, p=.93, \eta^2<.001]\). Both groups tended to make more correct choices for the mental cartoons than for the physical cartoons \([F(1,91)=4.02, p=.05, \eta^2=.04]\).

Accuracy scores for this subtest were also examined using a split-plot two-way ANOVA. There was no Group by Cartoon-type (physical; mental) interaction effect \([F(1,91)=0.85, p=.36, \eta^2=.01]\). A main effect for Group on performance accuracy was revealed \([F(1,91)=9.44, p=.003, \eta^2=.09]\) but no main effect of Cartoon-type on performance accuracy was found \([F(1,91)=0.04, p=.85, \eta^2<.001]\). Figure 5.10 displays group means by cartoon condition.
As with the previous subtask, the number of errors per error category was compared between groups using two–tailed $t$–tests (see Table 5.21). Again, for both groups most errors constituted partial and descriptive errors. There was a significant difference between groups for mean number of misconstructions and descriptive responses, with ALS participants committing more of these error types than controls. However, only the difference for the misconception category remained significant following a Bonferroni correction (adjusted $p<.01$).

A break-down of errors over the conditions revealed that both groups made significantly more partial errors in the mental condition [$F(1,91)=38.46, p<.001, \eta^2=.29$]; no other error types were influenced by condition, or influenced by the interaction of participant group and condition.

**Figure 5.10.: Cartoon Pairs subtask performance across cartoon conditions**

![Figure 5.10.](image)

ALS, patients (n=45); HC, healthy controls (n=48). Error Bars represent 95% CI for mean. Max score for each cartoon condition is 15
Table 5.21: Cartoon Pairs subtask errors

<table>
<thead>
<tr>
<th>Error Type</th>
<th>Mean (SD)</th>
<th></th>
<th>t(df)</th>
<th>p</th>
<th>d</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS (n=45)</td>
<td></td>
<td>HC (n=48)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>3 (1.3)</td>
<td></td>
<td>2.5 (17)</td>
<td>-1.62</td>
<td>.11</td>
<td>0.34</td>
</tr>
<tr>
<td>Misconstruction</td>
<td>1 (0.8)</td>
<td></td>
<td>0.4 (0.7)</td>
<td>-3.49</td>
<td>.001*</td>
<td>0.72</td>
</tr>
<tr>
<td>Description</td>
<td>1.7 (1.4)</td>
<td></td>
<td>1.1 (1.1)</td>
<td>-2.35</td>
<td>.02</td>
<td>0.49</td>
</tr>
<tr>
<td>Concrete</td>
<td>0.1 (0.3)</td>
<td></td>
<td>0.0 (0.2)</td>
<td>-0.53</td>
<td>.60</td>
<td>0.13</td>
</tr>
<tr>
<td>Omission</td>
<td>0.4 (0.6)</td>
<td></td>
<td>0.5 (1)</td>
<td>1.10</td>
<td>.27</td>
<td>-0.23</td>
</tr>
</tbody>
</table>

p–values from two–tailed t-test. Uncorrected significant results shown in bold. p<.05 Results significant following Bonferroni correction are shown in bold*–p<.01. d, Cohen’s d; 95% CI, confidence interval for difference between means. Note: Higher score indicates worse performance.

v) Written Scenarios subtask

Accuracy scores for the above task were compared between groups using a split–plot two–way ANOVA. No Group by Scenario–type (physical; mental) interaction effect was found [F(1,81)=0.44, p=.51, ηp²=.01]. A main effect for Group [F(1,81)=9.56, p=.003, ηp²=.12] and a main effect of Scenario–type on performance accuracy were found [F(1,81)=49.33, p<.001, ηp²=.38]. Figure 5.11. displays group means by scenario condition.

Errors were recorded for responses that did not meet criteria for full/explicit explanations (i.e. an accuracy score <2). The error categories were the same for the previous subtasks. The total errors per error category were summed and compared between groups (see Table 5.22). Partial errors constituted the most errors for both groups. Once again, patients committed significantly more misconstructions than controls; this difference remained significant following a Bonferroni correction (adjusted p<.01).

A break-down of errors over the conditions revealed that both groups made significantly more partial errors in the mental condition [F(1,81)=15.36, p<.001, ηp²=.12]; both groups made significantly more omission errors on the physical condition [F(1,81)=4.71, p=.03, ηp²=.06]. Both groups made significantly more misconception
errors on the mental condition \[ F(1,91)=15.36, p<.001, \eta^2=.12 \], but patients showed a strong trend for more errors on this condition than controls \[ F(1,91)=4.05, p=.05, \eta^2=.05 \].

**Figure 5.11.:** Written Scenarios subtask performance across scenario condition

ALS, patients (n=45); HC, healthy controls (n=38). Error Bars represent 95% CI for mean. Max score for each cartoon condition is 16.
Table 5.2: Scenarios subtask errors

<table>
<thead>
<tr>
<th>Error Type</th>
<th>Mean (SD) ALS (n=38)</th>
<th>HC (n=45)</th>
<th>t(df)</th>
<th>p</th>
<th>d</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td>4.8 (2.1)</td>
<td>4.4 (2.7)</td>
<td>-0.85 (81)</td>
<td>.39</td>
<td>0.19</td>
<td>-1.5; 0.6</td>
</tr>
<tr>
<td>Misconstruction</td>
<td>1.5 (1)</td>
<td>0.7 (0.8)</td>
<td>-4.01 (81)</td>
<td>&lt;.001*</td>
<td>0.87</td>
<td>-1.2; -0.4</td>
</tr>
<tr>
<td>Description</td>
<td>0.8 (1.1)</td>
<td>0.4 (0.8)</td>
<td>-1.69 (81)</td>
<td>.10</td>
<td>0.38</td>
<td>-0.7; 0.1</td>
</tr>
<tr>
<td>Concrete</td>
<td>0.1 (0.3)</td>
<td>0.1 (0.3)</td>
<td>-0.62 (81)</td>
<td>.53</td>
<td>0.14</td>
<td>-0.2; 0.1</td>
</tr>
<tr>
<td>Omission</td>
<td>0.2 (0.4)</td>
<td>0.2 (0.4)</td>
<td>-0.66 (81)</td>
<td>.51</td>
<td>0.14</td>
<td>-0.2; 0.1</td>
</tr>
</tbody>
</table>

*p*-values from two-tailed *t*-test. Results significant following Bonferroni correction are shown in **bold**. *p* <.01. *d*, Cohen’s *d*; 95% CI for difference between means. *Note*: Higher score indicates worse performance.

vi) Happé Task: Single–case analysis

A previous ALS study that used the current task found a spectrum of performance in 16 patients, ranging from normal to impaired (Gibbons *et al.*, 2007). In light of those findings, the number of individual deficits for the physical and mental cartoon conditions in each group was examined using the single–case methods as described in Section 5.2.2.3. Significantly more patients than controls showed impairments on both conditions for the Cartoon Inference (C–Inference) subtask and the physical condition of the Scenario subtask. When a Bonferroni correction was applied (adjusted *p*<.008), significant differences remained for the physical condition of the C–Inference subtask only. A trend for a difference in proportions was shown for the mental condition of the Cartoon Pairs (C–Pairs) subtask. These results and the number of impairments per group for each condition are shown in Table 5.23.

Dissociation of performance between physical versus mental conditions was examined at the individual level. Although proportionally more patients than controls showed dissociations on all three subtasks, none of these differences were significant. A summary of these results is presented in Table 5.24. The number of participants per group who showed isolated impairments on either the physical or mental conditions, as well as those who showed simultaneous impairment on both conditions is summarised in Table 5.25.
### Table 5.23: Number of impairments on conditions of Happé Cartoon and Scenario subtasks

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>$X^2$ (df)</th>
<th>$p$</th>
<th>$\phi_c$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C–Inference</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical ALS</td>
<td>13 (28.8)</td>
<td>10.49 (1)</td>
<td>.001*</td>
<td>.34</td>
<td>0.1; 0.4</td>
</tr>
<tr>
<td>Mental HC</td>
<td>2 (4.2)</td>
<td>6.01 (1)</td>
<td>.01</td>
<td>.25</td>
<td>0.02; 0.3</td>
</tr>
<tr>
<td><strong>C–Pairs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical† ALS</td>
<td>4 (8.9)</td>
<td>—</td>
<td>.68</td>
<td>.05</td>
<td>-0.1; 0.2</td>
</tr>
<tr>
<td>Mental† HC</td>
<td>7 (15.6)</td>
<td>—</td>
<td>.07</td>
<td>.19</td>
<td>-0.0; 0.3</td>
</tr>
<tr>
<td><strong>Scenarios</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical ALS</td>
<td>9 (23.7)</td>
<td>4.82 (1)</td>
<td>.03</td>
<td>.24</td>
<td>0.02; 0.3</td>
</tr>
<tr>
<td>Mental† HC</td>
<td>7 (18.4)</td>
<td>—</td>
<td>.15</td>
<td>.22</td>
<td>0.00; 0.3</td>
</tr>
</tbody>
</table>

*p*–values from two–tailed Chi–square tests except † Fisher–Boschloo exact test. Uncorrected significant results shown in **bold–** $p<.05$. Results significant following Bonferroni correction are shown in **bold**– $p<.008$; 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions.

### Table 5.24: Dissociation of performance on conditions of Happé Cartoon and Scenario subtasks

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>$p$</th>
<th>$\phi_c$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dissociation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C–Inference</td>
<td>5 (11.1)</td>
<td>.09</td>
<td>.18</td>
<td>-0.0; 0.2</td>
</tr>
<tr>
<td>C–Pairs</td>
<td>1 (2.2)</td>
<td>&gt;.99</td>
<td>.01</td>
<td>-0.1; 0.1</td>
</tr>
<tr>
<td>Scenarios</td>
<td>7 (18.4)</td>
<td>.14</td>
<td>.18</td>
<td>-0.0; 0.3</td>
</tr>
</tbody>
</table>

C–Inference and C–Pairs ALS (n=45), HC (n=48); Scenarios ALS (n=38), HC (n=45). $p$–values from two–tailed Fisher–Boschloo exact test. $\phi_c$, Cramer’s V; 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions.
Table 5.25: Summary of impaired performance across conditions of Happé Cartoon and Scenario task

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>ALS (n=45)</th>
<th>HC (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartoon Inference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical &amp; Mental</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Physical only</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mental only</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cartoon Pairs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical &amp; Mental</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Physical only</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mental only</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Scenarios</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical &amp; Mental</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Physical only</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mental only</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

5.2.3. Behaviour

Means for the self-rated FrSBe $T$–scores are presented in Table 5.26. Contrary to expectation, controls rated themselves as having a higher premorbid level of behavioural dysfunction than ALS patients. Differences between patients and controls for premorbid $T$–scores were significant for the Total premorbid score, the Apathy subscale and the Executive Dysfunction subscale. These differences remained statistically significant following a Bonferroni correction (adjusted $p<.006$). However, patients reported a higher level of current apathy compared to controls. For current behaviour $T$–scores, a significant difference between groups for the Apathy subscale was found, although this did not remain significant following a Bonferroni correction. No significant differences between groups were found for the remaining current subscales or total score.
Split-plot ANOVAs, with Group as the between-subjects factor and Time (premorbid; current) as the within-subjects factor were conducted on FrSBe total and subscale scores:

$T$–scores differed as a function of Time for the Total score $[F(1,97)=32.94, \, p<.001, \, \eta^2=.25]$], Apathy $[F(1,97)=66.88, \, p<.001, \, \eta^2=.41]$ and Executive Dysfunction $[F(1,97)=10.43, \, p=.002, \, \eta^2=.10]$ subscales. Current $T$–scores on the Disinhibition subscale were not significantly different from premorbid levels $[F(1,97)=0.36, \, p=.55, \, \eta^2=.001]$. No main effects of group were found for the total score $[F(1,97)=2.57, \, p=.11, \, \eta^2=.03]$ or Apathy $[F(1,97)=0.1, \, p=.76, \, \eta^2<.001]$ and Disinhibition $[F(1,97)=1.98, \, p=.16, \, \eta^2=.02]$ subscales. However, there was a group effect for the Executive Dysfunction subscale $[F(1,97)=5.19, \, p=.03, \, \eta^2=.05]$.

A significant Group by Time interaction for the Total FrSBe score was found $[F(1,97)=36.23, \, p<.001, \, \eta^2=.27]$. This interaction is illustrated in Figure 5.12. While the patients’ total behavioural scores increased significantly over time, the control group showed a reduction on the total score scale.

A breakdown of scores across the subscales revealed Group by Time interactions for all three subdomains: Apathy $[F(1,97)=49.98, \, p<.001, \, \eta^2=.34]$, Disinhibition $[F(1,97)=7.03, \, p=.01, \, \eta^2=.07]$ and Executive Dysfunction $[F(1, 97)=17.44, \, p<.001, \, \eta^2=.05]$. The direction of change for the Apathy subscale was the same for both groups, but a greater increase in apathy was indicated for patients on this domain. The interaction for Apathy is illustrated in Figure 5.13. For the Disinhibition and Executive Dysfunction subscales, both patient subscale scores increased over time. Although premorbid and current scores were higher than the ALS group, the control group showed reduced scores over time for both domains. The interactions for these domains are displayed in Figures 5.14 and 5.15, in turn.
Table 5.26.: Self–rated FrSBe T–scores

<table>
<thead>
<tr>
<th>FrSBe</th>
<th>Mean (SD)</th>
<th>t(df)</th>
<th>p</th>
<th>d</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>T–score</td>
<td>ALS (n=51)</td>
<td>HC (n=48)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (pre.)</td>
<td>51.4 (12.3)</td>
<td>60.1 (13.7)</td>
<td>3.34 (97)</td>
<td><strong>.001</strong></td>
<td>-0.67</td>
</tr>
<tr>
<td>Total (cur.)</td>
<td>60.1 (14.4)</td>
<td>59.9 (14.1)</td>
<td>-0.1 (97)</td>
<td>0.93</td>
<td>0.01</td>
</tr>
<tr>
<td>Apathy (pre.)</td>
<td>47.6 (11.3)</td>
<td>54.5 (10.9)</td>
<td>3.12 (97)</td>
<td><strong>.002</strong></td>
<td>-0.63</td>
</tr>
<tr>
<td>Apathy (cur.)</td>
<td>61.1 (15.3)</td>
<td>55.6 (11.8)</td>
<td>-1.9 (97)</td>
<td><strong>.05</strong></td>
<td>0.40</td>
</tr>
<tr>
<td>Disinhib. (pre.)</td>
<td>55.3 (13.3)</td>
<td>60.8 (15.5)</td>
<td>1.9 (97)</td>
<td>0.06</td>
<td>-0.38</td>
</tr>
<tr>
<td>Disinhib. (cur.)</td>
<td>57.3 (12.4)</td>
<td>59.5 (15)</td>
<td>0.82 (97)</td>
<td>0.41</td>
<td>-0.17</td>
</tr>
<tr>
<td>Exec. Dys. (pre.)</td>
<td>51.2 (12.3)</td>
<td>59.5 (12.5)</td>
<td>3.33 (97)</td>
<td><strong>.001</strong></td>
<td>-0.67</td>
</tr>
<tr>
<td>Exec. Dys. (cur.)</td>
<td>55.8 (12.7)</td>
<td>58.9 (13.3)</td>
<td>1.14 (97)</td>
<td>0.26</td>
<td>-0.20</td>
</tr>
</tbody>
</table>

**Note:** Participants were asked to rate their behaviour at present time and approximately 2 years prior. p–values are from two–tailed t–tests; Uncorrected significant results shown in **bold**–p<.05. Results significant following Bonferroni correction are shown as **bold**–p<.006; d, Cohen’s d; 95% CI, confidence interval for difference between means. Disinhib., Disinhibition; Exec.Dys., Executive Dysfunction; pre., premorbid; cur., current.

In both groups, mean domains scores did not meet criteria for “caseness” according to standard cut–off criteria (T–score ≥65). Nonetheless, the relative proportions of each group satisfying criteria for “caseness” was examined (see Table 5.27.). A two–tailed Chi–square test revealed a significant difference between the ratio of cases in each group for the premorbid total FrSBe score only. Proportionally more controls than ALS patients were classified as a ‘case’ for this domain. This difference did not remain significant following a Bonferroni correction (adjusted p<.006). Proportionally more controls than patients satisfied these criteria for all the other domains, with the exception of the current Apathy subscale. However, the differences in proportions were not statistically significant.
Figure 5.12.: Line graph representing a significant interaction for FrSBe Total

ALS, patients (n=51); HC, healthy controls (n=48).

Figure 5.13.: Line graph representing a significant interaction for Apathy

ALS, patients (n=51); HC, healthy controls (n=48).
Figure 5.14.: Line graph representing a significant interaction for Disinhibition

ALS, patients (n=51); HC, healthy controls (n=48).

Figure 5.15.: Line graph representing a significant interaction for Executive Dysfunction

ALS, patients (n=51); HC, healthy controls (n=48).
Table 5.27.: Proportions of groups satisfying FrSBe ‘caseness’ criteria

<table>
<thead>
<tr>
<th>FrSBe</th>
<th>N (%)</th>
<th>$X^2$ (df)</th>
<th>$p$</th>
<th>$\phi_c$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS (n=51)</td>
<td>HC (n=48)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (pre.)</td>
<td>7 (13.7)</td>
<td>17 (35.4)</td>
<td>6.30</td>
<td>.01</td>
<td>.25; 0.03; 0.4</td>
</tr>
<tr>
<td>Total (cur.)</td>
<td>15 (29.4)</td>
<td>18 (37.5)</td>
<td>0.73</td>
<td>.39</td>
<td>.09; -0.1; 0.3</td>
</tr>
<tr>
<td>Apathy (pre.)</td>
<td>6 (11.8)</td>
<td>7 (14.6)</td>
<td>0.17</td>
<td>.68</td>
<td>.04; -0.1; 0.2</td>
</tr>
<tr>
<td>Apathy (cur.)</td>
<td>17 (33.3)</td>
<td>10 (20.8)</td>
<td>1.95</td>
<td>.16</td>
<td>.14; -0.1; 0.3</td>
</tr>
<tr>
<td>Disinhib. (pre.)</td>
<td>12 (23.5)</td>
<td>17 (35.4)</td>
<td>1.69</td>
<td>.19</td>
<td>.13; -0.1; 0.3</td>
</tr>
<tr>
<td>Disinhib. (cur.)</td>
<td>12 (23.5)</td>
<td>16 (33.3)</td>
<td>1.17</td>
<td>.28</td>
<td>.11; -0.1; 0.3</td>
</tr>
<tr>
<td>Exec. Dys. (pre.)</td>
<td>9 (17.6)</td>
<td>16 (33.3)</td>
<td>3.22</td>
<td>.07</td>
<td>.18; 0.0; 0.3</td>
</tr>
<tr>
<td>Exec. Dys. (cur.)</td>
<td>12 (23.5)</td>
<td>15 (31.3)</td>
<td>0.74</td>
<td>.39</td>
<td>.09; -0.1; 0.3</td>
</tr>
</tbody>
</table>

$p$-values from two-tailed Chi-square test. Uncorrected significant results shown in bold—$p<.05$. $\phi_c$, Cramer’s V. 95% CI, Newcombe-Wilson hybrid confidence interval for difference between proportions. Disinhib., Disinhibition; Exec.Dys., Executive Dysfunction; pre., premorbid; cur., current.

The number of participants for which behavioural ratings changed from ‘non–case’ levels to meeting ‘caseness’ criteria, and vice versa, over the two time points are shown in Table 5.28. Proportionally more patients than controls progressed from the ‘non–case’ level to meeting ‘caseness’ status from premorbid to current time points for all FrSBe scores. Conversely, proportionally more controls than patients, who reported premorbid levels of ‘caseness’ on the FrSBe domains, showed a downward direction of change from ‘caseness’ to ‘non–case’ levels. Between group differences for these proportions were not significant (results not shown). Within the patient group, McNemar tests found that the percentage of patients satisfying ‘caseness’ increased significantly between time points for Total FrSBe and Apathy (see Table 5.29). These differences remained significant following a Bonferroni correction (adjusted $p<.013$). For the control group, there were no significant changes in the proportions of ‘cases’ between the time points for any of the domains (results not shown).
Table 5.28.: ‘Caseness’ status over time points

<table>
<thead>
<tr>
<th>FrSBe</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS (n=51)</td>
</tr>
<tr>
<td>Total: pre. ‘non-case’ to curr. ‘caseness’</td>
<td>8 (15.7)</td>
</tr>
<tr>
<td>Total: pre. ‘caseness’ to curr. ‘non-case’</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Apathy: pre. ‘non-case’ to curr. ‘caseness’</td>
<td>12 (23.5)</td>
</tr>
<tr>
<td>Apathy: pre. ‘caseness’ to curr. ‘non-case’</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Disinhib.: pre. ‘non-case’ to curr. ‘caseness’</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>Disinhib.: pre. ‘caseness’ to curr. ‘non-case’</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>Exec. Dys.: pre. ‘non-case’ to curr. ‘caseness’</td>
<td>3 (5.9)</td>
</tr>
<tr>
<td>Exec. Dys.: pre. ‘caseness’ to curr. ‘non-case’</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Disinhib., Disinhibition; Exec.Dys., Executive Dysfunction; pre., premorbid; cur., current. ‘caseness’, T score ≥ 65; ‘non-case’; T score ≤ 65.

Table 5.29.: Comparison of the proportion of patients satisfying ‘caseness’ between premorbid and current time points

<table>
<thead>
<tr>
<th>FrSBe</th>
<th>N (%)</th>
<th>X²(df)</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=51 ALS</td>
<td>Premorbid</td>
<td>Current</td>
<td></td>
</tr>
<tr>
<td>Total FrSBe</td>
<td>7 (13.7)</td>
<td>15 (29.4)</td>
<td>8 (1)</td>
<td>.005*</td>
</tr>
<tr>
<td>Apathy</td>
<td>6 (11.8)</td>
<td>17 (33.3)</td>
<td>9.31 (1)</td>
<td>.002*</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>12 (23.5)</td>
<td>12 (23.5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Exec. Dys.</td>
<td>9 (17.6)</td>
<td>12 (23.5)</td>
<td>3 (1)</td>
<td>.08</td>
</tr>
</tbody>
</table>

p-values from McNemar tests. Results significant following Bonferroni correction are shown in bold* – p<.013. Exec.Dys., Executive Dysfunction; 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions (paired).
5.2.4. Mood

Section 5.2.1. displayed group medians for HADS A and HADS D scores. No significant differences were reported between groups. A further examination of these scores was conducted to investigate the relative proportions of patients and controls who satisfied revised criteria for ‘caseness’ on these measures (Gibbons et al., 2011). In addition, a HADS Total score was calculated for inclusion in subsequent analyses. Previous studies have found that the HADS subscales are highly correlated and have recommended the summation of subscale scores to create a single factor as an index of psychological distress (Crawford et al., 2001; Smith et al., 2002). This suggestion has been supported statistically by studies in non–ALS populations (Marinus et al., 2002; Martin et al., 2004; Pallant & Tennant, 2007). Support for the use of the modified HADS Total score for the purposes of research in ALS exists (Gibbons et al., 2011). Here the HADS Total score will be referred to as a measure of overall mood rather than psychological distress, in order to avoid confusion with alternative definitions that exist in the ALS literature for this latter term (e.g. Rabkin et al, 2009 vs. Goldstein et al, 2006). The Gibbons et al (2011) revised HADS criteria for case level, borderline case level and non–case level of anxiety and depression are shown in Table 5.30. HADS Total score cut–offs for ‘possible’ mood disorder and ‘probable’ mood disorder is also shown in this table. According to these criteria, the HADS D medians for patients (\(Mdn=2\)) and for controls (\(Mdn=1\)) are within the non–case level range for depression. The HADS A medians for patients (\(Mdn=4\)) and controls (\(Mdn=3\)) are within the non–case level range for anxiety (see Section 5.2.1).

Table 5.30.: Gibbons et al (2011) revised HADS criteria for caseness

<table>
<thead>
<tr>
<th>Scale</th>
<th>Case Level</th>
<th>Borderline Case Level</th>
<th>Non–Case Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS Total</td>
<td>≥ 21</td>
<td>17 – 20</td>
<td>≤ 16</td>
</tr>
<tr>
<td>HADS A</td>
<td>≥ 9</td>
<td>7 – 8</td>
<td>≤ 6</td>
</tr>
<tr>
<td>HADS D</td>
<td>≥ 8</td>
<td>5 – 7</td>
<td>≤ 4</td>
</tr>
</tbody>
</table>

3 Gibbons et al (2011) refer to criteria cut-off points for the HADS Total as ‘probable’ and ‘possible’ mood disorder in keeping with Pallant & Tennant (2007).
HADS A and HADS D scores (which were highly correlated, \( \rho = .56, p < .001, n=104 \)) were summed to create HADS Total scores. A Mann–Whitney \( U \) test revealed no significant difference between patients (\( Mdn=6 \)) and controls (\( Mdn=6 \)) on this score, \( U(-0.7)=1240.5, \ p=.49, \ r=.07 \). According to the criteria, medians for both groups are not indicative of mood disorder.

The group proportions of participants satisfying criteria for case level and borderline case level for depression and anxiety are shown in Table 5.31. There were no significant differences between the ratio of patients and controls satisfying the revised criteria.

<table>
<thead>
<tr>
<th>Table 5.31.: Proportions of participants by group meeting HADS criteria</th>
<th>N (%)</th>
<th>( X^2 (df) )</th>
<th>( p )</th>
<th>( \phi_c )</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS (n=55)</td>
<td>HC (n=49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS D Borderline cases</td>
<td>9 (16.4)</td>
<td>5 (10.2)</td>
<td>0.84 (1)</td>
<td>.36</td>
<td>.09</td>
</tr>
<tr>
<td>HADS D cases†</td>
<td>3 (5.5)</td>
<td>0 (0)</td>
<td>—</td>
<td>.23</td>
<td>.16</td>
</tr>
<tr>
<td>HADS A Borderline cases†</td>
<td>4 (7.2)</td>
<td>5 (10.2)</td>
<td>—</td>
<td>.69</td>
<td>.05</td>
</tr>
<tr>
<td>HADS A cases</td>
<td>9 (16.3)</td>
<td>6 (12.2)</td>
<td>3.57 (1)</td>
<td>.55</td>
<td>.06</td>
</tr>
<tr>
<td>HADS Total possible†</td>
<td>2 (3.6)</td>
<td>0 (0)</td>
<td>—</td>
<td>.45</td>
<td>.13</td>
</tr>
<tr>
<td>HADS Total probable†</td>
<td>2 (3.6)</td>
<td>0 (0)</td>
<td>—</td>
<td>.45</td>
<td>.13</td>
</tr>
</tbody>
</table>

\( p \)-values from two–tailed Chi–square test except † Fisher–Boschloo test. \( \phi_c \), Cramer’s V. 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions.
5.2.5. Personality

T–scores for the Big–Five personality dimensions (Neuroticism, N; Extraversion, E; Openness, O; Agreeableness, A; Conscientiousness, C) were calculated according to gender–corrected norms from the questionnaire’s manual (See Chapter 4). Group means for the domain T scores and the results of two–tailed t–tests for group comparisons on these domains are presented in Table 5.32. Controls reported significantly higher levels of N than patients, while patients reported significantly higher rates of C than controls. These differences did not remain significant following a Bonferroni correction (adjusted $p<.01$).

Cut–off scores for levels of each domain T–score are also provided by the manual. The proportions of patients and controls falling into the extreme cut–off categories (Very high; Very low) are presented in Table 5.33. Significantly more controls than patients fell within the Very high N categories and the very low E categories. Differences in these proportions did not remain significant following a Bonferroni correction (adjusted $p<.005$). Significantly more controls than patients fell within the very low C category; the difference in case ratio remained significant following a Bonferroni correction.

According to the NEO–FFI manual, the N domain measures traits of anxiety, hostility, depression, self-consciousness, impulsiveness and ability to cope with stress. The four control participants who showed very high levels of N met criteria for case level HADS A and one also met criteria for borderline HADS D, suggesting that the high scores on N might be capturing these participants’ elevated mood levels. When the four control participants showing very high levels of N were removed from the analyses, the trend for between–group differences on this domain disappeared, $t(94)=1.26, p=.21, 95\%$ CI [-1.5; 6.5].
Table 5.32.: Self–reported NEO–FFI T–scores

<table>
<thead>
<tr>
<th>NEO–FFI T–score</th>
<th>Mean (SD)</th>
<th>t(df)</th>
<th>p</th>
<th>d</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(min 25; max 75)</td>
<td>ALS (n=52)</td>
<td>HC (n=48)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroticism</td>
<td>44.3 (8.9)</td>
<td>48.8 (12.3)</td>
<td>2.1 (85.8)</td>
<td>.04</td>
<td>-.42</td>
</tr>
<tr>
<td>Extraversion</td>
<td>54.1 (9.2)</td>
<td>50.4 (11.5)</td>
<td>-1.8 (98)</td>
<td>.07</td>
<td>.36</td>
</tr>
<tr>
<td>Openness</td>
<td>50.8(11.8)</td>
<td>55.1 (10.6)</td>
<td>1.9 (98)</td>
<td>.06</td>
<td>-.40</td>
</tr>
<tr>
<td>Agreeableness</td>
<td>49 (10.5)</td>
<td>47.3 (11.1)</td>
<td>-0.82 (98)</td>
<td>.42</td>
<td>.16</td>
</tr>
<tr>
<td>Conscientiousness</td>
<td>50.3 (9.6)</td>
<td>44.8 (13.9)</td>
<td>-2.3 (82.5)</td>
<td>.03</td>
<td>.46</td>
</tr>
</tbody>
</table>

*p–values from two–tailed t-tests; d , Cohen’s d; 95% CI for difference between means. Uncorrected significant results shown in bold –p<.05.

Table 5.33.: Self–reported NEO–FFI cut–off categories

<table>
<thead>
<tr>
<th>NEO–FFI</th>
<th>N (%)</th>
<th>X² (df)</th>
<th>p</th>
<th>φc</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high (range 66: 75)</td>
<td>ALS (n=52)</td>
<td>HC (n=48)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N – Very high†</td>
<td>0 (0)</td>
<td>4 (8.3)</td>
<td>—</td>
<td>.04</td>
<td>.21</td>
</tr>
<tr>
<td>N – Very low</td>
<td>8 (15.3)</td>
<td>9 (18.8)</td>
<td>0.2 (1)</td>
<td>.66</td>
<td>.05</td>
</tr>
<tr>
<td>E – Very high†</td>
<td>4 (7.7)</td>
<td>4 (8.3)</td>
<td>—</td>
<td>&gt;.99</td>
<td>.21</td>
</tr>
<tr>
<td>E – Very low†</td>
<td>0 (0)</td>
<td>4 (8.3)</td>
<td>—</td>
<td>.04</td>
<td>.21</td>
</tr>
<tr>
<td>O – Very high</td>
<td>4 (7.7)</td>
<td>8 (16.6)</td>
<td>1.9 (1)</td>
<td>.17</td>
<td>.14</td>
</tr>
<tr>
<td>O – Very low†</td>
<td>3 (5.8)</td>
<td>2 (4.2)</td>
<td>—</td>
<td>&gt;.99</td>
<td>.04</td>
</tr>
<tr>
<td>A – Very high†</td>
<td>3 (5.8)</td>
<td>4 (8.3)</td>
<td>—</td>
<td>.68</td>
<td>.05</td>
</tr>
<tr>
<td>A – Very low†</td>
<td>5 (9.6)</td>
<td>5 (10.4)</td>
<td>—</td>
<td>&gt;.99</td>
<td>.01</td>
</tr>
<tr>
<td>C – Very high†</td>
<td>2 (3.8)</td>
<td>5 (10.4)</td>
<td>—</td>
<td>.22</td>
<td>.13</td>
</tr>
<tr>
<td>C – Very low</td>
<td>4 (7.7)</td>
<td>15 (31.3)</td>
<td>9.0 (1)</td>
<td>.003*</td>
<td>.30</td>
</tr>
</tbody>
</table>

*p–values from two–tailed Chi–square test except † Fisher–Boschloo testφc, Cramer’s V; 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions. Uncorrected significant results shown in bold –p<.05. Results significant following Bonferroni correction are shown as bold*–p<.005.
5.2.6. Empathy

Mean scores on the IRI subscales are shown in Table 5.34. T–tests did not find any significant differences between patients and controls on any of the subscales.

Table 5.34.: Self–reported IRI ratings

<table>
<thead>
<tr>
<th>IRI subscales</th>
<th>Mean (SD)</th>
<th>t(df)</th>
<th>p</th>
<th>d</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(min 7; max 35)</td>
<td>ALS (n=55)</td>
<td>HC (n=49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perspective Taking</td>
<td>17 (5.2)</td>
<td>18.2 (4)</td>
<td>1.28 (102)</td>
<td>.20</td>
<td>0.26</td>
</tr>
<tr>
<td>Fantastical Thinking</td>
<td>11.6 (4.8)</td>
<td>12.3 (4.8)</td>
<td>0.77 (102)</td>
<td>.44</td>
<td>0.15</td>
</tr>
<tr>
<td>Empathic Concern</td>
<td>19.3 (5.3)</td>
<td>19.2 (4.1)</td>
<td>-0.12 (100.1)</td>
<td>.91</td>
<td>0.02</td>
</tr>
<tr>
<td>Personal Distress</td>
<td>8.8 (4.8)</td>
<td>9.6 (5.2)</td>
<td>0.77 (102)</td>
<td>.44</td>
<td>0.16</td>
</tr>
</tbody>
</table>

\(p\)–values from two–tailed \(t\)–tests, \(d\), Cohen’s \(d\); 95% CI for difference between means.

5.2.7. Emotional lability

Each domain (Laughing, Crying, Smiling) has a maximum score of 31 yielding a total maximum score of 93 (ELQ Tot), with higher scores reflecting higher levels of emotional lability. Median tests found significant differences between groups for the ELQ Tot and the Crying and Smiling domains. The ELQ Tot and Crying domains remained significant following a Bonferroni correction (adjusted \(p<.013\)). No differences were found between groups for the Laughing domain. Medians are presented alongside statistical tests results in Table 5.35.
Table 5.35.: Self–reported ELQ ratings

<table>
<thead>
<tr>
<th></th>
<th>Medians (MAD/IQR)</th>
<th>$X^2$ (df)</th>
<th>$p$</th>
<th>$\phi_c$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS (n=55)</td>
<td>HC (n=49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELQ Tot</td>
<td>7 (0/20)</td>
<td>0 (0/5)</td>
<td>10.3 (1)</td>
<td>.001*</td>
<td>.32</td>
</tr>
<tr>
<td>ELQ Laugh</td>
<td>0 (0/18)</td>
<td>0 (0/0)</td>
<td>2.78 (1)</td>
<td>.10</td>
<td>.16</td>
</tr>
<tr>
<td>ELQ Cry</td>
<td>0 (0/12)</td>
<td>0 (0/0)</td>
<td>12.5 (1)</td>
<td>&lt;.001*</td>
<td>.35</td>
</tr>
<tr>
<td>ELQ Smile</td>
<td>0 (0/1)</td>
<td>0 (0/0)</td>
<td>4.04 (1)</td>
<td>.05</td>
<td>.20</td>
</tr>
</tbody>
</table>

$p$–values from Medians Test. Uncorrected significant results shown in **bold** – $p$<.05. Results significant following a Bonferroni correction are shown as **bold** – $p$<.013 $\phi_c$, Cramer’s V; 95% CI, Hodges-Lehmann confidence interval for difference between medians.

5.2.8. Patient Subgroups: medicated patients vs. non medicated patients

The patient group comprised a subgroup of patients who were receiving psychoactive medication for disease management (n=15, see Appendix VII). Since psychoactive substances have shown to influence cognitive performance and the processing of emotionally–salient information in healthy participants (Delaveau *et al.*, 2011; Pringle *et al.*, 2011), it is plausible that the overall patient group performance might have been influenced by the presence of medicated patients. For this reason, the two patient subgroups (n=40, ‘not medicated’; n=15, ‘medicated’) were compared on measures of cognitive and emotional processing, personality, behaviour and empathy. A summary of these analyses follow:

**A. Demographic and Disease variables**

The subgroups did not differ significantly for any of the demographic variables (see Appendix VII.a.).

**B. Executive function and EMOSOC composites**

A one–way MANOVA found no significant difference between patients and controls on the combined dependent variable (composite scores) (see Appendix VII.b.). The proportion of patients impaired did not differ between groups for either the Executive
function composite \(X^2(1) = 0.68, p = .41, \phi_c = .11\) or the EMOSOC composite [Fisher–Boschloo exact test; \(p = .41, \phi_c = .05\)].

C. Executive function component scores and Hayling task

No significant differences between subgroups were found for any of the executive function components scores. Similarly, subgroups did not differ on the error and latency scores of the Hayling task (see Appendix VII.c.). The proportions of patients impaired on the executive components and Hayling scores in each subgroup were compared; no significant differences were found (see Appendix VII.d.).

D. EMOSOC components

Subgroups were compared on the components of emotional processing and social cognition (see Appendix VII.e.). A significant difference was found for the TASIT EET component (emotion evaluation), with medicated patients performing significantly worse than non–medicated patients. This difference was not significant following a Bonferroni correction (adjusted \(p < 0.007\)). According to Cohen’s (1988) conventions, the effect size for the difference in means was within the medium range. No significant differences between subgroups were found for any of the other components. The proportions of patients impaired on the EMOSOC components were compared between subgroups; no significant differences were found (see Appendix VII.f.).

E. Language and Memory

Subgroups did not differ significantly on the GNT score or the CVLT measures (see Appendix VII.g.), with the exception of the CVLT delayed cued recall trial on which medicated patients showed superior performance relative to non–medicated patients. This difference was not significant following a Bonferroni correction \((p < 0.013)\). On the basis of Cohen’s (1988) conventions, effect sizes associated with the immediate recall, short delay recall and delayed cued recall trials of the CVLT were within the range of medium to large. The proportion of impaired patients \((n = 5, \text{non–medicated patients}; n = 0, \text{medicated patients})\) on this trial was not statistically different between subgroups (Fisher–Boschloo exact test, \(p = .50, \phi^c = .17, 95\% \text{ CI } [-0.1; 0.3]\)).
F. Behaviour, mood, personality, empathy and emotional lability

Ratings for the IRI (empathy) domain scores\(^4\) were compared between subgroups (see Appendix VII.h.). Once again, no significant differences were found between subgroups on these scores. Ratings for premorbid and current FrSBe \(T\)-scores were also compared between subgroups (see Appendix VII.i.). No differences between subgroups on any of the FrSBe domains were found for either time period. In addition, there were no differences between groups for the ELQ domains (see Appendix VII.j.).

Ratings for NEO–FFI domain \(T\)-scores\(^5\) were compared between subgroups (see Appendix VII.k.). Initially, subgroup differences for N were found at the uncorrected significance level, with medicated patients (\(M=49\), SD=8.7, \(n=13\)) showing higher levels of N than non–medicated patients (\(M=42.7\), SD=8.6, \(n=39\)), \(t(50)=-2.27, p=.03\), \(d=0.73\), 95% CI [-1.18; -0.72]. However when mood (HADS Total scores) was entered as a covariate in an ANCOVA, the difference between groups was no longer significant, \(F(1,49)=3.37, p=.07\), \(\eta^2=.06\). Correlational analyses did not find a significant relationship between variable N and any of the measures of interest. No significant differences for any of the other NEO–FFI domains were found.

\(^4\) IRI domains: Perspective taking (PT); Fantasy thinking (FS); Empathic Concern (EC); Personal Distress (PD)

\(^5\) NEO–FFI domain \(T\)-scores: N, Neuroticism; E, Extraversion. O, Openness; A, Agreeableness; C, Conscientiousness.
5.2.9. Inter–relationship between executive functioning and emotional processing and social cognition in ALS

In order to examine Hypothesis Three that executive (dys)function will be the main predictor of performance on tests of emotional processing and social cognition, with smaller contributions from behaviour, mood, personality and empathy (above and beyond patients’ demographic and disease symptoms) a multiple regression (MR) analysis was conducted.

Composite scores were recalculated using the patients’ scores, instead of the healthy control participant scores as had been done in Section 5.2.2.1. This was undertaken in order to investigate the relationship between these two domains in ALS patients, rather than with respect to healthy control participants. The composite scores were computed by subtracting the mean score of the ALS group from each ALS participant’s score on each test and then dividing by the standard deviation for the ALS group. The creation of these composites, as before, aimed to reduce the likelihood of making Type 1 errors that might occur if regressions of each individual neuropsychological score were undertaken.

The composite scores were constructed using the same component scores outlined in Section 5.2.2.1. The Cronbach’s alpha coefficients for these composite scores are shown in Table 5.36.; both were greater than .70, suggesting satisfactory internal consistency of each score.

<table>
<thead>
<tr>
<th>Composite</th>
<th>Number of items</th>
<th>Cronbach’s Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive function</td>
<td>5</td>
<td>.80</td>
</tr>
<tr>
<td>Emotional Processing and Social Cognition (EMOSOC)</td>
<td>7</td>
<td>.88</td>
</tr>
</tbody>
</table>

Table 5.36.: Internal consistency of ALS–only composite scores
The selection of predictors

The selection of possible predictors was based on theory and statistical criteria. A list of the potential predictors under the domains of interest is shown in Table 5.37. Bivariate correlational analyses were conducted to determine the presence of significant relationships between potential predictor variables and the EMOSOC composite (unadjusted $p<.05$). These variables were then entered into a MR with the EMOSOC as the outcome, controlling for demographic variables.

Demographic variables: The correlations between EMOSOC and demographic variables were as follows: Age ($r=.44, p=.001, n=55$); Education ($r=-.29, p=.03$), WASI FSIQ ($rho=-.48, p=.001, n=48$) and WTAR–predicted FSIQ ($rho=-.4, p=.004, n=51$). However, Education was moderately to strongly correlated with WASI FSIQ ($rho=.48, p=.001, n=48$) and WTAR–predicted FSIQ ($rho=.59, p<.001, n=51$). Moreover, not all patient participants were able to complete both IQ measures due to physical disability. Therefore, Education acted as a proxy for intellectual functioning in the analyses. Gender did not correlate significantly with the EMOSOC score.

Disease variables: Disease symptom severity, disease duration and disease progression rate did not correlate with the EMOSOC outcome.

Executive: A significant association between the Executive and EMOSOC composite scores was found in the ALS group ($r=.61, p<.001, n=55$). Neither of the Hayling error scores nor the latency score correlated with the EMOSOC composite.

Behaviour: The FrSBe Total score correlated significantly with the EMOSOC composite ($r=.3, p=.04, n=51$), as did the Apathy ($r=.33, p=.02, n=51$) and Executive Dysfunction ($r=.41, p=.003, n=51$) subscales. These three variables correlated strongly with each other ($.7 < r < .9$). The FrSBe Total score showed the strongest correlation with the EMOSOC score. Therefore, only the FrSBe Total score was used in the final regression model.

Mood: The HADS Total score correlated significantly with EMOSOC ($r=-.28, p=.04, n=55$).
Table 5.37.: Domains of interest for possible predictors of EMOSOC

<table>
<thead>
<tr>
<th>Domain</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic (control variables)</strong></td>
<td>Age</td>
</tr>
<tr>
<td><strong>Disease parameters (control variables)</strong></td>
<td>ALSFRS–R: Total, bulbar severity, limb severity, respiratory severity subscale scores.</td>
</tr>
<tr>
<td><strong>Executive</strong></td>
<td>Executive function composite score</td>
</tr>
<tr>
<td><strong>Behaviour</strong></td>
<td>FrSBe: Total, Apathy, Disinhibition, Executive Dysfunction subscale scores.</td>
</tr>
<tr>
<td><strong>Mood</strong></td>
<td>HADS Total</td>
</tr>
<tr>
<td><strong>Personality</strong></td>
<td>NEO–FFI: Neuroticism, Extraversion, Openness, Agreeableness, Conscientiousness T–scores.</td>
</tr>
<tr>
<td><strong>Empathy</strong></td>
<td>IRI: Perspective Taking, Fantasy Thinking, Empathic Concern, Personal Distress scores.</td>
</tr>
</tbody>
</table>

For abbreviations see pgs. 13-16.

**Personality:** Only the **Openness** T–score of the NEO–FFI correlated significantly with EMOSOC ($r=-.32$, $p=.02$, $n=52$).

**Empathy:** None of the IRI subscales correlated with the EMOSOC score.
Some patients did not complete the FrSBe (n=4) and NEO–FFI (n=3) measures due to fatigue and time constraints. A MR to determine the relative contributions of the Executive function composite, the FrSBe Total, the HADS Total and the Openness T–score to the EMOSOC composite, controlling for age and years of formal education was conducted. Since the hypothesis expected a higher contribution from executive functioning than behaviour, personality and mood to the outcome, the variables were entered in a hierarchical design in the following blocks:

**Block 1:** Age and education (control variables)

**Block 2:** FrSBe Total, HADS Total and Openness T–score

**Block 3:** Executive function Composite

Results of this analysis are shown in Table 5.38. When variables Age and Education were entered into the first model, $R^2=.240$ (adjusted $R^2=.206$) was significantly different from zero, $F(2,45)=7.11$, $p=.002$. Both Age and Education significantly predicted the EMOSOC scores (Age: $t(46)=2.99$, $p=.004$; Education: $t(46)=-2.23$, $p=.03$).

In the second model, the addition of the behaviour, mood and personality variables did not reliably improve $R^2$, $R^2=.330$ (adjusted $R^2=.250$), $F(3,42)=1.87$, $p=.15$, but the model remained significantly different from zero, $F(5,42)=4.13$, $p=.004$. Only Age remained a significant predictor of EMOSOC scores, $t(46)=1.65$, $p=.04$.

In the third model, the addition of the Executive function composite scores significantly improved $R^2$, $R^2=.516$ (adjusted $R^2=.445$), $F(1,41)=15.81$, $p<.001$. At this final model, with all predictor variables entered into the equation, $R^2=.516$ was significantly different from zero, $F(6,41)=7.29$, $p<.001$. The adjusted $R^2=.445$ value indicated that 44.5% of the variability in the EMOSOC composite was explained by the model. Inspection of the standardised regression coefficients indicated that as the Executive function composite scores increased by 1 SD (0.68), the EMOSOC composite scores increased by 0.49 SD. Executive function was the only significant predictor of EMOSOC, $t(46)=3.98$, $p<.001$.

These results support Hypothesis Three that executive function would contribute more to performance on emotional processing and social cognition in ALS, than behavioural empathy, mood and personality factors (controlling for demographic and disease variables).
Table 5.38.: Predictors of EMOSOC composite

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Standard Error B</th>
<th>Standardised β</th>
<th>95% CI for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Constant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.31</td>
<td>0.01</td>
<td>0.39*</td>
<td>0.01; 0.1</td>
</tr>
<tr>
<td>Education (years)</td>
<td>-0.05</td>
<td>0.02</td>
<td>-0.29</td>
<td>-0.1; -0.01</td>
</tr>
<tr>
<td>2. Constant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.002</td>
<td>0.01</td>
<td>0.29</td>
<td>0.001; 0.1</td>
</tr>
<tr>
<td>Education (years)</td>
<td>-0.03</td>
<td>0.03</td>
<td>-0.17</td>
<td>-0.1; 0.0</td>
</tr>
<tr>
<td>FrSBe Tot</td>
<td>0.01</td>
<td>0.01</td>
<td>0.23</td>
<td>-0.0; 0.0</td>
</tr>
<tr>
<td>HADS Tot</td>
<td>-0.03</td>
<td>0.02</td>
<td>-0.2</td>
<td>-0.1; 0.0</td>
</tr>
<tr>
<td>Openness</td>
<td>-0.01</td>
<td>0.01</td>
<td>-0.13</td>
<td>-0.0; 0.0</td>
</tr>
<tr>
<td>3. Constant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.02</td>
<td>0.01</td>
<td>0.20</td>
<td>0.0; 0.0</td>
</tr>
<tr>
<td>Education (years)</td>
<td>-0.01</td>
<td>0.03</td>
<td>-0.06</td>
<td>-0.1; 0.4</td>
</tr>
<tr>
<td>FrSBe Tot</td>
<td>0.01</td>
<td>0.01</td>
<td>0.10</td>
<td>-0.0; 0.0</td>
</tr>
<tr>
<td>HADS Tot</td>
<td>-0.03</td>
<td>0.02</td>
<td>-0.24</td>
<td>-0.1; 0.0</td>
</tr>
<tr>
<td>Openness</td>
<td>-0.01</td>
<td>0.01</td>
<td>-0.11</td>
<td>-0.2; 0.0</td>
</tr>
<tr>
<td>Executive Function</td>
<td>0.48</td>
<td>0.12</td>
<td>0.49*</td>
<td>0.2; 0.7</td>
</tr>
</tbody>
</table>

N=48. Results significant at p<.05 shown in bold. Results significant at p<.001 in bold*. 1. R²=.240, adjusted R²=.266; 2. R²=.330, adjusted R²=.250; 3. R²=.516, adjusted R²=.445.

5.3. Summary of results

This section provides a review of the chapter’s findings. Results which were significant following a Bonferroni correction for multiple comparisons will be outlined. Uncorrected significant findings (significant at p<.05) will be described as trends or tendencies towards group differences.

5.3.1. Participant characteristics

The ALS (n=55) and control (n=49) participants were well matched for demographic variables, such as age, years of education and gender. There was no between–group difference for the HADS depression and anxiety subscales. Similarly, there was no between–group difference regarding the number of participants in each group who
reported having previously seen a GP or psychiatrist regarding mental health problems. Proportionally more controls than patients were single, but this was not considered clinically relevant. Participants were also matched on IQ estimates; no group differences on the WASI Full–scale IQ estimate or the WTAR premorbid Full–scale IQ estimate were found.

5.3.2. Composite scores

ALS patients showed greater impairment (higher scores) than controls on the canonical variate created by the multivariate procedure. In support of Hypothesis One, univariate analyses conducted on transformed data revealed that patients showed higher scores compared to controls on the Executive function and EMOSOC composite, indicating worse performance in these domains. Inspection of the discriminant function coefficients from untransformed data indicated that the Executive function composite showed greater weighting than the EMOSOC composite and maximally differentiated the group membership. This suggests that the Executive function composite contributed more to group differences on the canonical variate than the EMOSOC composite.

A. Individual executive function component scores

Following the finding that ALS patients showed greater impairment on the Executive function composite than controls, performance across individual components of the composite was explored. Between–group differences were found for the D–KEFS card sorting tasks. Relative to controls, patients showed greater impairment for the number of card sorts made and the descriptive responses provided on this task. A between–group trend was also observed for one measure of verbal fluency; patients showed poorer performance for generating four–letter C–words than control participants.

B. Individual EMOSOC component scores

Relative to the control group, ALS patients performed significantly worse on the EMOSOC composite, when transformed data was compared between groups. For the untransformed EMOSOC composite data, a trend for poorer patient performance was observed. Further investigation was conducted to examine the nature of differences between the participants groups on individual measures of the composite. Significant group differences were found for the Happé cartoon and scenarios subtasks only, with patients performing significantly worse than controls for all three subtasks.
5.3.3. Single–case analysis

A. Composites

Single–case analyses revealed that proportionally more patients than controls showed impairments on the Executive and EMOSOC composites; however, the differences in proportions were not significantly different. The profile of impaired performance across composites was compared between groups. Proportionally more patients than controls showed concurrent impairments on the Executive and EMOSOC composites; proportionally more patients than controls showed isolated impairments on the Executive composite and proportionally more patients than controls showed isolated impairments on the EMOSOC composite. None of the differences in these proportions were significantly different. Dissociations of performance between the Executive and EMOSOC composites were found for three patients (none were found for controls). For all three patients, the directions of these dissociations indicated that patients were impaired on the Executive composite but unimpaired on the EMOSOC composite.

B. Executive and EMOSOC components

Single–case analyses revealed that proportionally more patients than controls showed impairments on all of the Executive function components; however, only the proportion between groups for the S–words verbal fluency index was significant following a Bonferroni correction. The proportions of patients impaired on the C–words verbal fluency index tended to be higher than the control participants, but this was not significant following the correction. In the ALS sample, 45.4% of patients were impaired on at least one executive component. This is contrasted with 14.3% of the participants from the control sample.

Of the EMOSOC components, the proportion of impaired cases for the patient group was significantly greater than that of the control group for the Cartoon Inference subtask only. In the ALS sample, at least 41.8% of patients were impaired on at least one EMOSOC component. This is contrasted with 12.3% of the participants from the control sample.
5.3.4. Individual tests of cognition

A. Language and Memory

No between–group differences were found for either the GNT or CVLT measures. Similarly, the proportion of impaired participants was not significantly different between groups.

B. Executive function: Hayling task

Since the Hayling task did not correlate positively or strongly with the components of the Executive function composite, group performance on this measure was examined separately. Patients committed significantly more Category A and Category B error responses than controls, but the group means for the latency score were not statistically different. Single–case analyses revealed a tendency for the patient group to show proportionally more impairments than the control group on all the Hayling measures, including the latency score.

C. Emotional processing and social cognition: TASIT and Happé

More detailed analyses were conducted on the TASIT and Happé Cartoon and Scenario subtests. Between–group analyses conducted on performance of the TASIT subtasks revealed no group differences for the emotion evaluation test or the social inference tests (minimal and enriched social information subtests).

Analyses conducted on the performance of the Happé Cartoon and Scenario subtests showed between–group differences for performance accuracy for all three subtests, with the patient group performing worse than the control group. Within–group analyses found that both groups performed better on the mental cartoon trials than the physical cartoon trials. Conversely, for the scenarios subtest, both groups performed better on the physical scenario trials than the mental scenario trials.

Error scores were also compared between groups for the three subtests. On the Cartoon Inference subtask, ALS patients committed significantly more partial and descriptive errors than controls. Both groups made significantly more partial errors on the mental compared to the physical condition. While ALS patients made significantly more descriptive errors on the mental condition relative to the physical condition, the reverse was true for control participants. On the Cartoon Pairs subtask, ALS patients made significantly more misconception errors, and showed a trend for more descriptive
errors than controls participants. On the Scenarios subtask, patients committed significantly more misconstruction errors than controls. Both groups made significantly more misconstruction errors on the mental condition, but patients showed a strong trend for more errors on this condition than controls.

Individual case analysis revealed the proportions of participants in each group showing impaired performance for the physical and mental conditions of each subtask. Significantly more patients than controls showed impairments for the physical condition of the single cartoon inference subtask. ALS patients also showed more impairments than controls for the mental condition of the same task; however this did not remain significant following a Bonferroni correction. Similarly, a greater proportion of impairment was found in the ALS group for the physical condition of the Scenarios subtask; however, this difference also did not remain significant following the correction.

Dissociation of performance between the physical and mental condition was examined; although proportionally more patients than controls showed dissociations on all three subtasks, none of these differences were significant.

5.3.5. Behaviour

Behaviour, as measured by the FrSBe, was compared between groups. Contrary to Hypothesis Two, patients did not report higher behavioural symptoms than the controls for either the premorbid and current time period. Controls reported significantly higher premorbid behavioural symptoms for the Apathy, Executive dysfunction and Total FrSBe domains. There was a trend for patients to report higher levels of current Apathy. Significant interactions of group membership and time were found for all the domains of the FrSBe. For the FrSBe Total domain, patients’ scores increased significantly over time while the controls’ total behavioural scores decreased. Both groups reported an increase in Apathy over time, but the magnitude of increase for this domain was larger in the patient group. For the Executive dysfunction and Disinhibition domains, patients’ scores increased over time while control scores decreased.

The proportions of participants who satisfied criteria for ‘caseness’ (T ≥65) were also compared between groups. There was a trend for proportionally more controls than patients to satisfy ‘caseness’ criteria on the premorbid FrSBe Total domain. Within the patient group, the proportion of patients that satisfied ‘caseness’ for Apathy and the
FrSBe Total domains increased significantly from the premorbid to the current time point. This pattern was not demonstrated in the control participant group.

5.3.6. Mood, personality, empathy and EL

Patients and controls did not differ significantly on median HADS A and HADS D scores. A composite score of the two mood measures, HADS Total, also did not differ between groups. None of the medians for the mood scores were indicative of mood disorder according to the revised criteria (Gibbons et al., 2011). The proportion of participants satisfying ‘caseness’ and ‘borderline case level’ was compared between groups; no significant group differences were found.

Personality domains of the NEO–FFI were also compared between groups. There was a tendency for controls to report higher levels of neuroticism than patients. There was a tendency for patients to report higher levels of conscientiousness than controls. The proportions of patients and controls meeting criteria for ‘extreme levels’ of the personality domains (very high; very low) were also compared between groups. There was a trend for more controls than patients to fulfil criteria for very low levels of extraversion. Significantly more controls than patients fulfilled criteria for very low levels of conscientiousness. There was also a trend for more controls (n=4) than patients (n=0) to fulfil criteria for very high levels of neuroticism. However, the four controls who met criteria for very high levels on the Neuroticism (N) domain, also met criteria for ‘caseness’ on the HADS A, suggesting that the high scores on N might be capturing these participants’ elevated mood levels. When the four control participants showing very high levels of N were removed from the analyses, the trend for between–group differences on this domain disappeared. No between–group differences were found for any of the empathy domains of the IRI measure.

Patients and controls were compared for the presence and degree of emotional lability. Patients showed significantly higher scores on the crying subscale of the ELQ. The overall ELQ score was also significantly higher for patients compared to control participants. There was a tendency for patients to report higher levels of pathological smiling. No difference was observed between the groups for the laughing subscale.
5.3.7. Patient subgroups: medicated and non–medicated patients

A subset of patients were receiving psychoactive medication for disease management (n=15). Since psychoactive medication may affect cognitive performance, this subset of patients was compared with non–medicated patients on the cognitive composites; components and measures of language, memory, behaviour and personality. The patient subsets did not differ significantly on demographic variables. There were no between–group differences for the Executive function or EMOSOC composites. In addition, no differences were found between patient subgroups for any of the Executive function components or the Hayling error measures. Moreover, there were no differences between subgroups for the proportion of patients impaired on the Executive function components or Hayling scores. There was a trend for medicated patients to perform worse on the emotion evaluation subtask of the TASIT than non–medicated patients; the associated effect size was within the medium range, according to Cohen (1988) conventions. The proportion of impaired patients per group on this measure was not significant. There were no significant group differences for any of the remaining EMOSOC components and no group differences for the proportions of patients impaired on these measures.

There were no differences between patient subsets on measures of empathy, behaviour and personality. There was no significant difference between patient groups on the language measure. There was a trend for medicated patients to perform better than non–medicated patients on the delayed cued recall trial of the CVLT. Although not significant, medicated patients also performed better on the immediate recall and short delay recall trials. According to Cohen’s (1988) conventions, the effect sizes associated with these three trials ranged from medium to large. Single–case analysis did not find significant differences between the proportions of impaired patients in each subset for either the language score or the memory trials.

5.3.8. The relative contributions of executive function, personality, mood, empathy and behaviour to emotional processing and social cognition in ALS patients

Correlational analyses identified the following predictors which were entered into a final hierarchal regression model: Age; years of formal education (control variables); Executive function composite; FrSBe Total score, HADS Total and NEO–FFI Openness. The results of the final regression analysis support Hypothesis Three.
Executive function contributed most to the performance of ALS patients on measures of emotional processing and social cognition, with smaller, albeit non–significant, contributions from behavioural, personality and mood factors.

5.4. Discussion of findings

This chapter reports an investigation of cognitive functioning in ALS patients with a focus on executive function and the processing of emotional and social information. It also explores differences in mood, behaviour, personality and empathy between ALS patients and control participants. Finally, it examines the relative contribution of executive function, mood, personality, empathy and behaviour to emotional and social cognition in ALS. This section will consider the position of the study’s findings within the current ALS cognitive literature and discuss its theoretical implications. The limitations specific to the study design are also discussed. Clinical implications, general limitations and recommendations for future research are addressed in the General Discussion (Chapter 7).

5.4.1. Hypothesis One: Profile of executive impairment and changes in emotional processing and social cognition in ALS

It was hypothesised that, consistent with previous reports, the neuropsychological assessment of participants would reveal (i) impaired performance of ALS patients relative to controls on domains of executive functioning and (ii) the processing of emotional and social cognition. The results of the multivariate analyses in Section 5.2.2.1. support this hypothesis by demonstrating that, as a group, ALS participants performed significantly worse than control participants on a super–ordinate variable of the two domains. Univariate analyses showed that patients showed significantly higher (more impaired) domain composite scores than controls. Further support for the hypothesis was provided by the single–case analysis in Section 5.2.2.3. which found significantly higher proportions of patients than controls meeting criteria for impairment across the component scores constituting the composite indices. In addition, Section 5.2.2.4. reports ALS deficits on separate executive function tasks not included in the Executive function composite and also describes impaired ALS performance on a task measuring social cognition.
A. Executive function

Analyses of the individual components of the Executive function composite score showed that ALS patients demonstrated significant performance decrements on the D–KEFS card sorting test relative to controls. The D–KEFS measures several factors of executive function, such as the ability to perceive, form and express conceptual relationships; the initiation of problem–solving behaviour and the ability to inhibit prior behavioural responses so as to abandon established sorting rules in search of novel ones. All participants were screened prior to the test administration with a screening pre–test (see Chapter 4, Section 4.4.3.3.), making it unlikely that these impairments were due to language comprehension or visuoperception difficulties. Instead, the impaired patient performance might reflect generalised deficits in concept formation and/or response initiation alongside a tendency to provide more concrete descriptions of conceptual relationships. Previous studies of concept formation and sorting behaviour in ALS have used the WCST and found inconsistent results (see Chapter 2, Section 2.2.1.1.). Where group differences have been found on the WCST, ALS impairment has been attributed to difficulties with cognitive set–shifting and inhibition. Similarly, the impaired sorting behaviour demonstrated by patients on the current task may provide further evidence for an inability to engage cognitive and behavioural flexibility. Libon et al (2012) reported that patients’ free sorting behaviour on the D–KEFS was associated with scores on tests of verbal fluency and action naming, suggesting that impairments in executive resources and semantic knowledge might contribute to sorting performance. Previous evidence for impaired action knowledge in ALS has been suggested (Grossman et al., 2008); however, the current study did not assess action naming, so was unable to examine if a degraded action/semantic network contributed to patients’ poorer sorting scores.

Further evidence for executive dysfunction in the ALS participants is supported by the findings of proportionally more patients than controls showing impairments on the verbal fluency indices. ALS patients as a group showed a trend for longer latencies (thinking times) on the C–word condition compared to controls, although this trend disappeared when non–parametric data were analysed in a sensitivity analysis. The study supports previous research which has identified verbal fluency impairments in ALS patients after controlling for motor dysfunction (Abrahams et al., 1997; Abrahams et al., 2004; Abrahams et al., 2005a; Abrahams et al., 2005b; Abrahams et al., 2000; Stukovnik et al., 2010), even though group differences were not significant following
the Bonferroni adjustment. More correctly, the results indicate heterogeneity in fluency performance within the ALS group, with only a subset of patients showing impairments.

ALS patients demonstrated normal performance on the Brixton Test, a measure of rule attainment, concept formation and cognitive flexibility (Burgess & Shallice, 1997). The Brixton Test has not been widely used in ALS research, but impairments have been noted in two previous ALS studies (Staios et al., 2013; Taylor et al., 2013), as well as FTD patients (Lough et al., 2006). It is possible that participant characteristics (both patients and controls) in the current study differed from those of other studies which have found group differences on the VFI and Brixton Tests. Chapter 7 explores this issue in more detail as a possible study limitation.

Analyses of the three scores of the Hayling Test revealed variable patient performance across these indices. The latency score is a measure of the difference in the times taken to generate words in the ‘Sensible Completion’ (SC) condition and the ‘Unconnected Sentences’ (US) condition. It offers an index of inhibitory ability for prepotent responses, while controlling for confounds of possible dysarthria. No group difference for this score was found, in keeping with a previous study (Wicks et al., 2009). However, single–case analysis revealed a trend for proportionally more patients than controls to exhibit impairments on this measure. In addition, on average, patients committed significantly more Category A and Category B errors than controls, a finding which has been reported elsewhere (Lillo et al., 2012b). Single–case analysis also revealed a trend for proportionally more patients than controls identified as impaired on the basis of these scores. The presence of Category A responses indicates that patients more often than controls failed to suppress a logically appropriate response upon completing sentences in the US condition. The Category B errors suggest that patients avoided responding with an obviously sensible word but completed sentences with words that were connected in meaning with the subject of the sentence or the sensible word to be suppressed. The presence of these errors further suggests that, compared to controls, patients experienced more difficulty with the response suppression demands of the task. Their presence might also explain why no between–group impairment for the latency score was found: patients may have responded impulsively (i.e. quickly) at the expense of suppression effort. The results corroborate previous findings of inefficient inhibitory process in ALS patients which have used other paradigms, such as the Stroop (Frank et al., 1997; Gibbons et al., 2007; Hanagasi et al., 2002; Rusina et al., 2010; Sterling et al., 2010) and negative priming (NP) tasks (Abrahams et al., 1997; Goldstein
et al., 2011). However, these studies vary in their use of controls for motor impairment and the adoption of the latency score in the current study suggests that a subset of patients may show true inhibition impairments, independent of motor slowing.

B. Emotional processing and social cognition

Following the identification of a between–group effect for the transformed EMOSOC composite score, performance on the individual components of the composite was compared between groups. More detailed analyses comparing between–group performance on individual tests of emotion and social cognition were also conducted. The present investigation revealed that, as a group, ALS patients demonstrated comparable performance with healthy controls on the RME and TASIT subtests. The proportions of impaired cases on these measures were also comparable between groups. However, group differences for all three subtasks of the Happé task were found; single–case analyses revealed proportionally more ALS impairments for the single cartoon abstraction subtask.

Regarding the RME, the current findings are in keeping with those of Cavallo et al, (2011a), who also found that group– and individual–level analyses did not reveal significant differences between ALS patients and controls. Together, these studies’ findings are inconsistent with a smaller study from Girardi et al (2011) who reported a strong trend for between–group differences on this measure. Cavallo et al (2011a) explain that since the RME is a ToM measure that requires the comprehension of social emotions but not social situations, unlike their other experimental task in which group differences were found, normal ALS performance on the RME might be attributed to the measure’s inability to detect select deficits in the understanding social scenarios. A similar argument might suffice for the interpretation of the current study’s findings of RME performance, particularly since group differences were found for the Happé social cartoons and scenario task. However, the TASIT task, which includes subtests that simulate everyday social interaction, did not elicit group differences. Alternatively, intact RME performance for patients in this and Cavallo et al’s (2011a) study might be explained by a lack of impaired emotional processing in patients. Girardi et al (2011) found that patient performance on the RME correlated strongly with performance on a basic emotion recognition task, a measure on which the patient group was also impaired relative to controls. In the current study, ALS patients performed similarly to controls
on the emotional evaluation task (EET) of the TASIT; suggesting the appraisal of basic emotions to be intact in the current patient group.

The lack of group difference for the emotion recognition task in the current study is consistent with recent studies using the same dynamic TASIT EET task in non–demented patients (Savage et al., 2013; Staios et al., 2013). Savage et al (2013) found that within their ALS group which comprised demented and non–demented patients, only the ALS–FTD patients showed impaired emotion recognition on this measure, relative to controls. Although the current study did not directly compare non–demented and demented ALS patients, it lends some support to the notion that emotion processing deficits are not a feature of the non–demented form of the disease. That said, these findings are in contrast with earlier studies that have reported impaired emotion recognition in non–demented patients on static measures of facial emotion (Girardi et al., 2011; Lillo et al., 2012b; Zimmerman et al., 2007), but consistent with others that report no such deficit (Papps et al., 2005; Savage et al., 2013; Staios et al., 2013).

Studies in ALS vary by method and criteria used for screening of cognitive impairment. The inconsistencies across ALS studies might therefore be the result of undiagnosed ALS–FTD patients contributing to mean performance in studies finding positive results. Moreover, the use of psychoactive substances for disease management by some patients might also influence the performance of patient samples, as the current study found a trend for impaired performance of medicated compared to non–medicated patients on this measure (the implication of this finding is discussed more broadly in Chapter 7). Studies of emotional processing in ALS often do not specify psychoactive use as an exclusion criterion, or report and control for such substances. Alternatively, the nature of the TASIT task might aid emotion recognition in patients who would otherwise perform poorly on traditional static emotion tasks. The TASIT task includes other contextual information, such as dialogue and speaker’s intonation, which may assist patients in determining the correct emotion portrayed by the actors. That is to say, non–demented patients may indeed have a select difficulty in decoding ‘rudimentary emotion’ from faces on the basis of structural information alone, but that this difficulty is mitigated in their real–world experiences of emotion recognition through auxiliary cognitive processes that are sensitive to other aspect of emotional display. More studies using both static and dynamic measures of basic emotion identification in non–demented ALS patient samples (e.g. Savage et al, 2013) are needed to substantiate this suggestion.
The current study failed to find evidence that ALS patients are impaired at interpreting higher order social interactions, such as those which incorporate sarcasm and deceit, on measures of realistic social scenarios. This is at variance with Staios and colleagues’ (2013) findings that ALS patients were impaired relative to controls in interpreting simple and paradoxical sarcastic statements. The inconsistent findings might have resulted from differences in sample characteristics between the studies. A comparison of demographic and disease symptom data does not suggest gross discrepancies between patient groups. Furthermore, similar sampling methods and exclusion criteria were applied in both studies. Since Staios and his colleagues did not include a comprehensive measure of executive functioning, it is difficult to compare the relative profiles of cognitive impairment between the patient samples. Nonetheless, distinct executive difficulties existing between the patient groups may have been present and could account for the incompatible results. For example, the previous study found that patients were significantly impaired on the Brixton Test; a result which was not replicated in the current study. Instead, ALS patients in the current research showed impaired performance on the D–KEFS card–sorting task. Both tests are sensitive to rule attainment, adherence and switching; but the rules of the former task are more abstract and responses are not prepotently determined by the stimulus situation (Shallice et al., 1996). The contextual processing required by the Brixton Test (e.g. the anticipation of future pattern sequences) might therefore be more analogous to social rule attainment and adherence in real world environments than that of the D–KEFS. Thus the nature and/or degree of executive dysfunction in patients may have differed between studies, possibly contributing to the different results obtained on the TASIT.

The current study found that the patients showed impaired performance relative to the controls on a task requiring the interpretation of humorous cartoons and social stories. This replicates previous research using the same task in a smaller group of non–demented ALS patients (Gibbons et al., 2007), although in that study group effects on the cartoon subtasks were masked by the heterogeneity of performance within the ALS group. It also resonates with an early study which used the task to assess mental attribution in FTD patients (Snowden et al., 2003). In the current study, between–group effects for accuracy were found for all three subtasks. Unlike the previous studies, effects for the cartoon condition were also found for the single cartoon inference and scenarios subtests: both groups performed worse on the physical compared to the mental condition on the single cartoon task but for the scenarios task, the reverse was
true. This might indicate that the physical cartoon stimuli were more difficult than the mental cartoon stimuli, while the mental stories may have been more difficult than the physical stories. On the paired cartoon subtask, both groups identified the correct (‘funny’) cartoon on a forced–choice trial more often under the mental condition, further indicating disproportionate difficulty between the conditions. Moreover, single–case analyses revealed that proportionally more ALS patients than controls showed impairments on the physical cartoons of the single cartoon subtask. For the same task, only a trend for proportionally more impairments on the mental cartoons was found for patients compared to controls. Patients also showed a trend for proportionally more impairments than controls on the physical story condition compared to controls. Notably, no select ToM deficit was demonstrated by the ALS patients for any of the subtasks, in keeping with patterns of impairment previously found in ALS (Gibbons et al., 2007) and FTD patients (Snowden et al., 2003) on the task. A lack of isolated ToM deficit specific to ALS participants suggests that the poorer overall performance by the ALS participants might be attributed to a general impairment in executive, or inferential, ability in these patients. The contribution of executive function to social cognition in ALS is discussed in Section 5.4.4.

The analyses of errors provided an insight into the qualitative differences in responses between the groups. For both groups, the largest proportion of errors for all three subtests were partial errors, in which participants gave accurate inferences but which were incomplete or not explicitly stated, even after prompting from the researcher. Proportions between groups for these errors were not significantly different. For the single cartoon inference subtask, patients provided proportionally more descriptive responses than controls; indicating that they were able to describe and integrate the contents of the cartoons but failed to draw inferences beyond their contents. This replicates the pattern of errors previously shown by ALS patients (Gibbons et al., 2007). A trend for this error type was again demonstrated by patients relative to controls on the paired cartoon abstraction subtask. In addition, patients showed proportionally more misconstruction errors (faulty inferences) on the paired cartoon and social stories subtasks. Notably, for the cartoon pairs task, both groups committed more misconstruction errors on the physical condition. This affirms the earlier suggestion that the physical cartoons might be harder than the mental cartoons. On the scenario task, while both groups made more misconstructions on the mental condition, there was a strong trend for patients to commit more of these errors on this condition relative to
controls. This indicates that while both groups showed more difficulty with drawing accurate inferences regarding the thoughts, feelings and intentions of characters in the stories than those regarding logical rules of the situations, patients showed a tendency for more difficulty with these ‘mental’ inferences than the controls. This pattern differs from that of the previous studies which showed that FTD and bulbar ALS patients’ errors were characterised by concrete responses, in which participants failed to integrate the contents of the cartoons or stories into a thematic narrative regardless of cartoon or story condition (Gibbons et al., 2007; Snowden et al., 2003). By comparison, concrete responding was relatively rare for both participant groups in the current study. The qualitative differences between these studies may be due to more impaired cognitive status of the FTD and bulbar ALS groups. In the Gibbons et al (2007) study, for example, bulbar patients performed significantly worse than non–bulbar patients and controls (who did not show concrete responding) on background tests of neuropsychological function.

The misconstructions demonstrated by the patient group might relate to the impulsive responding demonstrated by the pattern of errors found for patients on the Hayling task. On items where patients were unable to comprehend the ‘joke’ or the story content fully they may have provided their ‘best guess’ before sufficient reflection. Mean response times did not differ between groups, but time to respond may not be the best index of reflection quality. The descriptive errors found on the cartoon subtasks may relate to the presence of deficient concept formation skills or impaired cognitive flexibility, as indicated by patients’ performance on the D–KEFS. For example, a lack of mental flexibility might prevent patients from conceiving alternative meanings, such as the non–literal interpretation of the stories or cartoons, thereby preventing inferences to be drawn beyond their contents. This might similarly account for the misconception errors as patients offer their own idiosyncratic interpretation instead. For the scenarios subtask, misconstructions might have resulted from the memory demands of the task as, unlike the cartoon trials, stimuli were not presented in full view during participant responding. Patients may have confabulated erroneous inferences because they could not remember specific details of the story, although this is not compatible with the presence of mainly partial errors shown by patients on all three subtasks. On the other hand, these findings might be the result of scoring bias; however, the second rater was blind to the participants’ diagnoses and inter–rater agreements for error responses were high.
The Happé task has previously been criticised for using humour as well as social and non-social situations in the same experimental category (i.e. across both mental and physical conditions) (Cavallo et al., 2011a; Meier et al., 2010). In addition, within the mental condition, the cartoons and stories require both cognitive (thoughts) and emotional (feelings) attribution, with an emphasis on the former. The condition also does not distinguish between first-order and second-order mental state attributions. Selectivity of ToM ability has been shown in ALS patients using other cartoon tasks. Patients have demonstrated deficits in attributing emotional rather than cognitive states to cartoon characters (Cerami et al., 2013), as well as a difficulty inferring the mental states of characters involved in social as opposed to private situations (Cavallo et al., 2011a). The lack of specificity between conditions in the Happé task may render it a less sensitive assay of ToM ability. The use of alternative ToM measures, which differentiate between the subcomponents of ToM or social contexts, might have provided greater scope to identify select deficits in the patients or qualify the relationship between ToM and executive dysfunction in ALS.

The finding that impairments were elicited on the Happé task and not the TASIT social inference subtasks might be due to the greater complexity of the former measure. The Happé task requires the integration of information presented in the abstract form of static cartoons and scenarios; it also requires the effortful expression of this integration into a coherent narrative. The TASIT, by comparison, is a more passive experience. It provides the physical (i.e. visual and auditory) context of the presented situation and requires a simple ‘yes’, ‘no’ or ‘don’t know’ answer. This closed-ended question format may prevent detailed examination of erroneous responses. For example, patients and controls in the current study might have committed errors on the same items, but for distinct reasons. Open-ended questions, such as those from the Happé task, provide a qualitative account of differences in the inferences drawn between the participant groups. The drawback of the open-ended format; however, is that this is more verbally demanding and time-consuming which might preclude participation from patients with severe bulbar symptomology and fatigue. This was applicable to non-participation in the Happé task of the current study.

Furthermore, although stimuli from both tasks include situations of deceit and false belief, the TASIT includes items in which characters are being deliberately sarcastic (i.e. verbal irony), while the Happé task includes stimuli in which characters find
themselves in ironic situations (i.e. situational irony), but not necessarily experiencing another character’s ridicule. The manipulation of ridicule has been found to affect healthy participants’ ratings of sarcasm but not irony in written passages of social conversation (Lee & Katz, 1998). The presence of a ‘victim’ in the TASIT scenarios may therefore have aided the detection that sarcasm was at play in the enacted exchange, whereas the detection of irony on some items of the Happé subtasks relied on the participant’s appreciation that the outcome of the scenario was incongruous to what is generally expected; i.e. that the ‘order of things’ had been violated (Lucariello, 1994). Without the benefit of additional cueing, the latter detection exercise might have been more difficult or required more effortful abstraction.

C. Other cognitive domains

Although not a focus of the current research, memory and language were also examined as part of the neuropsychological battery. The ALS group did not differ significantly from the control group on either domain at the group or individual level.

Findings of memory impairments in ALS patients have been inconsistent for both verbal and visual stimuli (see Chapter 2, Section 2.2.1.3.). Where they are present, they are often interpreted as secondary to executive impairment. This position is supported by a meta–analysis which found a significant effect size for immediate but not delayed verbal memory (Raaphorst et al., 2010), a pattern of performance typically associated with frontally–mediated executive dysfunction (Lezak, 2004). However, recent evidence from a population study suggests that global memory impairment, independent of executive dysfunction, may exist in ALS (Phukan et al., 2012). While the current results provide evidence for executive dysfunction in the patient group, there is no evidence of executive–related memory disturbance. Although, the study relied on only one attenuated measure of verbal memory; a more thorough assessment of both verbal and visual memory may have rendered a different set of results.

The study did find a trend for performance differences on a delayed cued recall trial between medicated and non–medicated patients, with medicated patients performing better on this trial. The enhancing effects of antidepressants on memory processes in healthy participants have been indicated by meta–analysis (Repantis et al., 2009). Thus, SSRIs may have influenced patients’ performance on the CVLT in the current study. Alternatively, these findings might be influenced by the presence of an unexamined variable or interaction. Single–case analysis found no indication of memory impairment.
in the medicated group, suggesting that the effects of medication on performance for this trial, if any, were minimal. The inclusion of patients using psychoactive medication as a limitation specific to this study, as well as its implications for future ALS research are discussed in Chapter 7.

Language was assessed using a measure of confrontation naming. No ALS impairment was indicated, a result that contributes to the variability in findings associated with ALS performance on such measures (see Chapter 2, Section 2.2.1.2.). The use of only one language test in ALS cognitive research is pervasive; presumably due to the emphasis on executive dysfunction within the disease and the limitations imposed by patients' disability and fatigue on testing procedures. These reasons were, at least, applicable to the current study's design. The few language studies in non–demented ALS have identified impairments on measures of comprehension, syntax and spelling, verb processing and discourse (see Chapter 2, Section 2.2.1.2.). Further, recent evidence which used a comprehensive battery of language and executive function tasks suggested that language impairment in patients may be as prevalent if not more prevalent than executive dysfunction (Taylor et al., 2013). The use of only one language measure in the current investigation may therefore have limited its efficiency in identifying more subtle language deficits and should not be over interpreted.

5.4.2. Hypothesis Two: Profile of behavioural change in ALS

It was hypothesised that ALS patients would show higher premorbid and current behavioural dysfunction than controls. The results reported in Section 5.2.3. do not support this hypothesis. Patients self–ratings of premorbid behaviour were lower (less impaired) than controls’ retrospective self–ratings for the domains of Apathy, Executive Dysfunction and the Total FrSBe score. For the current scores, only a trend for a significant difference between groups for the Apathy subscale was observed. However, while patients reported increased behavioural dysfunction from premorbid to current ratings for the Total score and the domains of Executive Dysfunction and Disinhibition, the opposite direction of change was observed for controls. In both groups, levels of Apathy increased in the same direction, but patients reported a greater increase on this domain.

A comparison of the current patients’ mean self–rated FrSBe domain scores with other studies using self–report data are shown in Appendix VIII.a.. Apart from one study
(Chio et al., 2010), a pattern of predominant apathy characterises patients’ current behaviour across the samples (Girardi et al., 2011; Woolley et al., 2010a). The proportions of patients’ self–ratings meeting behavioural impairment on the current domain scores are greater than that reported by Witgert et al (2010), the largest study of behaviour in ALS to date (n=225, see Appendix VIII.b.). However, only informant data were used in that study and lower proxy ratings relative to patients has been indicated in other research (Girardi et al., 2011; Woolley et al., 2010a). The current finding of higher retrospective self–ratings for controls relative to patients has previously been noted in a UK study (Girardi et al., 2011). This might reflect pre–existing personality traits in the control participants which differ in some way from patients (see Section 5.4.3. and discussion in Chapter 7). Alternatively, it might suggest that the available FrSBe (American) norms are not appropriate for use in British samples as they may overestimate impairment.

A key finding from the behavioural results was that the direction and magnitude of change from retrospective to current behaviour differed between groups on the FrSBe domains. The greatest change for patients occurred on the Apathy domain, which examines initiation, motivation, persistence, interest in others and blunted affect. Increased apathy is one of the most commonly reported behavioural symptoms in ALS patients (see Chapter 2, Section 2.2.2.1.), but concern has been raised regarding some apathy items on the FrSBe which may load on motor disability or mood (Gibbons et al., 2008; Girardi et al., 2011; Witgert et al., 2010). In the current study, the patients’ increased ratings over time were unlikely affected by anxiety and depression, as median current mood scores did not differ from the control group and did not indicate mood disorder. Previous studies have also demonstrated raised apathy in non–depressed ALS patients (Gibbons et al., 2008; Grossman et al., 2007; Lillo et al., 2011; Lomen-Hoerth et al., 2003; Wicks et al., 2009; Witgert et al., 2010). All participants in this study were instructed to rate their behaviour independent of their physical (dis)ability; however, for patients responding to certain items (e.g. “Am slow moving, lack energy, inactive” or “Sit around doing nothing”) this may have been unrealistic, given the physical and practical consequences of the disease.

Smaller changes in patients’ self–ratings over time were shown on the Executive Dysfunction and Disinhibition subscales. The former domain assesses attention, planning, shifting responding and self–monitoring while the latter domain examines impulsivity and inappropriate social behaviour. These domains are less likely to be
affected by motor dysfunction (Witgert et al., 2010), thus the endorsements of raised post–illness levels by patients on these domains may substantiate the presence of true behavioural change in ALS. For the Executive Dysfunction and Disinhibition subscales, a decrease on these measures in the healthy control participants might reflect a tendency to attribute positive effects of ageing (i.e. experience and wisdom) on behaviours which have connotations of immaturity (e.g. “Do risky things just for the heck of it”). Another more obvious explanation for these patterns of results, applicable to both participant groups, is the influence of recall bias, the effect of which is impossible to measure.

Although not a formal investigation of the study, patients’ increased FrSBe scores over the course of their disease might correspond to their performance on tests of executive functioning. The D–KEFS card sorting task, a measure on which patients’ group performance was impaired relative to controls, requires participants to sustain attention, initiate and shift responding while maintaining motivation to persevere with the task demands; similar processes to those believed to be measured by the Apathy and Executive Dysfunction subscales. Further, the pattern of errors shown by ALS patients on the Hayling Test may indicate a tendency for impulsiveness and/or difficulty with inhibitory control, processes to which the Disinhibition subscale is believed to be sensitive. The relationship between patients’ behavioural change and performance on measures of emotional processing and social cognition is discussed in Section 5.4.4. The profile of the ALS patients’ cognitive and behavioural profile is discussed more broadly in Chapter 7.

In summary, patients’ self–rated scores on the FrSBe in the current sample do not indicate greater levels of behavioural dysfunction in relation to controls. However, changes in behaviour scores for patients over the course of their disease appear to be more substantial and in some cases differ in direction from controls over time. The behavioural change in the current patients is characterised by raised levels of apathy since before the onset of their disease, with more subtle changes in dysexecutive and disinhibited behaviours in the same direction.

5.4.3. Exploratory Research Question One: Mood, self–reported personality and empathy in ALS

Patients and controls were matched for mood, an aim to ensure that identified between–group differences on neuropsychological tests or responding on behavioural inventories
were not an artefact of differences on this variable. Median scores were not indicative of mood disorder and the proportions of participants per group meeting revised criteria for ‘caseness’ did not differ. Studies investigating mood in ALS have reported inconsistent estimates of elevated depression and anxiety in patients (see Chapter 2, Section 2.2.3.). Despite the variability in findings, the view that mood disturbance is rare in ALS persists. The current results would appear to support this view; however, the influence of selection bias should not be underestimated as patients who self-select themselves for research studies are unlikely to be suffering from low or disturbed mood. Further, it is possible that the study may have underestimated the prevalence of psychological change in the ALS sample due to the exclusion of patients with severe disability (Hogg et al., 1994; Hunter et al., 1993). Moreover, although the revised HADS measure used in this study shows satisfactory reliability and validity for use in ALS patients (Gibbons et al., 2011), it is not formally diagnostic of mood disorder. Furthermore, while a Rasch analysis supported the suitability of the revised HADS for the ALS population (Gibbons et al., 2011), there is no data on its appropriateness for use in the healthy adult population. Consequently, this might affect the application of the revised ‘caseness’ criteria to this participant group as well as comparisons of ‘caseness’ between the groups.

Patients’ self-rated scores on the Big Five personality domains did not differ significantly from those of control participants. A trend for higher levels of neuroticism in controls than patients was found. Similarly, a trend for more controls scoring within the very high range of the Neuroticism scale was observed. Four controls and no patients met criteria for very high levels of neuroticism. High scores on this scale suggest susceptibility for psychiatric problems but are not a measure of psychopathology per se (Costa & McCrae, 1992). Congruously, the four controls who scored in the very high range on this domain showed ‘caseness’ levels of anxiety on the HADS mood measure, suggesting that the personality scale may have captured the anxious dispositions of these participants. When these cases were eliminated from the analysis, the trend for between–group differences disappeared.

Patients showed a trend for higher levels on the domain of Conscientiousness than controls. This scale assesses facets of personality, such as self-discipline, work ethic and diligence (Costa & McCrae, 1992). Initially these results appear to resonate with findings from Brown & Mueller (1970) who described the ten patients in their study as showing a high level of internal locus of control and ‘hard–working’ behavioural styles.
However, proportionally more controls than patients showed very low levels of conscientiousness in further analyses. This suggests that the between–group difference in mean ratings for the Conscientiousness domain arose from more controls reporting very low levels of conscientiousness, rather than from a high proportion of patients displaying high levels of this trait. Therefore the study fails to support Brown & Mueller’s early finding. Of note, the results also do not replicate a previous study using the NEO–PI, which found that ALS patients’ mean scores for levels of openness were lower than those of a progressive disease control group (Grossman et al., 2006). Scores on this domain correlated with performance on the EMOSOC composite score; this relationship is discussed in Section 5.4.4.

The IRI subscales were designed to capture different facets of empathy (Davis, 1980); no differences between patients and controls on any of the domains were found. This may indicate that, unlike ALS–FTD, reduced empathic ability is not a feature of non–demented ALS. However, premorbid and current scores were not compared in the current sample, so the results are limited in their ability to infer individual patient changes since the onset of ALS.

Some caveats concerning the assessment of personality and empathy in the current study deserve consideration. The NEO–FFI is based on the Five–Factor Model (FFM) which, although widely accepted, has faced criticism for its adoption of a data–driven rather than a theory–driven approach to personality (a clustering of trait adjectives under factor analysis) and its limited scope of personality traits (see Block, 2010 for review). As such, personality characteristics which might be specific to the ALS patients (e.g. egotism, risk–taking) but not considered within the model (Paunonen & Jackson, 2000) were not assessed. In addition, the NEO–FFI is an abbreviated version of the NEO–PI, and collapses different facets of personality under each domain. This might have obscured differences or associations occurring at the lower–order levels of the scale (Schnabel et al., 2002).

The IRI was chosen in preference to other empathy measures, such as The Empathy Quotient (Baron-Cohen & Wheelwright, 2004), because it differentiates empathy into ‘cognitive’ and ‘emotional’ components, in keeping with neuroscience models of the construct (Decety & Jackson, 2006; Shamay-Tsoory et al., 2009). Criticisms regarding the ecological–validity of the questionnaire have been raised (Dziobek et al., 2008). Some of the items ask respondents to appraise their feelings towards hypothetical
situations involving fictional characters from novels or films rather than everyday personal exchanges involving other people (e.g. “After seeing a play or film, I have felt as though I were one of the characters”). Some responses therefore may not accurately reflect patient’s empathic behaviour in everyday life.

As already suggested, the FrSBe may be confounded by items which load on physical ability, a caveat which extends to the IRI and NEO–FFI. In addition, none of the measures assessed social desirability which may have attenuated, inflated or mediated relationships within the data obtained from participants. Furthermore, other biases which may have influenced responding in the patient group, such as psychological coping or denial mechanisms, were not assessed.

5.4.4. Hypothesis Three: The contributions of executive function, behaviour, mood, personality and empathy to emotional processing and social cognition in ALS

Hypothesis Three predicted that emotional processing and social cognition in ALS would be best predicted by executive function relative to behaviour, mood, personality and empathy. The results of Section 5.2.9. support this hypothesis.

The study demonstrated that executive dysfunction was the only predictor of socio–emotional processing in ALS when entered into a model comprising mood, personality and behaviour, while controlling for age and years of formal education. Correlational analyses did find that measures of apathy and dysexecutive behaviour correlated with the EMOSOC composite score, resonating with a previous study which found an association between apathy scores and a preference judgement task (Girardi et al., 2011). The study is also the first to consider the influence of personality and empathy on performance on social cognitive measures. The NEO–FFI Openness T–score was the only personality domain to correlate significantly with the EMOSOC composite. People who score low on this trait typically feel emotion less intensely than others and are less attentive to forms of experience, such as fantasy and intellectual curiosity (McCrae & John, 1992). The presence of this relationship is therefore meaningful. Surprisingly, levels of empathy did not correlate with the composite score; a relationship between empathy and socio–emotional impairments has been demonstrated in FTD patients (Shany-Ur et al., 2012). An absence of a significant correlation between these scores might indicate that self–perceived current empathic ability does not underlie socio–
emotional processing in non-demented ALS. Alternatively, the components of EMOSOC composite may not have measured empathy.

When personality and behaviour were entered into the model along with a measure of overall mood, the addition of these variables did not improve the variability explained in the composite and needless to say none were found to be significant predictors of the EMOSOC score. These findings may imply that ALS–related executive dysfunction, may sufficiently explain variability in socio–emotional processing above and beyond individual differences in mood, personality and behaviour. However, patients in the current sample did not show scores indicating clinical behaviour, mood disturbance or gross personality change. The interpretation of the outcome created by the regression procedure is therefore restricted to those ALS patients who do not show impairment on these domains.

The interpretation of the influence of executive function on emotion processing and social cognition in ALS is controversial. Several studies of non–demented ALS have noted moderate to strong relationships between patients’ executive dysfunction and impairments on measures of emotion recognition and ToM. Nonetheless, evidence from individual–case analysis suggests that patients may be exclusively impaired on either domain, or show concurrent impairments (see Chapter 2, Section 2.3.2.4.). Similarly, two patients in the current study showed concurrent impairments on the composites, five patients showed isolated impairments on the Executive composite and four patients showed isolated impairments on the EMOSOC composites (see Section 5.2.2.3., Table 5.13.). This profile suggests that for at least four patients, impairments on the measures of emotional processing and social cognition might have occurred independently from deficits in executive function. Nonetheless, three patients showed dissociations between their performances on the composites; the directions of these dissociations indicated that all patients were impaired on the Executive composite but unimpaired on the EMOSOC composite. No dissociation showed the reverse direction (i.e. impaired on EMOSOC but unimpaired on Executive composite). This result indicates that none of the isolated impairments on the EMOSOC composite described above were dissociated from patients’ performances on the Executive composite. Therefore, it remains possible that poor performance on the Executive function composite, while not poor enough to qualify for a deficit, might have contributed to the patients’ deficits on the EMOSOC composite.
Overall, the current study supports the position that deficits in emotional processing and social cognition in ALS reflect a primary deficit in executive function. However, the patients in the current study did not display significant impairments on several of the experimental tasks, such as the ability to recognise basic and social emotion or the ability to attribute mental and emotional states to characters in enacted scenarios. Instead, patients showed a profile of predominantly executive dysfunction, and the social cognition task on which impaired performance was elicited may have loaded more on executive resources than the other experimental tasks (see Section 5.4.1.).

5.4.5. Broader theoretical implications

A. Implications for the ALS – FTD cognitive continuum

The current research adopted a focussed study of executive functioning, emotional processing and social cognition in non–demented ALS patients. The neuropsychological battery included tests which have demonstrated sensitivity to impairments on these domains in patients with ALS–FTD and FTD, referred here collectively as ALS–FTD/FTD patients. The investigation of executive functioning in the current ALS group revealed impairments that are similar in nature to those reported in ALS–FTD/FTD. In particular, group level analyses showed that patients displayed difficulties with category formation, problem–solving and inhibitory control, while single–case analysis revealed that a subset of patients showed impairments on measures of verbal fluency. Similarly, significant behavioural differences did not exist between patients and matched controls at the current time point. However, increases in apathy, as well as dysexecutive and disinhibited behaviour since the onset of ALS were reported by the patients. Common cognitive processes and behavioural domains have been implicated in the cognitive profile of ALS–FTD/FTD patients (see Chapter 2, Section 2.1).

On the other hand, the investigation of emotional processing and social cognition failed to demonstrate impairments in emotion recognition with only partial support for impaired ability on a social cognition task. Impairment on the latter task was most likely due to a general impairment in executive function, rather than a select ToM deficit per se. As in ALS, the relationship between executive function and ToM in FTD is controversial. Executive impairment in FTD may mask specific ToM deficits, with more severe executive dysfunction associated with greater ToM impairment (Snowden et al., 2003). It has also been argued that executive function in FTD may support the general ability to process cartoons and stories but is not fundamental to the attribution
of mental states to the characters (Lough et al., 2006). A lack of specific ToM impairment displayed by patients in the current study is in keeping with Snowden et al’s (2003) observations in FTD patients. Nonetheless, dissociation of ToM and executive function has been demonstrated in ALS patients elsewhere (see Chapter 2, Section 2.3.2.4). Furthermore, the errors displayed by the current patients on the social cognition task differed from those displayed by a previous FTD group (Snowden et al., 2003). However, the qualitative differences between the groups may exist due to the more impaired cognitive status of the FTD patients. Deficits in the recognition of basic and social emotion are pronounced in bvFTD and some SD patients (Eckart et al., 2012; Fernandez-Duque & Black, 2005; Keane et al., 2002; Kipps et al., 2009; Omar et al., 2011; Rosen et al., 2004; Rosen et al., 2002; Snowden et al., 2008); whereas in non-demented ALS patients the evidence for impairment is inconsistent (see Chapter 2, Section 2.3.). One cross-sectional study has suggested that these deficits only emerge with the presence of FTD (Savage et al., 2013). Since the study excluded ALS–FTD patients it is not known whether the cognitive profile of current sample represents an intermediate position between classical ALS and the dementia forms of disease. Nonetheless, the primary executive dysfunction present in these patients supports the existence of ALS–FTD/FTD cognitive impairment within the non–demented ALS.

Evidence for the progression of FTD–like impairments in ALS patients provides the strongest support for a cognitive continuum between ALS, ALS–FTD and FTD. Without longitudinal data, it is difficult to determine whether the predominant pattern of executive impairment in the current patients will evolve to encompass socio–emotional impairments and eventually a full blown FTLD syndrome. The few longitudinal investigations of cognition in non–demented ALS have provided mixed evidence for progressive cognitive deterioration in such patients (see Chapter 2, Section 2.2.1.7.), and none have considered the longitudinal effects of ALS on emotion processing and social cognition. This raises an interesting recommendation for future research which will be discussed further in Chapter 7.

B. Implications for underling neural substrates in ALS cognitive change

Growing evidence from neuroimaging research has associated the profile of cognitive impairment in ALS with underlying cerebral dysfunction (see Tsermentseli et al., 2012 for review). The majority of studies have focused on the neural underpinnings of executive dysfunction, with relatively little exploration of possible correlates of
language disruption and changes to emotion and social processing, although neuroimaging studies in these latter areas are accumulating (Abrahams et al., 1996; Abrahams et al., 2004; Abrahams et al., 2003; Cerami et al., 2013; Goldstein et al., 2011; Grossman et al., 2008; Lule et al., 2007; Palmieri et al., 2010). In conjunction with the emerging cognitive neuroimaging literature in ALS, the current research provides possible insight into the neurological substrates of cognitive dysfunction in non–demented patients.

While no neuropsychological test is a pure assay of neuronal function, the current results indicate a profile of predominantly frontally–mediated executive impairment in the ALS group, with relative sparing of cognitive functions associated with emotion and social processing. In particular, patients demonstrated impairments on executive tasks which have been strongly associated with the functioning of frontal structures in ALS patients, such as the DLPFC and AC (Abrahams et al., 1996; Abrahams et al., 1995; Abrahams et al., 2004; Abrahams et al., 2003; Kew et al., 1993a). Furthermore, patients displayed a predominant pattern of increased apathetic behaviour since ALS onset; this pattern has previously been associated with WM reductions in the AC and right frontal gyrus (Tsujimoto et al., 2011; Woolley et al., 2011). By contrast, preserved emotion recognition, ToM and empathy in the current sample would suggest intact functioning of the OFC and/or vmPFC, which are regions strongly implicated in these domains (Eslinger, 1998; Gallagher et al., 2000; Heberlein et al., 2008; Hornak et al., 2003; Hornak et al., 1996; Shamay-Tsoory et al., 2009; Shamay-Tsoory et al., 2005; Stone et al., 1998). However, the contribution of OFC functioning to performance on traditional tests of executive function tasks has been suggested (Bertoux et al., 2012; Collette et al., 2001; Zald & Andreotti, 2010). As such, the error pattern demonstrated by the current patients on the response inhibition task has been associated with OFC impairment in lesion and dementia groups (Hornberger et al., 2010; Volle et al., 2012); providing partial support for other studies which have implicated this brain region in non–demented patients (Meier et al., 2010; Tsujimoto et al., 2011). Early OFC involvement is indicated in bvFTD and is suggested to account for the invariable breakdown in emotional and social behaviour associated with the disease (Rascovsky et al., 2011; Snowden et al., 2001; Wittenberg et al., 2008). The overall pattern of performance by the current ALS patients may suggest that while OFC dysfunction was sufficient to produce impairments on the response suppression task, it was not severe enough to elicit deficits in socio–emotional processing that are attenuated to those of
bvFTD patients. This may also explain why reduced empathy, personality change and minimal behavioural dysfunction, such as disinhibition, were not present in the current sample.
6. Caregivers of ALS patients

**Overview**

A primary aim of the work reported in the current chapter is to examine the impact of ALS on spousal caregivers of patients with the disease. In particular, this chapter will report findings from an investigation of four caregiver outcomes, namely mood, perceived burden, strain and marital satisfaction. It will attempt to determine the relative contribution of disease symptoms, patient cognition (as quantified by objective measures) and caregiver perceptions of cognitive–behavioural function to variability in these outcomes. For exploratory purposes, a comparison of caregivers’ and patients’ perceptions of patients’ levels of empathy, behaviour and personality are also compared. Whether caregiver–patient differences in the perceptions of these variables are associated with caregiver outcomes is also explored.

6.1. Introduction and hypotheses

Chapter Three provided an overview of a limited area within ALS research which is concerned with the experiences and challenges faced by spouses through caring for their ill relative. Early studies focussed on the consequences of patients’ mood and disease symptoms on the outcomes of caregivers. In recent years, the growing evidence for cognitive–behavioural change in non–demented ALS patients has shifted attention towards the impact of such changes on the caregiver. These studies have highlighted the importance of patients’ cognitive–behavioural changes, above and beyond their physical decline, to caregivers in terms of their mood, perceived strain and burden. The few studies which have explored the impact of ALS on the spousal relationship have observed associations between caregivers’ perceived marital quality and their perceptions of behavioural, communicative and psychosocial changes in their partners. These studies have relied on informant–reports of cognitive–behavioural change in patients and have not included objective measures of patients’ neuropsychological performance. ALS patients have shown impairments on standardised measures of executive function and, more recently, changes on measures that examine the processing of emotional and social information. No research to date has investigated whether patients’ test performance in these cognitive domains contributes to caregivers’ experiences of their spouse’s illness. In addition, little research has compared the perceptions of caregivers and their spouses on factors outside of the patient’s behaviour,
such as personality and empathy. Furthermore, there has been no exploration of caregivers’ perceptions of their spouse’s personality and empathy in the context of perceived cognitive–behavioural change and the consequences of these on caregiver outcomes.

**Hypothesis Four: Predictors of caregiver wellbeing**

The current study tests the hypothesis that objective measures of cognitive function and caregiver–perceived behavioural impairment in patients with ALS will contribute significantly to caregiver wellbeing (in terms of mood, perceived burden and strain), above and beyond patients’ disease status and symptoms. This hypothesis will be examined in Section 6.2.3.

**Hypothesis Five: Predictors of caregiver marital satisfaction**

The current study tests the hypothesis that objective measures of cognitive function and caregiver–perceived behavioural impairment in patients with ALS will contribute significantly to caregivers’ perception of marital satisfaction, above and beyond patients’ disease status and symptoms. This Hypothesis will be examined in Section 6.2.3.

**Exploratory Question Two: Comparisons between patients’ and caregivers’ perceptions of patients’ behaviour, empathy and personality**

This study explores differences between patients’ and caregivers’ perceptions of patients’ behaviour, empathy and personality and whether such differences are associated with caregiver outcomes (in terms of caregiver mood, perceived burden, strain and marital satisfaction). The study will also explore if caregivers’ perceived changes in patients’ personality and behaviour are associated with caregiver outcomes. This question is explored in Section 6.3.
6.2. Results

6.2.1. Participant demographics

A. Caregivers

Table 6.1. summarises the demographic information for the caregiver group (n=35). Four caregivers declined to report their date of birth, so average age was calculated from 31 participants. The average age of the caregiver group was approximately 58 years. All patient–caregiver dyads were married and had been so for an average of 32 years prior to the patient’s illness. The average number of years that caregivers and patients had been in a relationship was 33 years. The majority of caregivers in the study were female. Only three caregivers had contacted a GP or psychiatrist regarding mental health issues (prior to the onset of their partner’s ALS).

B. Demographics and clinical profile of respective patients

The demographic and disease profile of the patients whose spouses participated in the study are shown in Table 6.2. Patients had an average disease duration (months since symptom onset) of less than three years. The average diagnostic delay (months since symptom onset to diagnosis date) was approximately 15 months. Average age at time of symptom onset was approximately 61 years. Approximately 77% of patients had limb–onset disease. The majority of patients were receiving Riluzole, while 9 patients were receiving medication with psychoactive properties.

Table 6.1.: Caregiver demographics

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.7</td>
<td>(10.5)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.1</td>
<td>(3.7)</td>
</tr>
<tr>
<td>Relationship (years)</td>
<td>33.2</td>
<td>(13.0)</td>
</tr>
<tr>
<td>Relationship (years) before partner’s illness</td>
<td>31.6</td>
<td>(13.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>25</td>
<td>(71.4)</td>
</tr>
<tr>
<td>Men</td>
<td>10</td>
<td>(28.6)</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>35</td>
<td>(100.0)</td>
</tr>
<tr>
<td>Mental Health*</td>
<td>3</td>
<td>(8.6)</td>
</tr>
</tbody>
</table>

*Mental health=previous contact with a GP or psychiatrist regarding mental health.
Table 6.2.: Demographics and clinical profile of disease for ALS patients

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>N (%  )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60.9 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>14.2 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Months since onset</td>
<td>30.4 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Months since diagnosis</td>
<td>14.8 (12.2)</td>
<td></td>
</tr>
<tr>
<td>Age at symptom onset</td>
<td>58.6 (8.5)</td>
<td></td>
</tr>
<tr>
<td>ALFSFRS–R total score (max 48)</td>
<td>34.1 (8.2)</td>
<td></td>
</tr>
<tr>
<td>ALFSFRS–R bulbar severity score</td>
<td>9.3 (3.0)</td>
<td></td>
</tr>
<tr>
<td>ALFSFRS–R Limb severity score</td>
<td>14 (6.0)</td>
<td></td>
</tr>
<tr>
<td>ALFSFRS–R Respiratory severity score</td>
<td>10.8 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Median Disease progression rate†</td>
<td>0.46 (0.0/0.3)*</td>
<td></td>
</tr>
<tr>
<td>Epworth Sleepiness Scale Score</td>
<td>3.3 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Region of onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N ( %)</td>
<td></td>
</tr>
<tr>
<td>Limb</td>
<td>27 (77.1)</td>
<td></td>
</tr>
<tr>
<td>Bulbar</td>
<td>8 (22.9)</td>
<td></td>
</tr>
<tr>
<td>Currently receiving Riluzole</td>
<td>28 (80.0)</td>
<td></td>
</tr>
<tr>
<td>Currently receiving psychoactive medication</td>
<td>9 (25.7)</td>
<td></td>
</tr>
<tr>
<td>Mental Health**</td>
<td>6 (17.1)</td>
<td></td>
</tr>
</tbody>
</table>

∞ ALFSFRS–R: bulbar= items 1–3; Limb= items 4–9; respiratory=items 10–12; † Disease progression rate=(48-ALFSFRS–R Total) /months since symptom onset.* MAD/IQR ** Mental health= previous contact with a GP or psychiatrist regarding mental health.
6.2.2. Caregiver outcomes

6.2.2.1. Caregiver mood

The mean depression and anxiety levels for caregivers and their partners are summarised Table 6.3. The revised HADS scoring scheme (Gibbons et al., 2011) was used for both groups for purposes of comparison. A total score for overall mood, HADS Total, was calculated for the purpose of subsequent analyses. Caregivers reported significantly higher scores than the patient group for HADS A, HADS D and HADS Total scores. However, according to Gibbons et al (2011) criteria, the average level of anxiety was within the ‘borderline case level’ for both groups. The average level of depression for both groups was within the ‘non–case level’.

The proportion of participants per group who scored within the ‘case’ range of the HADS domains was also examined (see Table 6.4.). Significantly more caregivers than patients satisfied criteria for borderline and case–level anxiety. Significantly more caregivers than patients satisfied criteria for case–level depression. However, only the ratio for borderline case anxiety between groups remained significant following a Bonferroni correction (adjusted \( p < .008 \)).

Table 6.3.: HADS D and HADS A scores

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>( t(df) )</th>
<th>( p )</th>
<th>( d )</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caregivers (n=35)</td>
<td>ALS (n=35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS A</td>
<td>7.9 (3.8)</td>
<td>4.3 (3.7)</td>
<td>-3.97 (68)</td>
<td>(&lt;.001^*)</td>
<td>0.95</td>
</tr>
<tr>
<td>HADS D</td>
<td>4.3 (3.2)</td>
<td>2.5 (2.1)</td>
<td>-2.76 (55.8)</td>
<td>(.008^*)</td>
<td>0.66</td>
</tr>
<tr>
<td>HADS Total</td>
<td>12.2 (5.9)</td>
<td>6.9 (5.3)</td>
<td>-4.01 (68)</td>
<td>(&lt;.001^*)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

\( p \)–values from two–tailed \( t \)–test. Uncorrected significant results shown in \textbf{bold}–\( p < .05 \). Results significant following Bonferroni correction are shown in \textbf{bold}^*–\( p < .016 \). \( d \), Cohen’s \( d \); 95% CI for difference between means.

\(^6\) Gibbons \textit{et al} (2011) revised cut–offs: HADS A borderline case (7–8); HADS A case–level (≥9); HADS D borderline case (5–7); HADS D case–level (≥8); HADS Total possible case (17–20), HADS Total probable (≥21).
Table 6.4.: Proportions of participants by group meeting HADS criteria

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>ALS (n=35)</th>
<th>X² (df)</th>
<th>p</th>
<th>φ_c</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregivers (n=35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS A Borderline cases</td>
<td>10 (28.6)</td>
<td>1 (2.9)</td>
<td>8.74 (1)</td>
<td>.003*</td>
<td>.35</td>
<td>0.1; 0.4</td>
</tr>
<tr>
<td>HADS A cases</td>
<td>13 (37.1)</td>
<td>5 (14.3)</td>
<td>4.77 (1)</td>
<td>.03</td>
<td>.26</td>
<td>0.02; 0.4</td>
</tr>
<tr>
<td>HADS D Borderline cases</td>
<td>7 (20)</td>
<td>7 (20)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>-0.2; 0.2</td>
</tr>
<tr>
<td>HADS D cases†</td>
<td>7 (20)</td>
<td>0 (0)</td>
<td>—</td>
<td>.01</td>
<td>.33</td>
<td>0.1; 0.4</td>
</tr>
<tr>
<td>HADS Total possible†</td>
<td>3 (8.6)</td>
<td>1 (2.9)</td>
<td>—</td>
<td>.49</td>
<td>.12</td>
<td>-0.1; 0.2</td>
</tr>
<tr>
<td>HADS Total probable†</td>
<td>5 (14.3)</td>
<td>1 (2.9)</td>
<td>—</td>
<td>.13</td>
<td>.20</td>
<td>-0.0; 0.3</td>
</tr>
</tbody>
</table>

*p-values from two-tailed Chi–square test except † Fisher–Boschloo test. Uncorrected significant results shown in **bold–p<.05. Results significant following correction are shown in **bold*–p<.008. φ_c, Cramer’s V. 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions.

6.2.2.2. Caregiver strain

*Morris Strain Scale (MSS)*

Results are reported for 35 caregivers. The mean total score for the strain scale was 26.9 (SD=5.3, possible range of scores: 6 – 42). An investigation of correlations of the scale dimensions found that currently felt strain correlated positively with caregivers’ anticipation of strain felt in a year’s time (r=.50, p=.002); how much caregivers perceived the patient’s illness was affecting other areas of the caregiver’s life (r=.68, p<.001) and how much control caregivers felt they had over their reaction to their partner’s illness (r=.64, p<.001).
6.2.2.3. Caregiver burden

One caregiver did not complete the ZBI, therefore results are reported for 34 caregivers. The mean score for total burden was 29.4 (SD=14.1; maximum possible score: 88). A cut–off score for the ZBI total score of 17 or higher indicates a high level of burden (Bedard et al., 2001; Lillo et al., 2012a; Zarit et al., 1980). When this criterion was applied in the current study, 28 (82.4%) of the caregivers reported a high level of burden (see Figure 6.1.).

Figure 6.1.: Proportion of caregivers reporting high level of burden

![Proportion of caregivers reporting high level of burden](chart.png)

n=34.
6.2.2.4. Caregiver marital satisfaction

Three caregivers did not complete the MIS. Therefore, results are reported for 32 participants. Caregivers rated the quality of their marital relationship with the patient currently and two years prior to the onset of the patient’s illness. A total score for both premorbid and current marital satisfaction was obtained from summing 24 items of the scale (maximum possible score: 96; higher scores indicates higher marital satisfaction). Scores for both timeframes are shown in Table 6.5. A paired sample $t$–test showed a significant difference between premorbid and current ratings, with caregivers rating their marital satisfaction as lower since the onset of their partner’s ALS.

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>$t(df)$</th>
<th>$p$</th>
<th>$d$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premorbid</td>
<td>76.1 (15.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>70.2 (18.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t(df)$</td>
<td>3.04 (31)</td>
<td></td>
<td>.005</td>
<td>0.35</td>
<td>1.9; 9.8</td>
</tr>
</tbody>
</table>

N=32, $p$–values from two–tailed paired sample $t$–tests. Significant results shown in **bold** $p$<.05. SD, standard deviation.; $d$, Cohen’s d for paired samples, 95% CI, confidence interval for differences between means.
6.2.3. Predictors of caregiver outcomes

The current study set out to recruit a minimum of 49 patients and their spouses (see power analysis, Chapter 4, Section 4.6.2). However, while 55 patients were recruited, only 44 spouses were available for invitation to the study (see Chapter 4, Section 4.2.2.). Of these caregivers, only 35 consented to take part in the research, with some caregivers not completing all of the measures (n=5); leading to a reduction in statistical power.

As stated in the hypotheses in Section 6.1., the study’s objective was to determine the relative contribution of patients’ cognitive, behavioural and disease factors to caregiver outcomes, in terms of mood, perceived strain, burden and marital satisfaction. Since the sample size was small, the strategy for selecting predictors to be entered into a regression was based on both theory and statistical criteria. This allowed for a reduction in the number of predictors entering the final models. Potential predictor variables were selected on the basis of past research and the objectives of the study (see Table 6.6. for list of these variables). The informant–rated FrSB (FrSB–I) and ELQ (ELQ–I) were used to measure patients’ behaviour. Bivariate correlational analyses were conducted to determine significant relationships between potential predictors and caregiver outcome variables. Variables which showed significant relationships with the outcomes (unadjusted \( p < .05 \)) were entered into a forward selection multiple regression (MR) to determine which variables best predicted the relevant outcome. Following these initial analyses, the significant predictors were entered into a hierarchical regression.

**Selection of predictors**

**Caregiver depression:** The correlates of caregiver HADS D included ALSFRS–R Tot \( (r = -.38, p = .02, n=35) \), ALSFRS–R Limb \( (r = -.44, p = .008, n=35) \) and informant–rated current Apathy \( (r = .42, p = .02, n=33) \). The ALSFRS–R Tot and ALSFRS–R Limb variables correlated strongly \( (r = .86, p < .001, n=32) \); however the assessment of VIF and tolerance values indicated multicollinearity was not substantial. A forward selection MR indicated that **ALSFRS–R Limb** was the only variable to enter the model \( (\beta = -.22, SE = .09, \text{standardised } \beta = -.42, t(31) = -2.6, p = .01, 95\% \text{ CI } [-.4; -.05]) \), \( R^2 = .18 \), adjusted \( R^2 = .15 \), \( F(1,31) = 6.75, p = .01 \).
Table 6.6.: Domains of interest for potential predictors of caregiver outcomes

<table>
<thead>
<tr>
<th>Domain</th>
<th>Measures</th>
</tr>
</thead>
</table>
| Disease      | ALSFRS–R: Total score, limb severity, bulbar severity, respiratory severity subscale scores  
               | Disease duration (months since ALS onset)                                  
               | Disease progression rate                                                   |
| Cognitive    | Executive function composite score                                        |
               | EMOSOC composite score                                                     |
               | Hayling Test Error and latency scores                                      |
| Behaviour    | FrSBe–I: Total score; Apathy, Disinhibition, Executive Dysfunction subscale scores. |
               | ELQ–I: Total score                                                        |
| Miscellaneous| Relationship years                                                         |
               | Caregiver’s age                                                            |


**Caregiver anxiety:** The correlates of caregiver HADS A included FrSBe–I Tot current ($r=.40, p=.02, n=33$) and ELQ–I Tot ($r=.38, p=.03, n=34$). Forward selection MR indicated that only the **FrSBe–I Tot current** entered the model ($\beta=.12$, standardised $\beta=.40$, $t(30)=2.4, p=.02$, 95% CI [.02; .23]), $R^2=.16$, adjusted $R^2=.13$, $F(1,30)=5.65$, $p=.02$.

**Caregiver strain:** The correlates of MSS score included ALSFRS–R Tot ($r=-.4, p=.02, n=35$), ALSFRS–R limb ($r=-.45, p=.006, n=35$), EMOSOC ($r=-.03, p=.04, n=35$), informant–rated current Apathy score ($r=.35, p=.05, n=33$), FrSBe–I Tot current ($r=.35, p=.05, n=33$) and ELQ–I Tot ($r=.41, p=.02, n=34$). A forward selection MR indicated **ALSFRS–R Limb, ELQ–I Tot and EMOSOC** remained in the model, $R^2=.41$, adjusted $R^2=.35$, $F(3,28)=6.61, p=.002$. An inspection of regression coefficients showed that only **ELQ–I Tot and EMOSOC** were significant predictors of strain (see Table 6.7.).
Caregiver burden: The correlates of the ZBI score included ALSFRS–R Tot ($r=-.59$, $p<.001$, $n=34$); ALSFRS–R Limb ($r=-.66$, $p<.001$, $n=34$), informant–rated current Apathy ($r=.63$, $p<.001$, $n=32$), informant–rated current Disinhibition ($r=.51$, $p=.003$, $n=32$), informant–rated current Executive Dysfunction ($r=.51$, $p=.003$, $n=32$), FrSBe–I Total current ($r=.69$, $p<.001$, $n=32$). Case diagnostics from an initial MR analyses found that one participant showed a substantial influence over the model’s predictive capacity (Cook’s distance=3.3). After removal of this participant from the analyses, multicollinearity statistics indicated that the strong correlation between ALSFRS–R Tot and ALSFRS–R Limb ($r=.88$, $p<.001$, $n=31$) was problematic. Since ALSFRS–R Limb showed the strongest correlation with the ZBI score, this variable was selected for the model. A forward selection MR indicated **ALSFRS–R Limb and FrSBe–I Total current** remained in the model, $R^2=.85$, adjusted $R^2=.84$, $F(2,28)=80.6$, $p<.001$. An inspection of the regression coefficients showed that both variables predicted burden significantly (see Table 6.8).

**Summary:** ALSFRS–R Limb was associated with all the caregiver outcomes, except anxiety. The FrSBe–I Total current scores predicted anxiety and burden. Although, ALSFRS–R Limb, ELQ–I Tot and EMOSOC were selected for the regression model to predict variability in caregiver strain, only ELQ–I Tot and EMOSOC were found to be significant predictors in the final model.
Table 6.7.: Predictors of perceived strain

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Standard Error B</th>
<th>Standardised β</th>
<th>95% CI for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Constant</td>
<td>32.3</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALSFRS–R Limb</td>
<td>-0.36</td>
<td>0.1</td>
<td>-.42</td>
<td>-0.7; -0.1</td>
</tr>
<tr>
<td>2. Constant</td>
<td>30.5</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALSFRS–R Limb</td>
<td>-0.33</td>
<td>0.1</td>
<td>-.39</td>
<td>-0.6; -0.1</td>
</tr>
<tr>
<td>ELQ–I Tot</td>
<td>0.14</td>
<td>0.1</td>
<td>.35</td>
<td>0.01; 0.3</td>
</tr>
<tr>
<td>3. Constant</td>
<td>29.72</td>
<td>2.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALSFRS–R Limb</td>
<td>-0.24</td>
<td>0.1</td>
<td>-.28</td>
<td>-0.5; 0.0</td>
</tr>
<tr>
<td>ELQ–I Tot</td>
<td>0.17</td>
<td>0.1</td>
<td>.43*</td>
<td>0.1; 0.3</td>
</tr>
<tr>
<td>EMOSOC</td>
<td>-2.25</td>
<td>0.9</td>
<td>-.37</td>
<td>-4.2; -0.3</td>
</tr>
</tbody>
</table>

N=32. Results significant at p<.05 shown in **bold**. Results significant at p<.01 shown in **bold***. 1. $R^2=.18$, adjusted $R^2=.15$; 2. $R^2=.30$, adjusted $R^2=.25$; 3. $R^2=.41$, adjusted $R^2=.35$.

Table 6.8.: Predictors of perceived burden

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Standard Error B</th>
<th>Standardised β</th>
<th>95% CI for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Constant</td>
<td>-37.5</td>
<td>10.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FrSBe–I Total</td>
<td>1.1</td>
<td>0.2</td>
<td>.78*</td>
<td>0.7; 1.4</td>
</tr>
<tr>
<td>2. Constant</td>
<td>-14.2</td>
<td>7.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FrSBe–I Tot</td>
<td>0.9</td>
<td>0.1</td>
<td>.69*</td>
<td>0.7; 1.2</td>
</tr>
<tr>
<td>ALSFRS–R Limb</td>
<td>-1.1</td>
<td>0.2</td>
<td>-.51*</td>
<td>-1.5; -0.8</td>
</tr>
</tbody>
</table>

N=31. Results significant at p<.01 shown in **bold***. 1. $R^2=.60$, adjusted $R^2=.59$; 2. $R^2=.85$, adjusted $R^2=.84$. 
Measures of caregiver outcome, namely the HADS A, HADS D, MSS and ZBI scores demonstrated moderate to high positive intercorrelations. MIS premorbid and MIS current did not show strong or significant associations with any of these variables, with the exception of the ZBI and MIS current scores (see Appendix IX.). For this reason, the investigation of caregiver outcomes was separated into two stages, in keeping with the separate hypotheses. The first analysis considers the impact of ALS on caregivers’ ‘wellbeing’, quantified here by measures of mood, perceived strain and burden. The second analysis considers the impact of ALS on caregivers’ perceived marital satisfaction.

6.2.3.1. Caregivers’ wellbeing

As the measures of mood, strain and burden showed moderate to high intercorrelations, a global outcome measure (Wellbeing) was computed using the following formula from Goldstein et al. (2006a):

$$\text{Wellbeing} = \frac{1}{3} \times \left[ \frac{\text{HADS Total}}{\text{SD (HADS Total)}} + \frac{\text{MSS}}{\text{SD (MSS)}} + \frac{\text{ZBI}}{\text{SD (ZBI)}} \right]$$

A higher global score indicated less wellbeing. One caregiver did not complete the burden measure, so for this participant the strain and mood scores were standardised and summed before being multiplied by 0.5 to create a global score. Combining these outcome measures offers a conservative approach to examining predictors of caregiver experience (Goldstein et al., 2006a). For the computation of HADS Total see Chapter 5, Section 5.2.4.

In order to test Hypothesis Four that cognitive and behavioural impairments in patients will contribute more to caregivers’ wellbeing than patients’ disease status, a hierarchical regression was conducted using the predictors identified in the preceding forward selection procedures. The dependent variable was Wellbeing. The independent variables were entered in the following blocks:

**Block 1:** ALSFRS–R Limb

**Block 2:** FrSBe–I Tot current; ELQ–I Tot and EMOSOC

Results of the regression model are shown in Table 6.9. The total model explained 45.4% (adjusted $R^2$) of the variance in Wellbeing, $F(4,27)=7.43, p<.001$. The results
indicated that as ALSFRS–R Limb increase by 1 SD (6; higher score indicates better limb function), the global outcome decreased by 0.37 SD and suggests that ALSFRS–R Limb is a significant predictor of Wellbeing \( [t(27)=-2.54, p=.02] \). Independently, as FrSBe Tot increased by 1 SD (12.8; higher scores indicate higher behavioural dysfunction), the global outcome score increased by 0.35 SD and suggest that the FrSBe Total score is also a significant predictor of Wellbeing \( [t(27)=2.3, p=.03] \). The ELQ Tot and EMOSOC scores were not significant predictors of global caregiver outcome. This fails to support Hypothesis Four that both objective measures of cognition and caregiver–rated behavioural indices will contribute to caregiver wellbeing, controlling for patients’ disease symptoms. However, it does highlight the individual contribution of caregivers’ perceptions of patients’ behaviour to this outcome.

Table 6.9.: Predictors of Wellbeing

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Standard Error B</th>
<th>Standardised ( \beta )</th>
<th>95% CI for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Constant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALSFRS–R Limb</td>
<td>2.0</td>
<td>0.2</td>
<td>-.55*</td>
<td>1.6; 2.4</td>
</tr>
<tr>
<td></td>
<td>-0.1</td>
<td>0.01</td>
<td></td>
<td>-0.07; -0.02</td>
</tr>
<tr>
<td>2. Constant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALSFRS–R Limb</td>
<td>0.9</td>
<td>0.4</td>
<td>-.37</td>
<td>0.02; 1.8</td>
</tr>
<tr>
<td>FrSBe–I Tot</td>
<td>-0.03</td>
<td>0.01</td>
<td>.35</td>
<td>-0.06; -0.01</td>
</tr>
<tr>
<td>ELQ–I Tot</td>
<td>0.01</td>
<td>0.01</td>
<td>.23</td>
<td>&lt;0.01; 0.02</td>
</tr>
<tr>
<td>EMOSOC</td>
<td>-0.1</td>
<td>0.1</td>
<td>-.21</td>
<td>-0.29; 0.05</td>
</tr>
</tbody>
</table>

N=32. Results significant at \( p<.05 \) shown in **bold**. Results significant at \( p<.01 \) shown in **bold**. \( R^2=.30, \) adjusted \( R^2=.28; 2. R^2=.52; \) adjusted \( R^2=.454. \)
6.2.3.2. Caregivers’ marital satisfaction

In order to test Hypothesis Five that patients’ cognitive and behavioural impairment will contribute more to caregivers’ perceptions of current marital satisfaction than disease symptoms, the same selection procedure for predictors was used.

Current caregiver marital satisfaction: The correlates of the MIS current scores included informant–rated current Apathy ($r = -0.37$, $p = 0.04$, n=31), informant–rated current Executive Dysfunction ($r = -0.49$, $p = 0.005$, n=31), FrSBe–I Tot current ($r = -0.54$, $p = 0.002$, n=31). A forward selection MR indicated that only FrSBe–I Tot current entered the model, $R^2 = 0.30$, adjusted $R^2 = 0.27$, $F(1,29) = 12.12$, $p = 0.002$, $\beta = -0.78$, SE = 0.22, standardised $\beta = -0.54$, $t(29) = -3.48$, $p = 0.002$, 95% CI for $\beta$ [-1.24; -0.33].

FrSBe–I Tot current scores were entered into a hierarchical MR analysis to predict current MIS scores, while controlling for premorbid MIS scores. Case diagnostics from an initial MR analysis revealed that one participant showed a substantial influence on the predictability of the model (Cook’s Distance=1.6). This case was subsequently removed from the analysis.

The final MR analysis results are shown in Table 6.10. The model explained 78.1% (adjusted $R^2$) of the variance in caregivers’ current marital satisfaction, $F(2,27) = 52.68$, $p < 0.001$. The results indicated that as premorbid MIS scores increase by 1 SD (15.5), current MIS increased by 0.68 SD and suggests that premorbid marital satisfaction is a significant predictor of current marital satisfaction [$t(27) = 7.59$, $p < 0.001$]. Independently, as FrSBe Tot–I score increased by 1 SD (9.8), current MIS score decreased by 0.42 SD and suggest the FrSBe–I Total current score is also a significant predictor of current marital satisfaction [$t(27) = -4.65$, $p < 0.001$].

This fails to support Hypothesis Five that both objective measures of patient cognition and caregiver–rated behaviour will contribute to caregivers’ perceived marital satisfaction more than the patients’ disease severity (as measured by ALSFRS–R scores). However, as before, it does highlight the individual contribution of caregivers’ perceptions of patients’ behaviour to this outcome.
Table 6.10.: Predictors of current marital satisfaction

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Standard Error B</th>
<th>Standardised β</th>
<th>95% CI for B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Constant</td>
<td>-0.8</td>
<td>10.3</td>
<td>-21.9; 20.4</td>
<td></td>
</tr>
<tr>
<td>MIS premorbid</td>
<td>0.9</td>
<td>0.1</td>
<td>.79*</td>
<td>0.7; 1.2</td>
</tr>
<tr>
<td>2. Constant</td>
<td>57.8</td>
<td>14.8</td>
<td>27.4; 88.3</td>
<td></td>
</tr>
<tr>
<td>MIS premorbid</td>
<td>0.8</td>
<td>0.1</td>
<td>.68*</td>
<td>0.6; 1.0</td>
</tr>
<tr>
<td>Total FrSBe score</td>
<td>-0.8</td>
<td>0.2</td>
<td>-.42*</td>
<td>-1.1; -0.4</td>
</tr>
</tbody>
</table>

N=30. Results significant at p<.01 shown in bold*.1.R²=.633, adjusted R²=.620; 2. R²=.796; adjusted R²=.781

6.3. Exploratory study

6.3.1. Caregivers’ perceptions of patients’ EL

Median scores of patients and caregivers ELQ ratings are shown in Table 6.11. One caregiver did not complete this measure. Thus, comparisons of ratings are reported for 34 couples. Wilcoxon signed–rank tests revealed no significant differences for ratings on the Total ELQ and the domain scores.

Table 6.11.: Comparison of patient and caregiver ELQ ratings

<table>
<thead>
<tr>
<th></th>
<th>Median (MAD/IQR)</th>
<th>Ties</th>
<th>z(df)</th>
<th>p</th>
<th>r</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caregivers (n=34)</td>
<td>ALS (n=34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELQ–TOT</td>
<td>5 (5/16)</td>
<td>6 (6/20)</td>
<td>9</td>
<td>-0.66</td>
<td>.51</td>
<td>.08</td>
</tr>
<tr>
<td>ELQ–Laugh</td>
<td>0 (0/7)</td>
<td>0 (0/16)</td>
<td>16</td>
<td>-0.31</td>
<td>.76</td>
<td>.09</td>
</tr>
<tr>
<td>ELQ–Cry</td>
<td>0 (0/9)</td>
<td>0 (0/12)</td>
<td>15</td>
<td>-0.48</td>
<td>.63</td>
<td>.08</td>
</tr>
<tr>
<td>ELQ–Smile</td>
<td>0 (0/0)</td>
<td>0 (0/6)</td>
<td>21</td>
<td>-1.61</td>
<td>.12</td>
<td>.01</td>
</tr>
</tbody>
</table>

p–values from two–tailed Wilcoxon–signed rank tests. r, Pearson’s correlation coefficient; Hodges–Lehmann confidence interval for difference between medians (paired).
6.3.2. Caregivers’ perceptions of patients’ empathy

Six caregivers did not complete the informant version of the Interpersonal Reactivity Index (IRI–I). Therefore, patients’ and caregivers’ ratings are compared for 29 couples. The mean patient– and caregiver–reported data for the four IRI subscales are shown graphically in Figure 6.2. Paired–sample *t*–tests revealed significant differences between patient– and caregiver–ratings on levels of Perspective Taking (PT), with the inspection of the mean scores suggesting that caregivers rated patients’ level of PT lower than patients rated themselves. This difference remained significant following a Bonferroni correction (adjusted *p*<.013). No differences between caregiver– and patient–ratings on the other three subscales were found.

**Figure 6.2.: Caregiver and patient IRI ratings**

Caregivers (n=29); ALS (n=29). Maximum score per subscale=28. PT, Perspective taking; FS, Fantasy thinking; EC, Empathic concern; PD, Personal distress. *Significant difference following a Bonferroni correction *p*<.013.
A discrepancy score for the PT scale was created by subtracting patients’ PT total scores from the caregivers’ PT total scores. Possible relationships between this discrepancy score and caregiver outcomes (mood, perceived strain, burden and marital satisfaction) were explored. As this investigation was exploratory, the alpha–level was not adjusted for multiple correlations. Significant positive relationships between the PT discrepancy score (\(M=-4.0, SD=6.8\)) and caregiver’s premorbid MIS scores (\(r=.45, p=.02, n=28\)) and current MIS scores (\(r=.42, p=.03, n=28\)) were found.

6.3.3. Caregivers’ perceptions of patients’ behaviour

Two caregivers did not complete the informant version of the Frontal Systems Behavioural Scale (FrSBe–I). Caregivers were asked to rate their spouse’s behaviour currently and premorbidly (at least two years prior to the onset of ALS). One–way repeated measures ANOVAs revealed that caregivers rated patients’ current behaviour significantly higher than premorbid levels for the total FrSBe score and the three domains of the scale. These differences remained significant following a Bonferroni correction (adjusted \(p<.013\)) (see Figure 6.3).

Comparisons of caregivers’ and patients’ ratings of premorbid and current behaviour were also examined using split–plot ANOVAs, with Rater (Caregiver; Patient) as the between–subjects factor and Time (Premorbid; Current) as the within–subject factors. One patient and two caregivers did not complete the FrSBe; results are therefore reported for 32 couples. Caregivers did not rate the change in patients’ behaviour since their ALS onset as different from the patients themselves [Total FrSBe: \(F(1,62)=0.10, p=.75, \eta^2=.001\); Apathy: \(F(1,62)=2.78, p=.10, \eta^2=.04\); Disinhibition: \(F(1,62)=21.13, p=.34, \eta^2=.02\); Executive Dysfunction: \(F(1,62)=0.05, p=.84, \eta^2<.001\)]. Both patients’ and caregivers’ ratings of the patients’ behaviour showed an increase in scores over time for all measures [Total FrSBe: \(F(1,62)=61.65, p<.001, \eta^2=.50\); Apathy: \(F(1,62)=119.35, p<.001, \eta^2=.66\); Disinhibition: \(F(1,62)=8.08, p=.006, \eta^2=.12\); Executive Dysfunction: \(F(1,62)=24.58, p<.001, \eta^2=.28\)]. There was a significant effect of Rater for the premorbid and current FrSBe total and domain scores, with the exception of the Disinhibition subscale score. For the significant group differences, caregivers tended to rate patients’ behaviour as higher (more impaired) than the patient’s rated themselves, both for premorbid and current behaviour (see Table 6.12.).
The proportions of caregivers’ FrSBe ratings which satisfied criteria for ‘caseness’ ($T$–score $\geq 65$) were examined. These proportions were compared to those from patients’ ratings of their own behaviour using a McNemar test. Table 6.13. displays the results of these analyses. For the premorbid ratings, caregivers rated proportionally more patients as satisfying ‘caseness’ than patients rated themselves, with the exception of the Apathy subscale. However, none of the differences in percentages were found to be statistically significant. For current behaviour ratings, caregivers again showed proportionally more endorsements of ‘caseness’ compared to patients. However, differences between percentages were only significant for the Apathy and Executive Dysfunction subscales. Only the difference for the Apathy subscale remained significant following a Bonferroni correction (adjusted $p<.006$).

Figure 6.3.: Caregiver ratings on FrSBe: premorbid compared to current behaviour

N=33. * Significant difference following a Bonferroni correction $p<.013$. Error bars represent 95% CI for mean.
Table 6.12.: Comparisons between caregiver and patient ratings of patient behaviour

<table>
<thead>
<tr>
<th>FrSBe T–scores</th>
<th>Mean (SD)</th>
<th>F(df)</th>
<th>p</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caregivers (n=32)</td>
<td>ALS (n=32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total FrSBe (pre.)</td>
<td>54.0 (11.4)</td>
<td>48.1 (11.6)</td>
<td>5.44 (1,62)</td>
<td>.02</td>
</tr>
<tr>
<td>Total FrSBe (curr.)</td>
<td>64.1 (12.8)</td>
<td>57.4 (11.5)</td>
<td></td>
<td>.08</td>
</tr>
<tr>
<td>Apathy (pre.)</td>
<td>51.8 (8.9)</td>
<td>45.3 (12.3)</td>
<td>9.76 (1,62)</td>
<td>.003*</td>
</tr>
<tr>
<td>Apathy (curr.)</td>
<td>69.4 (13.8)</td>
<td>58.2 (14.7)</td>
<td></td>
<td>.14</td>
</tr>
<tr>
<td>Disinhibition (pre.)</td>
<td>51.8 (12.7)</td>
<td>53.3 (13.6)</td>
<td>0.04 (1,62)</td>
<td>.84</td>
</tr>
<tr>
<td>Disinhibition (curr.)</td>
<td>55.0 (11.9)</td>
<td>54.8 (13.4)</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Exec. Dys. (pre.)</td>
<td>55.3 (11.7)</td>
<td>47.5 (11.3)</td>
<td>7.44 (1,62)</td>
<td>.008*</td>
</tr>
<tr>
<td>Exec. Dys. (curr.)</td>
<td>60.4 (13.3)</td>
<td>53.1 (11.1)</td>
<td></td>
<td>.12</td>
</tr>
</tbody>
</table>

*p–values from split–plot ANOVA. Uncorrected significant results shown in bold–p<.05. Results significant following Bonferroni correction are shown as bold*–p<.013. η², partial–eta squared. FrSBe, Exec.Dys., Executive Dysfunction; pre., premorbid; cur., current. Note: higher scores indicate greater impairment.

Table 6.13.: Comparisons of caregiver and patient FrSBe ratings satisfying ‘caseness’

<table>
<thead>
<tr>
<th>FrSBe</th>
<th>N (%)</th>
<th>X²(df)</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=33 Caregivers ALS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tot. FrSBe (pre.)</td>
<td>3 (9.4)</td>
<td>6 (18.8)</td>
<td>1.8 (1)</td>
<td>.18</td>
</tr>
<tr>
<td>Tot. FrSBe (curr.)</td>
<td>11 (34.4)</td>
<td>7 (21.9)</td>
<td>1.33 (1)</td>
<td>.25</td>
</tr>
<tr>
<td>Apathy (pre.)</td>
<td>4 (12.5)</td>
<td>3 (9.4)</td>
<td>2 (1)</td>
<td>.65</td>
</tr>
<tr>
<td>Apathy (curr.)</td>
<td>19 (51.4)</td>
<td>1 (3.1)</td>
<td>16.2 (1)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Disinhib. (pre.)</td>
<td>4 (12.5)</td>
<td>9 (28.1)</td>
<td>2.78 (1)</td>
<td>.10</td>
</tr>
<tr>
<td>Disinhib. (curr.)</td>
<td>5 (15.6)</td>
<td>4 (12.5)</td>
<td>0.11 (1)</td>
<td>.74</td>
</tr>
<tr>
<td>Exec. Dys. (pre.)</td>
<td>4 (12.5)</td>
<td>6 (18.8)</td>
<td>5 (1)</td>
<td>.48</td>
</tr>
<tr>
<td>Exec. Dys. (curr.)</td>
<td>10 (31.3)</td>
<td>1 (3.1)</td>
<td>7.36 (1)</td>
<td>.007</td>
</tr>
</tbody>
</table>

*p–values from McNemar tests. Uncorrected significant results shown in bold–p<.05. Results significant following a Bonferroni correction are shown in bold*–p<.006. 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions (paired). Disinhib., Disinhibition; Exec.Dys., Executive Dysfunction; pre., premorbid; cur., current.
The proportion of caregivers’ ratings of patients’ premorbid and current behaviour satisfying ‘caseness’ were also compared (n=33). Table 6.14. displays these results. For the total score and all domains, caregivers endorsed proportionally more patients as meeting ‘caseness’ for the current behaviour period than the premorbid period. The relative percentages of ‘cases’ between rating conditions were significantly different for all FrSBe domains, with the exception of the Disinhibition subscale. These differences remained significant following a Bonferroni correction (adjusted \( p<.013 \)).

Table 6.14.: Comparisons of caregiver premorbid and current FrSBe ratings satisfying ‘caseness’

<table>
<thead>
<tr>
<th>FrSBe</th>
<th>N (%)</th>
<th>( X^2(df) )</th>
<th>( p )</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Premorbid</td>
<td>Current</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total FrSBe</td>
<td>3 (9.1)</td>
<td>11 (33.3)</td>
<td>8 (1)</td>
<td>.005*</td>
</tr>
<tr>
<td></td>
<td>11 (33.3)</td>
<td>3 (9.1)</td>
<td>-40.3; -8.1</td>
<td></td>
</tr>
<tr>
<td>Apathy</td>
<td>4 (12.1)</td>
<td>19 (57.6)</td>
<td>15 (1)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td></td>
<td>19 (57.6)</td>
<td>4 (12.1)</td>
<td>-60.8; -25.5</td>
<td></td>
</tr>
<tr>
<td>Disinhibition</td>
<td>4 (12.1)</td>
<td>5 (15.2)</td>
<td>1 (1)</td>
<td>.32</td>
</tr>
<tr>
<td></td>
<td>5 (15.2)</td>
<td>4 (12.1)</td>
<td>-14.4; 7.44</td>
<td></td>
</tr>
<tr>
<td>Exec. Dys.</td>
<td>4 (12.1)</td>
<td>10 (30.3)</td>
<td>6 (1)</td>
<td>.01*</td>
</tr>
<tr>
<td></td>
<td>10 (30.3)</td>
<td>4 (12.1)</td>
<td>-33.3; -3.5</td>
<td></td>
</tr>
</tbody>
</table>

\( p \)-values from McNemar tests. Results significant following a Bonferroni correction are shown in bold*. \( p<.013 \). 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions (paired). Exec.Dys., Executive Dysfunction

Discrepancy scores for the FrSBe domains comparing caregiver and patient current ratings were created by subtracting patients’ FrSBe \( T \) scores from the caregivers’ FrSBe \( T \) scores. Possible relationships between these discrepancy scores and caregiver outcomes (mood, perceived strain, burden and marital satisfaction) were explored (see Table 6.15). As this investigation was exploratory, the alpha–level was not adjusted for multiple correlations. The discrepancy score for the current Total FrSBe score correlated positively with HADS A, Strain and Burden. There was also a positive correlation between the discrepancy score for current Executive Dysfunction and caregiver Burden.
Table 6.15.: Correlations between caregiver–patient FrSBe discrepancy scores and caregiver outcome scores

<table>
<thead>
<tr>
<th>Caregiver Outcome (n)</th>
<th>Discrepancy Score: Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS A (32)</td>
<td>.09 (.64)</td>
</tr>
<tr>
<td>HADS D (32)</td>
<td>.04 (.85)</td>
</tr>
<tr>
<td>Strain (32)</td>
<td>-.02 (.9)</td>
</tr>
<tr>
<td>Burden (31)</td>
<td>.14 (.47)</td>
</tr>
<tr>
<td>MIS premorbid (30)</td>
<td>-.18 (.34)</td>
</tr>
<tr>
<td>MIS current (30)</td>
<td>-.19 (.34)</td>
</tr>
</tbody>
</table>

*r* values from Pearson’s correlations. Uncorrected significant correlations (*p*<.05) are shown in **bold**.
Similarly, change scores for FrSBe domains comparing caregivers’ premorbid and current ratings were created by subtracting their premorbid ratings from their current ratings. Relationships between these change scores and caregiver outcomes were also explored, as above. Change scores for the Total FrSBe, Apathy and Executive Dysfunction scales were positively associated with measures of mood, strain and burden. The Disinhibition change score was positively associated with levels of depression, strain, and burden and negatively associated with current marital satisfaction. (see Table 6.16).

Table 6.16.: Correlations between caregivers’ FrSBe change scores and caregiver outcome scores

| Caregiver Outcome (n) | Change Score: Mean (SD) |  |
|----------------------|-------------------------|--|---|
|                      | Total change*           | Apathy change | Disinhib. change | Exec. Dys. change*  |
|                      | 0.2 (0.1;0.2)*          | 17.7 (11.9)   | 3.1 (6.8)        | 0.7 (0.5;0.9)*     |
| HADS A (33)          | .42 (.01)               | .47 (.006)    | .21 (.25)        | .39 (.03)          |
| HADS D (33)          | .46 (.007)              | .47 (.006)    | .41 (.02)        | .40 (.02)          |
| Strain (33)          | .53 (.001)              | .55 (.001)    | .56 (.001)       | .49 (.004)         |
| Burden (32)          | .54 (.001)              | .53 (.002)    | .40 (.02)        | .43 (.01)          |
| MIS premorbid (31)   | .06 (.75)               | .16 (.39)     | -.01 (.73)       | .16 (.38)          |
| MIS current (31)     | -.30 (.1)               | -.22 (.24)    | -.39 (.03)       | -.19 (0.31)        |

*r* values from Pearson’s correlations. Uncorrected significant correlations (*p*<.05) are shown in **bold**. *∞*, Naperian log transformed data.*back–transformed Mean (CI). **Note:** sensitivity analyses using untransformed data and non–parametric tests of association found the same pattern of significant results.
6.3.4. Caregivers’ perceptions of patients’ personality characteristics

Caregivers were asked to rate patients’ personality characteristics on the NEO–FFI currently and premorbidly (at least two years prior to the patient’s ALS onset). Patients rated their current personality only. Two–tailed paired samples t–tests found significant differences between caregiver– and patient–ratings for current personality. Caregivers’ ratings of patients’ current levels of Neuroticism (N) were significantly higher than the patients’ ratings of themselves for this domain. Caregivers rated patients as showing significantly lower current levels of Extraversion (E) and Conscientiousness (C) than patients rated themselves. When a Bonferroni correction was applied (adjusted $p<.01$), only the difference between ratings on the E subscale remained. These results are presented in Figure 6.4. One patient and five caregivers did not complete the NEO–FFI and thus results are reported for 29 couples.

For exploratory purposes, caregivers’ mean premorbid ratings were compared with patients’ mean current ratings of patient personality. No significant differences were found for any of the NEO–FFI domains (see Appendix X), suggesting that the discordance found between caregiver and patient ratings of current personality might be explained by the caregivers’ perceptions of their spouse’s personality change since the onset of ALS. To explore this proposal, two–tailed paired $t$–tests compared caregiver–ratings of patients’ premorbid and current personality characteristics (n=30). Caregivers rated patients’ as showing significantly higher levels of N currently than premorbidly. However, they rated patients as showing significantly lower levels of E and C than prior to disease onset. All differences remained significant following a Bonferroni correction (adjusted $p<.01$). These results are shown in Table 6.17.
Figure 6.4: Comparison of caregivers’ and patients’ NEO–FFI ratings for patients’ current personality

Table 6.17: Comparisons of caregivers’ NEO–FFI ratings for patients’ premorbid and current personality

<table>
<thead>
<tr>
<th>NEO–FFI T–scores (informant)</th>
<th>Mean (SD)</th>
<th>$t(df)$</th>
<th>$p$</th>
<th>$d$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premorbid</td>
<td>Current</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroticism</td>
<td>39.6 (12.5)</td>
<td>49.1 (15.9)</td>
<td>-4.45 (29)</td>
<td>&lt;.001*</td>
<td>-0.67</td>
</tr>
<tr>
<td>Extraversion</td>
<td>55.3 (12.3)</td>
<td>43.4 (11.5)</td>
<td>5.19 (29)</td>
<td>&lt;.001*</td>
<td>0.99</td>
</tr>
<tr>
<td>Openness</td>
<td>48.3 (12.8)</td>
<td>47.1 (13.2)</td>
<td>0.72 (29)</td>
<td>.48</td>
<td>0.09</td>
</tr>
<tr>
<td>Agreeable.</td>
<td>51.0 (14.6)</td>
<td>48.7 (14.8)</td>
<td>1.77 (29)</td>
<td>.09</td>
<td>0.16</td>
</tr>
<tr>
<td>Conscien.</td>
<td>50.2 (12.3)</td>
<td>45.0 (11.2)</td>
<td>3.68 (29)</td>
<td>.001*</td>
<td>0.44</td>
</tr>
</tbody>
</table>

$p$–values from two–tailed paired–sample $t$–tests. Results significant following Bonferroni correction are shown as **bold**–$p<.01$. Agreeable., Agreeableness; Conscien., Conscientiousness; $d$, Cohen’s $d$ for paired samples; 95% CI, confidence interval for difference between means.
Caregiver ratings which fell into the extreme cut–off categories (Very high; Very low) were examined and compared between time points using McNemar tests (see Table 6.18.). The proportion of patients endorsed as satisfying very high N was significantly greater for the current period than the premorbid period. The proportion of cases meeting very high levels of E significantly declined across time conditions, while the percentage of cases meeting very low levels of E increased significantly. However, none of these differences remained significant following a Bonferroni correction.

According to the NEO–FFI manual, the N domain measures traits of anxiety, hostility, depression, self–consciousness, impulsiveness and ability to cope with stress. Therefore, caregivers’ endorsements of very high levels of N might reflect their appraisals of the patients’ mood. However, none of the patients endorsed by caregivers as showing very high levels of current N met criteria for case level HADS A or HAD D. Although patients’ mood scores were self–rated rather than proxy–rated, this does suggest that the very high N endorsements were not influenced by displays of elevated mood in patients.

Table 6.18.: Caregivers’ ratings of patients’ behaviour satisfying NEO–FFI cut–off categories

<table>
<thead>
<tr>
<th>NEO–FFI N=30</th>
<th>N(%)</th>
<th>$X^2$ (df)</th>
<th>$p$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very high</strong></td>
<td><strong>Premorbid</strong></td>
<td><strong>Current</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range 66: 75)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Very low</strong></td>
<td>(range 25: 34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N – Very high</td>
<td>0 (0)</td>
<td>5 (16.7)</td>
<td>5 (1)</td>
<td>.03</td>
</tr>
<tr>
<td>N – Very low</td>
<td>9 (30)</td>
<td>5 (16.7)</td>
<td>2.7 (1)</td>
<td>.10</td>
</tr>
<tr>
<td>E – Very high</td>
<td>6 (20)</td>
<td>1 (3.3)</td>
<td>5 (1)</td>
<td>.03</td>
</tr>
<tr>
<td>E – Very low</td>
<td>2 (6.7)</td>
<td>7 (23.3)</td>
<td>5 (1)</td>
<td>.03</td>
</tr>
<tr>
<td>O – Very high</td>
<td>4 (13.3)</td>
<td>3 (10)</td>
<td>0.33 (1)</td>
<td>.56</td>
</tr>
<tr>
<td>O – Very low</td>
<td>2 (6.7)</td>
<td>4 (13.3)</td>
<td>2 (1)</td>
<td>.16</td>
</tr>
<tr>
<td>A – Very high</td>
<td>6 (20)</td>
<td>5 (16.7)</td>
<td>1 (1)</td>
<td>.32</td>
</tr>
<tr>
<td>A – Very low</td>
<td>5 (16.7)</td>
<td>6 (20)</td>
<td>0.33 (1)</td>
<td>.56</td>
</tr>
<tr>
<td>C – Very high</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>C – Very low</td>
<td>7 (23.3)</td>
<td>6 (20)</td>
<td>0.2 (1)</td>
<td>.65</td>
</tr>
</tbody>
</table>

$p$–values from McNemar tests. Uncorrected significant results shown in **bold**—$p<.05$. 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions (paired).
A comparison of caregivers’ and patients’ current personality ratings which were endorsed within the extreme cut-off categories (Very high; Very low) was also conducted for 29 couples (see Table 6.19.). Compared to patients, caregivers endorsed proportionally more patients’ as showing very low levels of E; however, this was not significant following a Bonferroni correction. Caregivers and patients did not differ significantly with regards to the proportion of cases endorsed as very high or very low for any of the other personality domains.

Table 6.19.: A comparison of caregivers’ and patients’ current NEO–FFI ratings satisfying cut-off categories

<table>
<thead>
<tr>
<th>NEO–FFI</th>
<th>N (%)</th>
<th>X² (df)</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range 66: 75)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N – Very high</td>
<td>4 (13.8)</td>
<td>0 (0)</td>
<td>4 (1)</td>
<td>.06</td>
</tr>
<tr>
<td>N – Very low</td>
<td>5 (17.2)</td>
<td>6 (20.7)</td>
<td>0.09 (1)</td>
<td>.76</td>
</tr>
<tr>
<td>E – Very high</td>
<td>1 (3.4)</td>
<td>3 (10.3)</td>
<td>1 (1)</td>
<td>.32</td>
</tr>
<tr>
<td>E – Very low</td>
<td>6 (20.7)</td>
<td>0 (0)</td>
<td>6 (1)</td>
<td>.01</td>
</tr>
<tr>
<td>O – Very high</td>
<td>3 (10.3)</td>
<td>2 (6.9)</td>
<td>0.2 (1)</td>
<td>.65</td>
</tr>
<tr>
<td>O – Very low</td>
<td>3 (10.3)</td>
<td>2 (6.9)</td>
<td>0.2 (1)</td>
<td>.65</td>
</tr>
<tr>
<td>A – Very high</td>
<td>5 (17.2)</td>
<td>1 (3.4)</td>
<td>4 (1)</td>
<td>.06</td>
</tr>
<tr>
<td>A – Very low</td>
<td>5 (17.2)</td>
<td>3 (10.3)</td>
<td>2 (1)</td>
<td>.16</td>
</tr>
<tr>
<td>C – Very high</td>
<td>0 (0)</td>
<td>1 (3.4)</td>
<td>1 (1)</td>
<td>.32</td>
</tr>
<tr>
<td>C – Very low</td>
<td>6 (20)</td>
<td>3 (10.3)</td>
<td>3 (1)</td>
<td>.08</td>
</tr>
</tbody>
</table>

*p*-values from McNemar tests. Uncorrected significant results shown in **bold**-p<.05. 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions (paired).
Discrepancy scores comparing caregiver and patients’ current ratings for the N, E and C current subscales were created by subtracting patients’ current domain total scores from the caregivers’ current domain total scores. Possible relationships between these discrepancy scores and caregiver outcomes (mood, perceived strain, burden and marital satisfaction) were explored. As this investigation was exploratory, the alpha–level was not adjusted for multiple correlations. A significant positive correlation was found for the E discrepancy score ($M=-10.1$, $SD=12.0$) and the current MIS score ($r=.50$, $p=.007$, $n=27$). No other significant relationships were found.

Similarly, change scores comparing caregivers’ premorbid and current ratings of patients’ personality characteristics for N, E and C were created by subtracting their premorbid ratings from their current ratings. Relationships between these scores and caregiver outcome scores were explored as above. Table 6.20 displays the correlations and the means and SDs for each change score. The N change score correlated positively with every caregiver outcome variable, with the exception of the MIS scores. The E and C change scores were negatively associated with the HADS D.

Table 6.20.: Correlations between caregiver NEO–FFI change scores and caregiver outcome variables

<table>
<thead>
<tr>
<th>Caregiver Outcome (n)</th>
<th>Change score: Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>9.5 (11.8)</td>
</tr>
<tr>
<td>HADS A (30)</td>
<td>.52 (.003)</td>
</tr>
<tr>
<td>HADS D (30)</td>
<td>.70 (.003)</td>
</tr>
<tr>
<td>Strain (30)</td>
<td>.43 (.02)</td>
</tr>
<tr>
<td>Burden (29)</td>
<td>.52 (.004)</td>
</tr>
<tr>
<td>MIS premorbid (28)</td>
<td>.18 (.36)</td>
</tr>
<tr>
<td>MIS current (28)</td>
<td>-.10 (.62)</td>
</tr>
</tbody>
</table>

$r$ values from Pearson’s correlations. Uncorrected significant correlations ($p<.05$) are shown in **bold**
6.4. Summary of results

This section summarises the findings from the current chapter. Results that were significant following a Bonferroni correction for multiple comparisons will be outlined. Uncorrected significant findings ($p<.05$) will be referred to as trends or tendencies, except in the case of exploratory correlational analyses where they will be referred to as (significant) associations or correlations.

6.4.1. Participant demographics

Thirty-five caregivers and a subset of 35 respective patients were involved in this aspect of the study. All caregiver–patient dyads were married and had been so for an average of 32 years before the onset of the patients’ illness. The majority of caregiver participants (72%) were female. The majority of patients had the limb–onset form of ALS (77%) and an average disease duration of less than three years.

6.4.2. Caregiver perceptions of mood, self–perceived strain, burden and marital satisfaction

Caregivers reported significantly higher scores for depression and anxiety than patients. The mean anxiety scores were within the ‘borderline case level’ for both groups according to revised cut–off criteria (Gibbons et al., 2011); significantly more caregivers than patients satisfied this criterion. More caregivers than patients satisfied criteria for ‘case level anxiety’ and ‘case level depression’, but the differences in proportions between groups were not significant following a Bonferroni correction.

The mean score for caregiver strain was 26.9 (SD=5.3). A mean score for burden was 29.4 (SD=14.1). A large proportion of caregivers (82.4%) satisfied criteria for high levels of burden. Caregiver ratings of marital satisfaction were significantly lower following the onset of their spouse’s illness than prior to the disease.

6.4.3. Predictors of caregiver outcomes

Forward selection regression analyses identified the following functional relationships:

i) Limb severity (ALSFRS–R Limb) significantly predicted caregiver depression and caregiver burden.

ii) Caregivers’ ratings of patients’ current behaviour (FrSBe–I Total current score) significantly predicted caregiver anxiety and caregiver burden.
iii) Emotional lability (ELQ–I tot) and performance on emotional processing and social cognition (EMOSOC composite) significantly predicted caregiver strain.

These predictors were entered into the model in order to assess their predictive capacity of a global outcome measure of caregiver wellbeing (a summation of standardised scores for mood, strain and burden). Only ALSFRS–R Limb scores and the caregiver–rated FrSBe Total current scores were found to be significant predictors of the global outcome scores.

In a separate multiple regression analysis, the FrSBe–I Total current score was found to be significant predictor of caregivers’ current marital satisfaction. When the FrSBe–I Total was entered into a hierarchical regression controlling for premorbid marital satisfaction scores, it remained a significant predictor in the model.

6.4.4. Caregiver perceptions of patients’ EL, empathy, behaviour and personality

The relative perception of patient behaviour was compared between caregivers and their spouses. There were no differences between caregivers and patients in ratings of patients’ emotional lability on any of the ELQ subscales or total score.

Caregiver ratings of patients’ levels of ‘perspective taking’ (PT) were significantly lower than patients’ ratings of themselves. Exploratory correlation analyses found that caregiver–patient discrepancy scores (proxy–ratings – self–ratings) for this empathy domain correlated positively with caregiver’s perceptions of premorbid and current marital satisfaction (i.e. the lower the caregiver’s rating of the patient’s level of PT relative to the patient’s self–rating, the lower the caregiver’s ratings of premorbid and current marital satisfaction).

Caregivers rated patients as showing higher levels of behavioural dysfunction following the onset of their illness than before their illness for all domains of the FrSBe measure. Further analyses which compared caregiver and patient ratings for the two time periods were conducted. Caregivers’ and patients’ ratings of the change in patients’ behaviour since their disease onset did not differ. Ratings from both groups increased significantly over time for all domains. However, caregivers rated patients as showing higher levels of premorbid and current behavioural dysfunction than patients rated themselves. This
was true for the domains of Apathy, Executive Dysfunction and the Total FrSBe score, but not for the Disinhibition domain.

The proportion of patients satisfying ‘caseness’ was compared between the rater groups. The proportion of caregivers’ ratings of patients’ ‘caseness’ was significantly different from that of patients for the current Apathy domain only, with caregivers endorsing more ‘cases’ than patients. Within the caregiver group, the proportion of ratings satisfying ‘caseness’ was compared between the premorbid and current rating periods. Differences in proportions were significant for the domains of Apathy, Executive Dysfunction and the Total FrSBe score; caregivers endorsed more ‘cases’ for the current period compared to the premorbid period.

Caregiver–patient discrepancy scores for FrSBe subscales and total score were computed. Exploratory correlation analyses revealed that the FrSBe total current discrepancy score was positively associated with caregiver anxiety, strain and burden. In addition, the Executive Dysfunction discrepancy score correlated positively with caregiver burden (i.e. the higher the caregiver’s ratings of the patient’s behavioural dysfunction on these domains relative to the patients’ self-ratings, the worse the caregiver’s self-ratings of anxiety, strain and burden). Similarly, change scores were also calculated for each FrSBe domain (caregivers’ current FrSBe ratings – premorbid FrSBe ratings of patients’ behaviour). Exploratory correlational analyses revealed that every FrSBe domain change scores correlated positively with caregiver measures of depression, strain and burden (i.e. the greater the perceived increase in the patient’s behavioural dysfunction on these domains, the worse the caregiver’s self-ratings of depression, strain and burden). The Disinhibition change scores correlated negatively with current marital satisfaction (i.e. the greater the perceived increase in the patient’s level of disinhibition, the lower the caregiver’s ratings of current marital satisfaction). The Total FrSBe change scores, the Apathy change scores and the Executive Dysfunction change scores correlated positively with caregiver anxiety (i.e. the greater the perceived increase in the patient’s behavioural dysfunction on these domains, the worse the caregiver’s self-rating of anxiety).

Caregivers rated patients as showing significantly lower levels of extraversion than patients rated themselves. There were trends for caregivers to rate patients as showing higher levels of neuroticism and lower levels of conscientiousness than patients rated themselves. A comparison of caregivers’ ratings of patient’s premorbid and current
behaviour found that caregivers rated patients as showing significantly higher levels of neuroticism, but significantly lower levels of extraversion and conscientiousness following the onset of ALS.

The proportion of caregivers’ ratings satisfying the extreme cut–off categories (Very high; Very low) was compared between premorbid and current time points. Caregivers endorsed more ‘very high’ cases of neuroticism in the current period than the premorbid period. Caregivers endorsed more ‘very high’ cases of extraversion in the premorbid period than the current period. Similarly, cares endorsed more ‘very low’ cases of extraversion in the current compared to the premorbid period. However, none of these proportions were significantly different following a Bonferroni correction. The proportion of caregivers’ and patients’ endorsements for cases meeting the extreme NEO–FFI cut–offs were compared. Proportionally more caregivers than patients rated patients as showing very low levels of extraversion; this was not significant following a Bonferroni correction. No differences in proportions were found between the groups for the remaining domains.

Caregiver–patient discrepancy scores for the NEO–FFI domain ratings were calculated. Exploratory correlational analyses revealed a positive association between the Extraversion (E) discrepancy score and current marital satisfaction (i.e. the lower the caregiver’s rating of the patient’s level of E relative to the patient’s self–rating, the lower the caregiver’s current marital satisfaction). Change scores comparing caregivers’ premorbid and current ratings of patients’ behaviour were also calculated for the personality domains. Exploratory correlational analyses revealed that the Neuroticism (N) change score correlated positively with caregiver outcomes of mood, strain and burden (i.e. the greater the perceived increase in the patient’s level of N, the worse the caregiver’s self–perceived level of strain and burden). The E and Conscientiousness (C) change scores correlated negatively with caregiver depression (i.e. the greater the perceived reduction in the patient’s level of E and C, the worse the caregiver’s self–reported depression).
6.5. Discussion of findings

This chapter reports an investigation of the impact of ALS on a subset of caregivers whose ill relative took part in the study. The main hypotheses consider whether objective measures of patients’ cognition and caregiver perceptions of patients’ behaviour contribute to caregivers’ wellbeing, in terms of their mood, perceived burden, strain and marital satisfaction. It also explores relative caregiver–patient perceptions of patients’ personality, behaviour and levels of empathy. This section will indicate the position of the study’s findings within the current ALS caregiver literature and discuss its theoretical implications. As before, the clinical implications, general limitations and recommendations for future research are addressed in the General Discussion (Chapter 7).

6.5.1. Hypothesis Four: Predictors of caregiver ‘wellbeing’: mood, perceived strain and burden

A relationship between patients’ cognitive–behavioural changes and caregivers’ perceived burden has previously been indicated in ALS research (Chio et al., 2010; Lillo et al., 2012a). However, these studies have never used objective measures of patients’ cognition alongside informants’ ratings of frontally–mediated behaviour in the assessment of caregiver outcomes. The current study therefore tested the hypothesis that objective measures of patients’ cognition and caregiver ratings of patient behaviour would contribute significantly to caregiver outcomes in terms of mood, perceived burden and strain, above and beyond patients’ disease status and symptoms.

Objective measures of patients’ cognition did not contribute to the global caregiver outcome score while caregiver–rated behavioural dysfunction in patients was a significant predictor. A similar pattern of results is usually demonstrated in caregivers of patients with MCI (see Dean & Wilcock, 2012 for review, although see Mcade et al, 2013); whereas objective cognitive measures alone are able to predict stress and burden in AD and FTD caregivers (Greve et al., 1994; Miller et al., 2013; Nelis et al., 2011). The results indicate that for caregivers of non–demented ALS patients the perceived severity of patients’ cognitive impairment might have a greater effect on caregiver wellbeing than patients’ actual cognitive impairment. On the other hand, this finding might have occurred because the patients for whom spouse data was available possibly did not show a great degree of cognitive dysfunction; or at least a degree at which patients’ everyday functioning was compromised. For example, perhaps mild to
moderate levels of executive impairment found in non-demented patients, which is only revealed upon detailed assessment of neuropsychological functioning, does not necessarily prevent patients from completing everyday duties that rely on such abilities (e.g. the planning of family finances). Therefore, since their spouse remains capable of everyday tasks, caregivers might not experience increased distress or burden associated with acquiring new duties that were previously shared with or completed exclusively by their spouse. In addition, while the FrSBe measures dysexecutive behaviour and disinhibition, it also assesses levels of apathy, a measurement that is not directly accessible by neuropsychological testing alone. Caregivers’ perceptions of behavioural impairment were highest for this domain (see Section 6.3.3.) and of the three FrSBe subdomains it correlated strongest with the Wellbeing composite. Thus patients’ apathetic behaviour may have been the most salient behavioural feature to the caregivers thereby arousing the most distress and burden. Alternatively, the use of composite scores as measures of cognition might have prevented the detection of possible relationships between patients’ performance on individual tests of neuropsychological functioning and the caregiver outcomes. Furthermore, a different set of tasks and an extended assessment of the other cognitive domains, such as language and memory, may have detected predictive relationships.

Patients’ limb severity was also found to significantly affect caregiver wellbeing: as ALSFRS–R scores for the domain decreased (greater functional impairment), the Wellbeing composite increased (reduced wellbeing). In fact, patients’ limb severity was associated with every caregiver outcome, except anxiety. The relationship between caregiver outcomes and patients’ physical symptoms in ALS is unclear. Limb severity of ALS patients has previously been correlated with caregiver depression (Chio et al., 2005; Goldstein et al., 1998), while overall physical impairment has been related to caregivers’ anxiety (Pagnini et al., 2010) and burden (Chio et al., 2005; Gauthier et al., 2007; Hecht et al., 2003; Pagnini et al., 2010). Some studies have found no such relationships (Boerner & Mock, 2012; Olsson et al., 2010b; Rabkin et al., 2009), while other research has emphasised the importance of behavioural above the physical aspects of ALS on caregivers (Chio et al., 2010; Lillo et al., 2012a). In the current study, both limb severity and behavioural dysfunction significantly contributed to caregivers’ burden, but while anxiety was predicted by perceived behavioural impairment, depression was predicted by patients’ limb severity. Anxiety and depression scores were also significantly associated with burden scores. These relationships might reveal the
specificity with which different ALS symptoms impact on caregivers: while both physical and behavioural changes affect the burden felt by caregivers, their reactions to the type of impairment might also differ. Patients’ functional impairment may lead to increased physical dependence on the caregiver, imposing restrictions upon caregivers’ personal time and needs (Chio et al., 2005; Hecht et al., 2003; Krivickas et al., 1997; Rabkin et al., 2009), their own physical health (Pagnini et al., 2010; Rabkin et al., 2000; Roach et al., 2009) and social relationships (Cobb & Hamera, 1986; Goldstein et al., 2006a; Ray & Street, 2006), not to mention the psychological burden associated with witnessing the restrictions that physical disability poses for their partners’ life (Goldstein et al., 1998). It is possible that these aspects of burden are expressed by caregivers in terms of increased depressive symptoms, possibly underlying a sense of hopelessness with the acknowledgment that their spouses’ condition will deteriorate and that their own circumstances will persist or worsen. In addition, behavioural dysfunction in patients, such as poor planning and decision–making, a lack of interest in completing ordinary tasks and increased impulsivity, may create burden for the caregiver as their role encompasses becoming the primary decision–maker (Merrilees et al., 2010; Oh & Schepp, 2013). However, these aspects of burden might be expressed by caregivers through increased anxiety, reflecting their alarm or confusion at their partners’ uncharacteristic demeanour or their anticipated inability to cope with the ensuing role–reversal as the disease progresses. It is important to note, however, that the current sample size was small and it is possible that other relationships, such as that between anxiety and limb severity or depression and behavioural impairment, may have been underestimated, thus compromising the suggestion that physical and behavioural symptoms pose differential effects on caregiver outcomes. This limitation considered, the results indicate that patients’ physical and behavioural symptoms may act in concert in their impact on caregivers of non–demented ALS patients.

The EMOSOC score did not predict the global caregiver outcome score, but it was found to predict caregiver strain in the initial analyses. However, the direction of the relationship between these variables was unexpected: as the EMOSOC scores increased by 1 SD, MSS scores decreased by 0.37 SD, indicating that higher impairment on the composite scores was associated with lower caregiver strain. This result is contrary to the hypothesis and difficult to interpret. It likely represents a spurious relationship due to a third variable or an interaction of variables which were not included in the regression or not measured at all. Caregiver–rated ELQ was also a significant predictor
of strain, in keeping with an earlier study which found that the total score predicted overall caregiver outcome (Goldstein et al., 2006a). This corroborates the notion that psychosocially salient aspects of ALS, such as EL, are important patient parameters in explaining caregiver outcomes.

Some limitations of this aspect of the study deserve consideration. The assessment of additional outcomes, such as caregivers’ health status and QoL, might have provided greater insight into caregiving experiences in ALS. Although patients identified their spouse as the primary informal caregiver, the study did not record the hours spent per day caring for their relative (Hecht et al., 2003) or the number of other care dependents (Goldstein et al., 2006a), which would have helped to determine the level of care involved. Several factors which have been shown to be pertinent to caregiving in ALS were not examined. These include, among others: spirituality (Pagnini et al., 2011); coping mechanisms (Haley et al., 1987; Murphy et al., 2009); perceived quality of social support (Goldstein et al., 2006a); and perceived level of support from health and social care services (Peters et al., 2012). Moreover, the measurement of caregivers’ attributional styles (Goldstein et al., 2000) might have identified a profile within the caregiver participants that showed greater susceptibility to reduced wellbeing. In addition, since patients’ mood and wellbeing has shown to be associated with caregiver outcomes (Rabkin et al., 2000), the study may have neglected important patient–parameters that could have further contributed to the caregivers’ experiences. Finally, this section of the research considered only the caregiver and therefore cannot determine the impact of ALS on patients and their spouses as a dyadic unit.

6.5.2. Hypothesis Five: Predictors of caregiver marital satisfaction

Following the finding that caregivers rated their levels of marital satisfaction as significantly reduced since the onset of their spouse’s illness, the current study explored predictors of current marital satisfaction, controlling for premorbid satisfaction levels. It was hypothesised that objective measures of cognition and caregiver–ratings of behavioural dysfunction would predict current marital satisfaction above and beyond patient disease factors. The results for caregivers’ marital satisfaction in Section 6.2.3. failed to support this hypothesis. While caregivers’ perceptions of total behavioural impairment in patients along with premorbid marital satisfaction scores predicted current marital satisfaction, neither the Executive function composite nor the EMOSOC composite were associated with caregivers’ perceived marital satisfaction.
Previous research identified that caregivers’ ratings of patient cognitive abilities on the Dysexecutive Questionnaire (see Wilson et al., 1998) explained 26.5% of the variance in marital satisfaction change scores (Goldstein et al., 1998). The current results are consistent with these findings, and showed that, together, premorbid marital satisfaction and the total scores on the FrSBe explained 78.1% of the variability of caregivers’ current marital satisfaction scores. Notably, premorbid marital satisfaction levels had a larger positive effect than the negative effect of the total FrSBe scores on current satisfaction levels. This indicates that the perceived relationship quality between patients and their spouses prior to ALS may protect against perceived loss of marital intimacy following the onset of disease, at least from the perspective of the caregiver. Current marital satisfaction was in turn negatively correlated with another caregiver outcome measure, perceived burden. This finding resonates with that from longitudinal data in which a relationship between caregiver–rated MIS scores and burden scores emerged at the 12 month study interval. At previous study intervals, MIS scores were predicted by caregivers’ perceptions of the patients’ psychosocial function. No measure of frontally–mediated behaviour was used (Atkins et al., 2010). In the current study, burden itself was predicted by the total behavioural score, indicating that the emergence of burden alongside reduced marital satisfaction in Atkins and her colleagues’ study may have been influenced by patients’ increased behavioural dysfunction over time. The current findings also indicate that while patients’ functional impairment may independently impact on caregivers’ perceptions of burden (in addition to depression, see Section 6.2.3.), it does not compromise caregivers’ perceptions of the quality of their relationship with their spouse. However, the MIS contains only one item of physical intimacy. Previous studies in ALS have noted decreased sexual interest and activity as well as increased sexual dissatisfaction in both ALS patients and their partners (O’Connor et al., 2008; Oh & Schepp, 2013; Wasner et al., 2004). A reduction in sexual interest and activity has been related in part to patients’ functional disability (Oyebode et al., 2013). Therefore, the inclusion of a measure that indexes sexual satisfaction in the current study may have identified a relationship between patients’ functional scores and marital satisfaction.

The current study found no associations between either of the cognitive composites or caregiver marital satisfaction; similar reasons to those outlined for the lack of relationships between the cognitive measures and caregiver wellbeing might account for this null finding (see Section 6.5.1.). The large majority of patients in the current sample
showed intact emotion recognition and processing of realistic social exchanges, suggesting that they do not experience difficulties with understanding everyday interpersonal exchanges. Previous studies of caregivers of dementia patients have indicated that emotion recognition difficulties relate to lower caregiver–ratings of relationship quality (Greve et al., 1994; Nelis et al., 2011). If, as Savage et al (2013) suggest, impaired emotion identification is only a feature of demented ALS patients, the inclusion of ALS–FTD patients for comparison with non–demented patients may reveal a relationship between reduced marital quality and socio–emotional deficits in demented patients only. However, intact emotion recognition and social behaviour does not presuppose that patients are insensitive to the needs and emotions of those around them. As indicated by the exploratory analyses (see Section 6.3.), caregivers’ ratings of patients’ empathy relative to patients’ own ratings of themselves indicated a lower ability or tendency to appreciate the perspective of others; the difference between group ratings correlated with marital satisfaction.

Perhaps for caregivers of non–demented ALS patients, the perception of the impact of the disease on their spouses’ psychosocial functioning (Atkins et al., 2010) rather than their actual executive or socio–emotional abilities are important predictors of marital satisfaction. The current study did not assess patients’ psychosocial function, precluding an examination of its predictive capacity alongside behavioural impairment in the regression model. However, the NEO–FFI used in the exploratory analyses (see Section 6.3.) did find that the caregiver–patient discrepancy score for levels of extraversion correlated with marital satisfaction. Similar to psychosocial measures, the E scale emphasises opportunities for social interaction, rather than social competence (see Sickness Impact Profile, Bergner et al, 1981, as used by Atkins et al., 2010). Reduced social interaction may correspond to decreased opportunities for caregivers’ to maintain social relationships on account of their caregiving duties. Social support has previously predicted caregiver marital satisfaction in cross–sectional (O'Connor et al., 2008) and longitudinal research (Atkins et al., 2010); thus the current study might have benefitted from examining the number and quality of relationships outside of the caregivers’ marriage to estimate their perceived quality of social support. These caveats withstanding, the current results highlight and affirm the importance of caregivers’ perceptions of patients’ behavioural impairment above the physical impact of ALS on the perceived quality of their relationship with their spouse.
6.5.3. Exploratory Question Two: Comparisons between patients’ and caregivers’ perceptions of patients’ behaviour, empathy and personality

The primary aim of the exploratory component of the study was to compare patients’ and caregivers’ ratings of patients’ empathy, emotional lability, personality and behaviour. As a secondary aim, it explored whether differences in caregiver and patient ratings or caregivers’ perception of change in the patient were associated with caregiver outcomes. For the convenience of interpretation, in this section caregivers’ ratings will be referred to as proxy–ratings while patients’ ratings will be referred to as self–ratings.

No differences were found between self and proxy–ratings on the ELQ, suggesting both parties perceived the same level of emotional lability in the patient. However, the presence of tied data was high (see Table 6.11.) which may have compromised the statistical power of the non–parametric test used.

With respect to the measures of empathy, proxy–ratings were significantly lower than self–ratings of ‘Perspective Taking’ (PT), meaning that, relative to patients, caregivers perceived patients as being less likely or less able to imagine the cognitive viewpoint of another. This corresponds with previous caregiver reports of increased self–centeredness and reduced concern for others in ALS patients (Gibbons et al., 2008). However, Empathic Concern (‘EC’), which assesses the tendency to perceive and respond emotionally to the emotional states of others, did not differ between the rater groups. This profile of interpersonal behaviour, as reported by the caregivers, might imply that patients are able to perceive and experience the emotions and feelings of those around them when they encounter overt examples, such as an emotionally–charged dispute, but show difficulty in anticipating or correctly identifying the more subtle or undisclosed intentions and thoughts of others. Caregivers may therefore perceive patients as being egocentric or indifferent to others’ feelings or intentions until they are made clear. Since neither group were asked to rate empathy retrospectively, it is not clear if this discrepancy represents the emergence of reduced cognitive empathy after the ALS onset or a pre–existing trait of which the patients are unaware or deny. Discrepancy scores between patients and their caregivers for this domain were associated with premorbid levels of marital satisfaction, possibly implying a long–standing trait prior to disease onset. The discrepancy score was also associated with current marital satisfaction. This may reflect caregivers’ appraisal that patients prioritise their needs above their own, creating resentment which becomes expressed in how they...
perceive the quality of their relationship with the patient. Alternatively, lower marital satisfaction either before or after the disease onset might influence caregivers’ perceptions of their spouses’ current empathic behaviour. However, a lack of significant differences between group ratings on the remaining empathy subscales argues against a consistent reporting bias by caregivers.

Reduced PT as measured by the IRI has been shown in bvFTD patients in previous studies, where discrepancies between self– and proxy–ratings extended to the EC domain (Hsieh et al., 2013; Rankin et al., 2006). Moreover, reduced overall empathy (a summation of caregivers’ PT and EC scores) has also been associated with lower relationship quality as perceived by the caregiver (Hsieh et al., 2013). A comparison of caregiver data between bvFTD and the current samples might imply that the nature of interpersonal change is similar between ALS and bvFTD patients; although distinguished on the basis of changes to emotional empathy in the latter patients. These distinctions may reflect differences in location and degree of underlying neurodegeneration between the patient populations (Rankin et al., 2006) and/or severity of impairment to the underlying cognitive processes that are required to interpret emotion from others (Shany-Ur et al., 2012).

In the current sample, the overall patient group showed no difficulty relative to controls on emotion identification, but did misinterpret the intentions and beliefs of cartoon and story characters (see Chapter 5, Section 5.2.2.4.). Although the empathy subdomains did not correlate with the composite for socio–emotional functioning, the profile of performance demonstrated across the socio–emotional tests by the overall patient group does resonate with a profile of reduced cognitive but intact emotional empathy as described by the carers of a subgroup of patients.

In terms of personality, caregivers rated patients’ as showing significantly lower levels of extraversion than patients rated themselves. There were also tendencies for proxy–ratings to indicate higher levels of neuroticism and agreeableness than patients’ self–ratings. When premorbid and current proxy–ratings were compared, significantly higher current ratings for Neuroticism (N) and significantly lower current ratings for Extraversion (E) and Conscientiousness (C) were indicated from prior to the onset of patients’ disease. Patients did not complete the premorbid NEO–FFI, and therefore perceived change in personality over the course of disease could not be compared between the groups. However, when caregivers’ ratings of patients’ premorbid
characteristics were compared with patients’ self–ratings of current characteristics, no significant differences were found, indicating that the inconsistencies between the rater groups for current behaviour might exist due to the caregivers’ perception of personality change in their spouse over time. Apart from a small study which found elevated neuroticism in male ALS patients (Peters et al., 1978), the current findings depart from those of previous investigations of personality in ALS patients which have noted a hard–working autonomous behavioural style (Brown & Mueller, 1970) and high levels of extraversion or “cheerfulness” (Veit, 1947). Methodological inconsistencies across these studies notwithstanding, the overall pattern of results from the ALS personality literature suggests little evidence for distinct personality characteristics in patients per se. Rather, the perceived personality change endorsed by caregivers might reflect perceptions of broader changes in patients’ cognition, emotional and social behaviour. For example, the E domain assesses interest and engagement in social interactions, situations from which patients might elect to withdraw because of a lack of interest or the anticipated inconvenience of their physical disability. Raised levels of N might correspond to caregivers attributing increased depression and anxiety in patients, while the C domain, which measures tendencies for proactive deliberation and self–discipline, might reflect perceptions of raised apathy and/or impulsiveness in patients.

In the current study, levels of apathy, dysexecutive behaviour and disinhibition, as measured by proxy FrSBe ratings, were significantly higher in the period following ALS onset than that prior to the patients’ disease. Caregivers and patients did not rate the change in behaviour since ALS onset as significantly different from each other; both groups were in agreement that behavioural impairment increased over time. However, caregivers rated higher levels of behavioural impairment for Apathy and Executive Function domains for both the premorbid and current period. In keeping with previous reports of caregiver ratings, there was a pattern of predominant apathetic behaviour, followed by executive dysfunction and lastly disinhibition (Chio et al., 2010; Grossman et al., 2006; Witgert et al., 2010). This pattern may conform to that described as the FTD–A behavioural subtype which is characterised by apathy, inertia and loss of volition (Snowden et al., 2001). Of the three subtypes, FTD–A is associated with predominant frontal lobe atrophy including the DLPFC and relatively less OFC deterioration that is typical of the disinhibited subtype (FTD–D, see Chapter 2, Section 2.1.1.).
Notably, discrepancy scores calculated to reflect discrepancies between self- and proxy-ratings for empathy, personality and behaviour were associated with caregivers’ outcomes. The lower the caregivers’ ratings of the patients’ tendencies or abilities for ‘perspective taking’ relative to patients’ self-ratings, the lower caregivers’ rated their premorbid and current marital satisfaction. Similarly, the lower the caregiver’s ratings of patients’ level of extraversion relative to the patients’ self-ratings, the worse caregivers perceived their current relationship with the patient. The discrepancy score for patients’ current overall behavioural dysfunction was associated with increased caregiver anxiety and worse caregiver strain and burden. Caregiver burden, in turn, was associated with discordant ratings between couples regarding patients’ current executive dysfunction. The more the caregiver overestimated patient’s behavioural dysfunction on these domains relative to the patients’ self-ratings, the worse the caregiver’s rated their own anxiety and feelings of strain and burden.

Change scores were also calculated to reflect caregivers’ perceptions of change in patients’ personality and behaviour since the onset of their ALS. Caregivers who perceived increased levels of neuroticism in patients over the course of their illness tended to report greater levels of anxiety, depression, strain and burden. Higher depression was also associated with caregivers who perceived greater reductions in extraversion and conscientiousness in patients following their disease onset. The relationship between caregivers’ outcomes and their perceptions of behavioural change in patients since the onset of ALS was also explored. The greater the perceived increase in the patient’s overall behavioural dysfunction and levels of apathy, executive dysfunction and disinhibition, the worse the caregiver’s self-ratings of depression, strain and burden. The greater the perceived increase in the patient’s level of disinhibition, the lower the caregiver’s ratings of current marital satisfaction. Finally, the greater the perceived increase in the patients’ levels of apathy, executive dysfunction and overall behavioural dysfunction, the worse the caregiver’s self-rating of anxiety.

Cautious interpretation should be applied regarding these difference and change scores which were simply calculated by subtracting responses from one participant group or time-point from another. While such scores might show face validity and be intuitively appealing, their psychometric properties have not been investigated. Therefore, the associations between these scores and the caregiver outcomes should be viewed as
purely exploratory. Due to the unadjusted multiple correlations, some of the statistically significant results could have occurred by chance. Furthermore, the identification of causal relationships is not possible due to the cross-sectional nature of these analyses. Nonetheless, these relationships highlight possible additional sources of diminished caregiver wellbeing and might argue for the inclusion of caregiver–perceived empathy and personality alongside behaviour in future studies of caregiver outcomes in ALS. Recommendations for this area of research are discussed in Chapter 7.

Whether the current inconsistencies in patient and caregiver reports are suggestive of lack of insight in patients is debatable. Anosognosia for behavioural impairment has been suggested to distinguish ALS–FTD patients from non–demented ALS patients. In fact, self–ratings of non–demented ALS patients have reported greater behavioural dysfunction than proxy–ratings (Abrahams et al., 2005b; Girardi et al., 2011; Woolley et al., 2010a). Nonetheless, an earlier study which found endorsements of greater behavioural impairment from ALS caregivers relative to patients attributed these differences to reduced insight in the patients (Chio et al., 2010). Moreover, there is some evidence to suggest that non–demented ALS patients lack insight into their cognitive impairment (Stukovnik et al., 2010). In the current study, patients’ ‘awareness’ was defined as a function of both patient and caregiver perspectives. However, it is not certain which ratings provide the most accurate appraisal. This question is important because the method chosen for quantifying patient characteristics may substantively influence the inferences drawn about the psychological and behavioural consequences of ALS. Rather than reduced insight, patients’ responses might have been influenced by denial coping mechanisms or social desirability biases. Similarly, a large majority (82.4%) of caregivers reported high levels of burden and reduced marital satisfaction since the onset of their spouses’ illness. It is possible that the caregivers’ perceptions of the patients may have been influenced by their own mood, feelings of burden, strain and affection for their partner. In addition, the caregivers’ own empathic behaviour and personality characteristics were not examined; these traits may have been projected onto their spouse or mediated their responding. More generally, these results illustrate the need to examine biases that can occur when measuring self– and informant–reported data in ALS. Chapter 7 proposes the means by which this might be achieved.
7. General Discussion

The studies reported in this thesis have documented several findings relating to the cognitive–behavioural profile of non-demented ALS patients and the impact that patients’ cognitive–behavioural change poses for the ALS caregiver. This final chapter will provide a summary of the main findings of the research and discuss the implications for the management of patients and their caregivers. Subsequently, the limitations of the current study are acknowledged and recommendations for future ALS research are considered.

7.1. Summary of main findings

7.1.1. Cognitive impairment in ALS

Chapter Five reported the results of the first study which tested the hypothesis that, relative to healthy controls, patients would show impaired performance on tasks measuring executive functioning and socio–emotional processing. In support of this hypothesis, the results indicated that ALS patients showed higher scores (greater impairment) than controls on a canonical variate created by a multivariate procedure. Univariate analyses revealed that mean composite scores created to reflect executive functioning and socio–emotional processing (EMOSOC) were significantly higher (more impaired) in patients than controls. Inspection of the discriminant function coefficients indicated that that group membership was maximally differentiated by performance on the Executive function composite, which showed greater weighting than the EMOSOC composite. This indicates that executive functioning contributed more to group differences on the canonical variate than socio–emotional processing.

Single–case analysis revealed that the relative proportion of participants impaired on either composite within each group did not differ significantly. Proportionally more patients than controls showed concurrent impairments on the Executive and EMOSOC composites; proportionally more patients than controls showed isolated impairments on the Executive composite and proportionally more patients than controls showed isolated impairments on the EMOSOC composite. However, none of the differences in these proportions were significantly different. Dissociations of performance between the Executive and EMOSOC composites were found for three patients (none were found for controls). For all three patients, the directions of these dissociations indicated that
patients were impaired on the Executive composite but unimpaired on the EMOSOC composite.

Performance on the individual components of the Executive function composite was compared between the groups. In addition, groups were compared on the Hayling Test, as this was not included in the Executive function composite (see Chapter 5, Section 5.2.2.1.). Following Bonferroni corrections and relative to control participants, ALS patients showed impaired performance on two tests of executive function: the D–KEFS card sorting task and the Hayling Test. A trend for impaired performance relative to controls on the VFI–S word condition was also found. Single–case analysis revealed that significantly more patients than controls were impaired on both conditions of the VFI. Trends for proportionally more patients than controls to show impairments on the Hayling latency and two error conditions were also found.

An investigation of the differences between participant groups on the EMOSOC components was also conducted. Patients performed significantly worse than controls on all the subtests of the Happé task; however, no between–group differences were observed for the RME and the three subtests of the TASIT. Single–case analysis revealed more patients than controls were impaired on the single cartoon abstraction test of the Happé task. This pattern of results suggests that the group differences obtained on the EMOSOC composite were driven by performances on the subtests of the Happé task.

More detailed exploratory analyses were conducted on the subtests of the TASIT and Happé tasks to investigate group performances on the conditions within the tests. Between–group analyses conducted on the performance of the TASIT subtasks revealed no group differences for the emotion recognition test or the two social inference tests (minimal or enriched social information subtests). For the Happé cartoon subtasks, within–group analyses found that both groups performed better on the mental (ToM) cartoon trials than the physical cartoon trials. Conversely, for the Scenario subtask, both groups performed better on the physical scenario trials than the mental (ToM) scenario trials. Qualitative information from the errors scores on these subtasks indicated that patients committed significantly more partial and descriptive errors than controls on the single–cartoon inference subtask, whereas they committed significantly more misconstructions on the forced–choice cartoon pairs and scenario subtask.
Groups were compared on one measure of language (confrontation naming) and memory. There were no differences between groups on either test. Overall, the pattern of impairments in the ALS sample indicated predominant executive dysfunction, with relative sparing of socio–emotional processing and intact language and memory functions. However, the limited number of tasks assessed from the other domains may have affected the ability to detect differences.

Because of the potential for psychoactive medication to affect cognitive performance on some of the tasks, within–patient group analyses were conducted to compare patients receiving psychoactive medication with those not receiving such medication. There was a trend for reduced performance in the medicated patient sample relative to the non–medicated patient sample on the emotion recognition task. Medicated patients also showed a trend for superior performance on a delayed cued recall trial compared to non–medicated patients.

7.1.2. Behavioural change in ALS

Contrary to Hypothesis Two, patients did not show higher levels of behavioural symptomatology than controls for both retrospective and current time periods. However, there was a trend for patients to report significantly higher levels of current Apathy than controls. Significant interactions between group membership and time were found for all domains of the FrSBe. Patients’ overall behaviour scores increased over time (i.e. from retrospective to current ratings), while controls’ overall scores decreased. This pattern was replicated for the Executive Dysfunction and Disinhibition subscales. For the Apathy subscale, both groups reported increased apathy with time, but the magnitude of the increase was greater for patients. Within the patient group, the proportion of patients that satisfied ‘caseness’ for Apathy and the FrSBe total domains increased significantly from the premorbid (retrospective) to current time point. This pattern was not demonstrated in the control group. Overall, the results of these analyses indicate a change in self–reported behaviour since the onset of ALS, with increases in apathy, dysexecutive behaviour and disinhibition relative to controls over the same time.
7.1.3. Mood, self-perceived personality and empathy in ALS

Patients and controls did not differ on measures of self-reported anxiety or depression; the median scores for either group were not indicative of mood disorder according to revised scoring criteria (Gibbons et al., 2011).

There was a trend for patients to report significantly higher current levels of conscientiousness than controls on the NEO–FFI scale. However, significantly more controls than patients had very low levels of conscientiousness. This suggests that the between-group difference in mean ratings for the Conscientiousness domain might have been an artefact of the control sample and not an indicator of a disease related change. There were no group differences for any of the empathy domains of the self-reported IRI measure.

7.1.4. Predictors of emotional processing and social cognition in ALS

In Chapter Five it was hypothesised that ALS patients’ executive (dys)function would be the main predictor of their performance on tests of emotional processing and social cognition, with smaller contributions from self-reported behaviour, mood, personality and empathy. Correlational analyses identified the following predictors which were entered into a final hierarchal regression model: Age; years of formal education (control variables); the Executive function composite; the FrSBe Total score, HADS T (the summation of HADS A and HADS D scores) and the NEO–FFI Openness score. The results of the final regression analysis supported the hypothesis. Executive function contributed most to the performance of ALS patients on a composite of emotional processing and social cognition, with smaller, albeit non-significant, contributions from behavioural, personality and mood factors.

7.1.5. Caregivers’ perceptions of mood, strain, burden and marital satisfaction

Caregivers self-reported significantly higher (worse) scores for depression and anxiety than patients’ self-reports. The mean anxiety scores were within the ‘borderline case level’ for both groups according to revised cut-off criteria (Gibbons et al., 2011); significantly more caregivers than patients satisfied this criterion. There was a trend for more caregivers than patients to satisfy criteria for ‘case level anxiety’ and ‘case level depression’.

Currently felt strain correlated positively and most strongly with how much caregivers felt that their partner’s illness affected other areas of their own life. It also correlated
positively with how much strain they anticipated feeling in a year’s time and how much control they felt they had over their own reactions to their partner’s illness. A large percentage of caregivers (82.4%) satisfied criteria for high levels of burden. Caregiver ratings of marital satisfaction were significantly lower following the onset of their spouse’s illness than they were reported to have been prior to the disease.

7.1.6. Predictors of caregiver outcomes

Chapter Six tested two hypotheses relating to caregivers’ outcomes; each will be described in turn. The first hypothesis predicted that objective measures of cognitive function and carer–perceived behavioural impairment in patients with ALS will contribute significantly to carer wellbeing (in terms of mood, perceived burden and strain), above and beyond patients’ disease status and symptoms. A series of forward selection multiple regressions identified the following functional relationships:

iv) Disease severity, as indicated by the ALSFRS–R Limb severity score, significantly predicted caregiver depression and burden, with burden further predicted by behavioural symptoms, as measured by the FrSBe total current score.

ii) The overall level of behavioural symptoms, as indicated by the FrSBe total current score, significantly predicted caregiver anxiety.

v) Emotional lability and performance on the emotional processing and social cognition tasks, which were indicated by the ELQ total and EMOSOC composite respectively, significantly predicted caregiver strain.

These predictors were entered into a final hierarchal regression model in order to assess their predictive capacity of a global outcome measure of caregiver wellbeing (a summation of standardised scores for mood, strain and burden). Only limb severity scores (ALSFRS–R Limb) and the caregiver–rated behavioural scores (FrSBe total current) were found to be significant predictors of the global outcome scores. These results fail to support the hypothesis that both objective measures of cognitive performance and caregiver–rated patient behaviour would predict caregiver outcomes. Instead, it highlights the combined roles of caregiver perceptions of patients’ behaviour and patients’ disease severity in the caregiving experience of ALS.

The second hypothesis predicted that objective measures of cognitive function and carer–perceived behavioural impairment in patients with ALS would contribute
significantly to caregivers’ perceived marital satisfaction, above and beyond patients’
disease status and symptoms. Separate multiple regression analysis found that the
FrSBe Total current score was a significant predictor of caregivers’ current marital
satisfaction. When the FrSBe Total was entered into a hierarchical regression
controlling for premorbid marital satisfaction scores, it remained a significant predictor
in the model. As before, these results fail to support the hypothesis that both objective
measures of cognitive performance and caregiver–rated patient behaviour would predict
caregiver outcomes.

7.1.7. Comparisons between patients’ and caregivers’ perceptions of patients’
empathy, behaviour and personality

Caregivers’ ratings of patients’ levels of ‘perspective taking’ (PT) were significantly
lower than patients’ self–ratings on the IRI. This indicates that, relative to the patients,
caregivers perceived patients as being less likely or less able to imagine the cognitive
viewpoint of another person. Exploratory correlation analyses found that caregiver–
patient discrepancy scores for this domain correlated positively with caregivers’
perceptions of premorbid and current marital satisfaction (i.e. the lower the caregiver’s
rating of the patient’s level of PT relative to the patient’s self–rating, the lower the
caregiver’s ratings of premorbid and current marital satisfaction).

The relative perception of patient behaviour was compared between caregivers and the
patients themselves. There were no differences between caregivers and patients in
ratings of patients’ emotional lability for any of the ELQ subscales or the total score. On
the FrSBe, like the patients themselves, caregivers rated patients as showing higher
levels of behavioural dysfunction following the onset of their illness than before their
illness for all domains. Between–group ratings of the change in patients’ behaviour
since their disease onset did not differ. Ratings from both groups increased significantly
over time for all domains. However, caregivers rated patients as showing higher levels
of premorbid and current behavioural dysfunction than patients rated themselves. This
was true for the domains of Apathy, Executive Dysfunction and the total FrSBe score,
but not for the Disinhibition domain.

Caregiver–patient discrepancy scores for FrSBe subscales and total score were
computed. Exploratory correlation analyses revealed that the current FrSBe Total
discrepancy score was positively associated with caregiver anxiety, strain and burden.
In addition, the current Executive Dysfunction discrepancy score correlated positively with caregiver burden (i.e. the higher the caregiver’s ratings of the patient’s behavioural dysfunction on these domains relative to the patients’ self–ratings, the worse the caregiver’s self–ratings of anxiety, strain and burden).

Change scores were also calculated for each FrSBe domain (by subtracting caregivers’ ratings of patients’ premorbid behaviour from their current behaviour). Exploratory correlational analyses revealed that all the FrSBe domain change scores correlated positively with caregiver measures of depression, strain and burden (i.e. the greater the perceived increase in the patient’s behavioural dysfunction on these domains, the worse the caregiver’s self–ratings of depression, strain and burden). The Disinhibition change score correlated negatively with current marital satisfaction (i.e. the greater the perceived increase in the patient’s level of disinhibition, the lower the caregiver’s ratings of current marital satisfaction). The Total FrSBe change score, the Apathy change score and the Executive Dysfunction change score correlated positively with caregiver anxiety (i.e. the greater the perceived increase in the patient’s behavioural dysfunction on these domains, the worse the caregiver’s self–rating of anxiety).

On the NEO–FFI, caregivers rated patients as showing significantly lower levels of Extraversion than patients rated themselves, with trends for higher levels of Neuroticism (N) and lower levels of Conscientiousness (C). Caregiver–patient discrepancy scores for the NEO–FFI domain ratings were calculated. Exploratory correlational analyses revealed a positive association between the Extraversion (E) discrepancy score and current marital satisfaction (i.e. the lower the caregiver’s rating of the patient’s level of E relative to the patient’s self–rating, the lower the caregiver’s current marital satisfaction). Change scores reflecting differences in caregivers’ premorbid and current ratings of the patients were also calculated for the personality domains. Exploratory correlational analyses revealed that the N change score correlated positively with caregiver outcomes of mood, strain and burden (i.e. the greater the perceived increase in the patient’s level of N, the worse the caregiver’s self–perceived level of strain and burden). The E and C change scores correlated negatively with caregiver depression (i.e. the greater the perceived reduction in the patient’s level of E and C, the worse the caregiver’s self–reported depression).
7.2. Clinical implications

7.2.1. ALS cognitive–behavioural change and the ALS clinic

Despite the noted limitations of the current research (see Section 7.3.), the results of this study corroborate the general position that cognitive–behavioural impairment in ALS is characterised by executive dysfunction and a range of behavioural change associated with frontal subcortical dysfunction. In particular, compared to healthy controls, patients showed difficulties on tasks requiring abstract and flexible thinking, problem-solving and inhibitory control. Whether these deficits manifest in patients’ daily lives can be inferred from behavioural data provided by patients or caregivers. Indeed, in addition to apathy, both patients and their caregivers in the current sample endorsed increased dysexecutive behaviour and disinhibition since the onset of ALS using the FrSBe; these endorsements appear to coincide with the profile of performance displayed by the patients on the executive function tasks. One might speculate that patients with this cognitive and behavioural profile may show problems with, or an indifference towards, managing financial affairs, planning for future events or arriving at decisions regarding their clinical care. Progressive physical disability may cause patients to withdraw from work or increasingly rely on others, thereby relieving patients of their usual cognitively–demanding duties. Difficulties with ordinary tasks may therefore go unnoticed by clinical teams until patients’ are required to manage and comply with palliative aids, such as communicative and respiratory support devices (Abrahams, 2013). Thus, ALS clinics should screen for cognitive and behavioural impairment in newly–diagnosed patients as soon as ethically and practically possible in order to detect possible difficulties and direct care strategies.

Along with apathy, ALS patients have been reported by caregivers as showing egocentricity and a ‘loss of interest in others’ (Gibbons et al., 2008). In the current study, caregivers rated patients as showing a lower ability or tendency to appreciate other people’s perspectives than patients rated themselves. This may indicate changes to patients’ interpersonal behaviour which patients either deny or of which they are unaware. On the other hand, proxy and self–ratings for patients’ level of empathic concern were similar. Furthermore, the current overall patient group showed no difficulty relative to controls on emotion identification, but did misinterpret the intentions and beliefs of cartoon and story characters. Clinicians should be aware that while ALS patients may respond appropriately to other people’s emotions, they may not
be able to anticipate or be responsive to the thoughts or intentions of those around them. This can place strain on the patient’s interpersonal relationships which become more important as the patient’s dependency on others increases with their functional decline. The implications for and education of the caregiver with regards to possible interpersonal changes in the patient should be considered in clinical consultations with ALS families (see Section 7.2.2.).

Although not supported in the present study, other cognitive functions such as language, memory, emotion processing and ToM have been reported as impaired in patients from other ALS studies, with evidence indicating these deficits occur independently or alongside executive dysfunction (see Chapter 2, Section 2.3.). This has led to the suggestion of a spectrum of cognitive dysfunction within ALS, with some authors (Abrahams, 2013; Goldstein & Abrahams, 2013; Taylor et al., 2013) suggesting the need for revision of the Strong et al’s (2009) consensus criteria (see Chapter 1, Section 1.5.3.) 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) or the choice and number of measures used in the study. An absence of executive impairment should not be taken as an indication of intact cognitive function in other domains.

Despite over 30 years of documented cognitive impairment in non–demented patients, only relatively recently have screening measures specific to ALS been developed. Initially screening tools emphasised the detection of executive dysfunction over other domains and varied in their use of controls for motor disability (e.g. Flaherty-Craig et al., 2006; Woolley et al., 2010b). The Edinburgh Cognitive and Behavioural ALS Screen (ECAS; Abrahams et al., 2013) is a brief (~15 – 20 min) multi–domain screening measure, assessing executive function, social cognition, language, memory and visuospatial functioning. It is designed to minimise the confounds of patients’ physical impairment on cognitive performance and is accompanied by a separate caregiver interview of the patient’s behaviour, with items also adapted to take into account ALS symptoms. Within the cognitive screen social cognition is assessed under the domain of executive functioning and comprises a simple ToM task in which preference judgments are made on the basis of eye–gaze direction (similar to that which was reported to be a sensitive measure by Girardi et al 2011). Whilst preference
judgements were not assessed in the current study, patients did show difficulties with inferring the thoughts and intentions of cartoon and story characters. Furthermore, their performance on ToM tasks appeared to be secondary to their executive dysfunction. The current study thus supports the inclusion of social cognition measures in ALS cognitive screens. It also provides some justification for their inclusion under the assessment of executive function, rather than as a stand-alone domain. Clinics with restricted resources will benefit greatly from using the ECAS as it identifies the severity and nature of cognitive and behavioural impairment in patients and will allow clinical teams to make informed and tailored care arrangements for patients and their families. Where severe cognitive deterioration is suspected, detailed neuropsychological testing can then corroborate comorbidity of FTD.

In bvFTD, emotion recognition and social cognitive deficits are pronounced and may be independent of executive dysfunction. For this reason, the inclusion of emotion recognition and social cognition measures to support a confirmation of a bvFTD diagnosis has been proposed (Sarazin et al., 2012; Schroeter, 2012). In the current study, ALS patients’ emotion recognition was intact. The current findings would not support the use of emotion recognition measures in clinic screening protocols for ALS patients. However, as emphasised throughout this thesis, reports of ALS impairments on such measures are inconsistent. In particular, it is suggested that the emergence of emotional processing deficits in ALS are strongly associated with the presence of FTD (Savage et al., 2013). Therefore, in–clinic screening might yet potentially benefit from the inclusion of emotional processing paradigms to identify ALS patients with possible FTD comorbidity.

7.2.2. ALS caregivers and the ALS clinic

The results of the present caregiver study join a growing body of work which underscores the effects of ALS that extend beyond the patient to corresponding family members. Perceived lack of support from health and social services has been associated with reduced mental health and higher strain in ALS caregivers (Peters et al., 2012); a finding which reinforces the duty of the ALS clinical team to address caregiver wellbeing.

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 limb–related
impairment, as well as behavioural dysfunction, were the main contributors to reduced caregiver wellbeing and marital satisfaction. 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. Thus, clinicians should be aware that ALS may bear common but unequal outcomes for patients and their caregivers. Moreover, care teams should be aware that the symptoms of ALS may pose differential effects upon caregivers. The current results revealed that while functional impairment predicted caregiver depression, behavioural dysfunction predicted caregiver anxiety; together, these symptoms predicted increased burden. Routine monitoring of the patient’s functional, cognitive and behavioural functioning may prepare the clinical team to tailor their support for caregivers.

Caregivers perceived patients as showing less cognitive empathy than patients perceived in themselves, reported changes in personality since the onset of their spouse’s ALS and endorsed higher levels of behavioural impairment in patients than patients did themselves. Discrepancies in patients and caregivers perceptions should be identified by clinics in order to examine and screen for the possibility of reduced awareness or use of coping strategies by patients. ALS caregivers who perceive patients as being supportive towards the caregivers’ problems have shown to be more likely to report finding positive experiences associated with caring for their ill relative (Boerner & Mock, 2012). Therefore, 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).

A large majority of caregivers reported a high level of burden and reduced marital satisfaction following their partner’s ALS onset. 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.
7.3. General 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.

7.3.1. Recruitment criteria, sampling bias and participant characteristics

The exclusion criteria adopted by the study in the recruitment of the patients were extensive and 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) and ALS–related factors (e.g. insufficient respiratory function; severe fatigue), the employment of these criteria may limit the representativeness of the current patient sample of the ALS population as a whole.

Initially it was planned that patients with an FVC of 70% and below were to be excluded from the study. In practice, this was difficult to implement as the research sites varied in their method and frequency of assessing respiratory functioning in their patients. In these instances, the study relied on the clinical judgement of the patient’s clinician and a standardised measure of respiratory function completed by the patient prior to participation. This might mean that the identification of cognitive dysfunction in the current study may have been influenced by the inclusion of patients who themselves or their clinician were unaware of subtle decrements in respiratory functioning.

At the start of the study, patients were excluded on the basis of receiving psychoactive medication. As the study progressed, this was found to be the greatest barrier to recruitment and, after much deliberation and consultation with research members, was relaxed, allowing patients who were receiving medication for ALS–related symptoms (e.g. EL, pain, stiffness) but not mood disorder to be recruited to the study. Analyses comparing the patient subgroups indicated that compared to non–medicated patients, patients receiving SSRIs and/or benzodiazepines showed a trend for superior performance on a delayed cued memory trial. In addition, a trend for worse performance by medicated patients on the basic emotion recognition task (TASIT EET) was found. These trends, however, were not sufficient to produce overall group
differences between patients and controls on the CVLT or EET. While the exclusion of psychoactive use is preferable, this is not always practical and may further reduce the representativeness of the patient sample to the wider ALS population. Further, the pattern of performance by medicated patients found in the current study might inform the future study of emotion processing and other cognitive functioning in ALS (see Section 7.4.1.).

A strength of the study is the nature of its multicentre recruitment from four tertiary care centres and one community–based healthcare hospice. Two–thirds 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.

Patients in the current study were ethnically homogeneous (mostly Caucasian), well–educated (an average of 14.5 years of formal education) and, as a group, were of high 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). Furthermore, Stern’s Cognitive Reserve Hypothesis states that persons with higher lifetime intellectual enrichment are better able to sustain neuropathological disease before or without succumbing to the clinical manifestation (e.g. dementia) of the disease (Stern, 2009). The theory is supported by evidence from cross–sectional and longitudinal research suggesting that higher levels of intelligence and educational attainment may act as preventive or compensatory factors in the development of age– and disease–related cognitive deficits (e.g. Meng & D’Arcy, 2012; Tucker-Drob et al., 2009). Potentially, the patients in the current study might demonstrate high cognitive reserve, and are thus relatively less susceptible to cognitive change; this possibly limits the inferences drawn regarding ALS performance on the current set of neuropsychological tests.
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. Of the spouses available for invitation, approximately one–fifth declined participation which may further have introduced sampling bias into this part of the study. Some caregivers maintained their care duties while working part– or full–time, and this might have influenced their willingness to take part in the study. 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 caregiver in the study endorsed ZBI scores that met cut–off criteria for substantial burden. Conversely, caregivers experiencing high levels of strain and burden may have been more motivated to take part to communicate their distress. Furthermore, as the study was interested in the impact of ALS on the marital relationship, only spouse caregivers were recruited. Thus, the comparability of the current findings with those of other studies whereby spousal and filial caregivers are analysed together cannot be assumed.

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), posing implications for the interpretation of group differences on measures of empathy personality and behaviour. Higher educational attainment and socioeconomic status are also suggested to predict research participation (Rosenthal & Rosnow, 2009); however, participants groups were matched on these variables.

7.3.2. Neuropsychological assessment

A. Patients and controls

Testing of patient participants was conducted in the patient’s home, as opposed to a controlled laboratory setting. However, this was necessary to accommodate the patients’
reduced mobility. Stringent testing protocols were followed for both participant groups regardless of venue, reducing systematic bias introduced by disparate testing contexts. The testing battery was long (approximately 6 hours) raising the risk of fatigue. For this reason testing was spaced out over a minimum of two sessions. Where fatigue was suspected or expressed, breaks were encouraged or the testing session was terminated. Controls were offered the same testing options, although this was rarely required. 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.

In common with several ALS studies; the selection of cognitive tasks was restricted by patients’ motor impairment or what tasks could be modified to accommodate their disability. The inclusion of more ecologically–valid tests of executive function (e.g. the motor–free Medication Scheduling Task, see Stukovnik et al, 2010) would have complemented the current set of measures; however, given the length of the battery and the possibility of patient fatigue, this was not practical. Nonetheless, the selected tasks possessed good validity and reliability (see Chapter 4) and have provided useful clinical information in relation to the patients’ cognitive difficulties. The limitations of the tasks used to assess socio–emotional processing were discussed in Chapter Five. As already mentioned, a limitation of the neuropsychological battery is that language and memory performance was estimated using only one task, potentially under–estimating patients’ dysfunctions in these domains.

B. Caregivers

The excessive time demands involved in caregiving are commonly cited as a barrier to research participation (Dura & Kiecolt-Glaser, 1990). For this reason, caregiver participants were able to determine the format of their participation: in a one–on–one interview with the researcher; answering questionnaires independently and returning these to the researcher or a combination of both. While this flexibility might have encouraged participation in some caregivers, the mode of participation may have influenced responding by participants. Self–administered questionnaire responding might have increased participants’ willingness to disclose information regarding sensitive items (Tourangeau & Yan, 2007), but they would not have benefitted from the presence of the researcher to clarify questions that arose during responding. Nonetheless, all caregiver participants received the same informed consent and
debriefing procedures which included opportunities to raise their concerns and enquires.

7.3.3. Statistical techniques and sample size

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.

Compared to other studies of emotional processing and social cognition in ALS, the current patient sample was relatively large (n=55). However, the caregiver sample was smaller (n=35) and this may have compromised the study’s ability to detect significant effects or relationships. 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 caregiver study. Thus the parsimonious regression models might have excluded patient and/or caregiver factors that could have explained additional variance in the criterion variables. Furthermore, and as already mentioned, the creation of composite scores to reduce the inflation of Type I error, may have masked significant associations in both studies. Moreover, a major methodological limitation of the current research is that the data are cross–sectional, and therefore precludes identification of causal relationships.

7.4. Directions for future research

In order to address some of the methodological limitations delineated in Section 7.3. as well as those present in the ALS literature, future research is required. In this section, recommendations for future studies of ALS are considered.

7.4.1. Neuropsychological assessment in ALS

The pattern of cognitive performance by the ALS patients in the current study was characterised by executive dysfunction, with relative sparing of socio–emotional
processing and intact language and memory functions. Deficits in patients were elicited on tasks believed to assess DLPFC (e.g. D–KEFS, VFI) and OFC (e.g. Hayling) functioning. Historically, measures that load on DLPFC function have predominated in ALS cognitive research. Only recently, with the suggestion of bvFTD–like behaviour and socio–emotional processing impairments, has OFC assessment gained similar attention. There are, of course, limits to the specificity of cognitive tests; nonetheless the current study suggests that the design of future ALS neuropsychological assessments should test the function of both neural regions. While beyond the scope of the current research, future ALS studies could systematically explore overlap and/or dissociations in DLPFC and OFC functioning in patients using these and other tasks (as per Meier et al., 2010) and examine their relative contribution to emotion recognition and/or ToM in patients.

A pervasive limitation of studies which focus on executive functioning or socio–emotional processing in ALS is the use of a single measure of language and/or memory. Phukan et al.’s population–based study indicated a heterogeneous profile of cognitive impairment in their non–demented ALS cohort, in which several phenotypes were differentiated by the presence of predominant or exclusive executive impairment, language and/or memory dysfunction (Phukan et al., 2012). Cognitive heterogeneity within ALS clinic–based samples is also well documented (see Chapter 2). Detailed assessment of each cognitive domain may be unrealistic for most ALS studies. The integration of a brief but multi–domain and ALS–specific cognitive battery, such as the ECAS (Abrahams et al., 2013), may circumvent time pressures and patients’ fatigue, while providing a sensitive screen for impairment on specific domains.

Detailed medical histories and clinical information should be obtained and used to screen for factors that might influence cognitive performance. The current results reported a trend of worse performance for psychoactive medicated patients compared to non–medicated patients on the emotion recognition test. Several cognitive studies do not report medication profiles for their patients. At most, some have excluded patients receiving SSRIs but not those using benzodiazepines. Further study is required to determine the effects of these medications on the cognitive performance and behaviour of patients, but in the interest of prudence, up–to–date patient medication profiles should be listed and the potential influence of psychoactive medication controlled for wherever possible.
Different methods were used to analyse the neuropsychological test scores of the current sample. Comparisons based on mean and median scores are useful for indicating overall differences between groups, but they may mask the potential heterogeneity of impairment within ALS samples. Single–case analysis is able to reveal the prevalence of impairments within a specific domain and is better positioned to identify subgroups within patient samples. For example, while no between–group differences were found for the VFI–S score in the current patient sample, single–case analysis revealed that significantly more deficits on this index were present in the patient group compared to the control group. The current study thus highlights the utility of combining between–group comparison with single–case analysis in ALS research to fully elucidate cognitive performance in patients.

The current study adopted novel single–case methods developed by Crawford and colleagues (2011) to test for (i) deficits on cognitive tasks and (ii) dissociations between composites or conditions within tasks, while (iii) controlling for the influence of covariates (age, years of education and gender; see Chapter 5, Section 5.2.2.3). Different techniques to identify deficits or dissociations in patients’ performance have been used in ALS research; possibly contributing to the variable prevalence of impairment reported across studies. The current methods show superior control for Type I and Type II error rates over other single–case methods, some of which have been used in ALS research (e.g. the z–score method) (Crawford & Garthwaite, 2005, 2012).

While the study did not evaluate different methods of impairment classification, it recommends the current methods for use in ALS investigations, particularly when control samples are modest or there is a need to partial out the effects of potential confounding variables.

The current study also supports the use of quantitative and qualitative (e.g. error scores) indices in ALS cognitive assessment, as was used to aid interpretation of patients’ performance on the Hayling test and Happé task. As well as characterising performance, qualitative information may also reveal impairment patterns that were masked by comparing groups on numerical scores alone.

Chapter Two provided a comprehensive overview of the several factors (e.g. onset type, presence of EL, etc.) that may influence cognitive status in ALS. However, the study itself did not distinguish patients’ performance on the basis of these factors. Future research could differentiate between bulbar– and limb–onset patients; those patients
with or without bulbar or EL symptomatology or MND phenotypes (PLS, PMA) to investigate potential disease markers for the susceptibility of cognitive change in ALS.

Finally, the inclusion of patients with FTLD subtypes would elucidate the boundaries between the mild and moderate cognitive–behavioural changes that can occur in ALS and the more overt cognitive–behavioural hallmarks of FTD. Studies comparing ALS and patients with FTD typically recruit bvFTD patients. Given the heterogeneous cognitive involvement demonstrated in non–demented ALS, it is recommended that studies also compare ALS patients with ALS–FTD and FTD patients who fulfil SD and PNFA criteria. Where it is unrealistic for patients with FTD to complete full test batteries, abbreviated versions of tasks could be employed for comparability.

7.4.2. The assessment of emotional processing and social cognition in ALS

The findings of the current study indicate the value of assessing emotional processing and social cognition in ALS patients using both static and realistic measures. Future studies using a range of media will help to further characterise the scope of socio–emotional deficits in ALS. Emotion processing should be assessed using several modalities (e.g. speech, faces, words, scenes) to determine if global or select emotion processing deficits are apparent in the disease. Social cognition measures should differentiate between different components of ToM, such as first–order and second–order ToM or cognitive and emotional ToM. In addition, several ToM tasks of graded difficulty (e.g. both with low and high executive demands) could be used in the same battery with the purpose of elucidating the nature of the underlying processes of ToM performance in ALS. Importantly, more work is required to determine whether the available social cognition tasks reliably measure ToM constructs; this is an issue that is acknowledged (Freedman & Stuss, 2011) but not widely debated or researched in the general neuropsychological literature.

The developers of the TASIT have shown it to be a valid and reliable assessment of the perception of realistic social exchanges (McDonald, 2012). However, as the contextual information is presented all at once (e.g. expression, language, tone, gesture), it is not possible to determine whether patients may indeed have difficulties interpreting specific social cues (e.g. prosodic emotion as opposed to facial emotion), but that these impairments are overcome by the presence of auxiliary cues. Administration of this test in the current study could have included presenting elements of the exchanges in isolation. For example, the emotion recognition test could have been presented without
the vocal content (i.e. audio on mute) or sincere and sarcastic conversation could have been presented without the visual content (i.e. audio only). ALS patients have previously shown difficulties recognising emotionally–toned sentences (Meier et al., 2010), which might extend to difficulties with linguistic cues used to indicate sarcasm, such as intonation and emphasis, in speech. Therefore, future studies could determine the specificity of these deficits.

The current study combined scores of emotional processing and ToM tasks under one composite of performance (EMOSOC). Future research could investigate the relationship between emotion processing and ToM. For example, impaired processing of negative emotion in bvFTD patients has been suggested to partially underlie their difficulties in discriminating between sincere and sarcastic statements (Kipps et al., 2009). The current study did not find emotion or sarcasm processing deficits in the patient sample, but future work could investigate whether or not differential impairments or dissociations on such items exist in ALS.

The advantage of obtaining qualitative information (e.g. error responses) from verbal–based social cognition measures has already been proposed (see Chapter 5); however, the verbal and time demands of such measures may be unsuitable for some ALS patients. Future work could shorten existing verbally–based measures, although this might jeopardise the sensitivity of the task. Alternatively, non–verbal measures which rely on picture–sequencing formats, such as comic strips (e.g. Ciaramidaro et al., 2007; Völlm et al., 2006) could be used.

Several studies of socio–emotional processing in ALS have either not assessed executive function or included a limited range of tasks to ascertain the construct (e.g. Papps et al., 2005; Schmolck et al., 2007; Staios et al., 2013; Zimmerman et al., 2007). The results of the present study exhort the inclusion of executive function measures alongside socio–emotional tasks to determine the role executive dysfunction plays in emotion processing and ToM in patients. Future research is required to determine whether the relationship between executive function and social cognition suggested by patients’ performance in the current study is reliable, as previous studies have noted independence of these constructs in ALS patients (Cerami et al., 2013; Girardi et al., 2011; Meier et al., 2010). Executive functioning alone was sufficient to predict a significant proportion of the variability in socio–emotional processing performance in the current patient sample. Nonetheless, a proportion of the variance remained
unexplained. Future research is needed to identify additional sources of variance, although some error variance will always be present. This might entail using improved measures of personality or empathic traits. Similarly, this could be achieved by assessing additional cognitive processes which could explain socio–emotional processing performance. For example, several studies of neurological patients have noted associations between ToM performance and the non–literal semantic–pragmatic aspects of language, such as the comprehension of metaphors and irony as well as the interpretation of idioms and proverbs (Champagne-Lavau & Joanette, 2009; Martin & McDonald, 2003; Monetta et al., 2009; Siegal et al., 1996; Sperber & Wilson, 2002). In turn, processing of non–literal speech has been correlated with executive function and semantic knowledge in bvFTD patients (Kaiser et al., 2013) and syntactic competence in aphasic patients (Papagno & Genoni, 2004). There is increasing recognition of language disruption, including semantic processing and syntactic comprehension, in non–demented ALS (see Chapter 2, Section 2.2.1.2.); this may co–occur or be independent of executive function (Taylor et al., 2013). Future research should investigate whether a complex relationship between executive function, language processing and social cognition can explain performance on ToM measures in ALS.

7.4.3. Assessment of personality, empathy and behaviour

Despite the concerns raised regarding the confounds of the several behavioural inventories used in ALS research, there remains a great need for validated ALS–specific measures. Some recently devised ALS screening batteries include behavioural items (e.g. ECAS, Abrahams et al, 2013; ALS-CBS, Woolley et al., 2010b) but these are early in the standardisation process. ALS studies of behavioural change should include control participants (this is currently not common in practice) and use measures which have been validated in the country in which the research is undertaken.

Future study of empathic behaviour in ALS might benefit from more ecologically–valid measures of empathy, such as the Multifaceted Empathy Test (MET, Dziobek et al., 2008) in which respondents rate their emotional response to photographic stimuli (emotional empathy) and infer mental states of individuals in scenes (cognitive empathy). Alternatively, observational studies of the extent to which patients are able to take the perspective of others, as well as their sensitivity and attachment to others in naturalistic settings are recommended, although studies of this kind might be difficult to implement.
Questions remain over whether caregivers’ reports should be accepted as the gold–standard for behaviour research in ALS. The current study found discordant perspectives between patients and their caregivers on the patients’ behaviour, empathy and personality traits. Future research should investigate the extent to which these perceptions differ and whether they represent psychological responses or biases in ALS patients and/or their caregivers or an indication of reduced awareness in patients. This might be achieved by incorporating measures of social desirability, denial, coping and the assessment of wider cognitive appraisals (e.g. Matuz et al., 2010) alongside self and proxy measures of patients’ behaviour and personality. Factors that may influence responding, such as mood and burden (or, in the case of patients, of feeling like a burden) should also be assessed. This could also potentially expand understanding of psychological adjustment in ALS patients and their caregivers.

**7.4.4. The assessment of caregivers of people with ALS**

The exploratory component of the caregiver study suggests that future studies of caregiver outcomes might benefit from measuring their perceptions of patients’ empathy and personality alongside behavioural change. Expansion of these findings may include measuring the outcomes of caregivers and patients in tandem to explore the unique challenges presented by ALS to individual members of the spousal unit, as well as the overall ALS dyad. The comparison of spousal and filial caregivers, as well as an inspection of gender differences in ALS caregiving was not possible in the current research and should be addressed in future work. Furthermore, there is a growing field of study that considers the positive aspects of caregiving (see Boerner et al., 2004; Carbonneau et al., 2010). This is a topic yet to be examined by caregiving studies in ALS. Future work should address the lack of research in this area in order to fully characterise caregiving experiences in ALS and develop better informed psychosocial interventions for ALS relatives.

**7.4.5. Longitudinal studies**

The majority of longitudinal studies of ALS cognitive change have focussed on the assessment of executive function over–time. Findings from these studies have been variable, with no consensus regarding the nature of the progression of cognitive dysfunction in the disorder (Chapter 2, Section 2.2.1.7.). To date, there have been no prospective studies of socio–emotional processing in ALS, with the exception of a
neuroimaging study that correlated alterations in patients’ brain response patterns over six–months with their evaluations of emotional stimuli at baseline (Lule et al., 2007). The current study recommends that future research investigates the progression of cognitive–behavioural change in ALS to determine whether or not the observed profiles of executive impairment and behavioural change revealed in the current patients would evolve to meet diagnostic criteria for FTD. In addition, given the finding of a predictive relationship between patients’ executive dysfunction and their performance on a composite of socio–emotional tests in the current results, future research should investigate the stability of emotional processing and social cognition in ALS patients alongside longitudinal assessments of executive function. If executive dysfunction in ALS is indeed progressive, as suggested by some studies (e.g. Robinson et al., 2006; Schreiber et al., 2005; Strong et al., 1999), it would be of value to investigate whether an emergence of deficits in emotion recognition and/or ToM ability occurs at a certain degree or stage of executive impairment or is independent of the presence and level of executive dysfunction. This design would be in a better position than the current cross–sectional design to substantiate a causal relationship between executive dysfunction and socio–emotional processing in ALS. Longitudinal assessment of other cognitive domains is also warranted since population–based research indicates distinct cognitive subtypes in ALS with separate clinical trajectories (Elamin et al., 2013). For example, the progression of social cognition deficits assessed alongside increasing language impairment and executive dysfunction would allow the delineation of complex relationships, if any, between these respective cognitive domains.

Longitudinal assessment of ALS patients is challenging due to high attrition associated with patients’ deaths and the variable and expeditious nature of disease progression. Certain neuropsychological tests become inappropriate as functional ability declines. Therefore, such studies should adopt measures that do not require motor function and which can be used to assess severely disabled patients. The advancement of brain–computer interface communication technologies might provide augmentative tools for future cognitive assessment in late–stage ALS (Cipresso et al., 2012).

Future research investigating the evolution of caregiver wellbeing and marital satisfaction alongside patients’ declining functional status and behavioural change is recommended; as these were the patient parameters which best predicted the caregiver outcomes in the cross–sectional analyses. Furthermore, although objective measures of
patients’ neuropsychological performance were not predictive of caregiver outcomes in the current cross-sectional design, there might be merit in investigating whether changes in cognitive indices over time (if any) explain variability in caregiving outcomes at different stages of disease. Future studies could also investigate whether or not the discrepancies between self- and proxy perspectives of patients’ behaviour, personality and empathy found in the exploratory component of the study become more disparate with time; and if discordant perceptions between the spousal partners contribute to caregivers’ experiences over the duration of the patient’s illness.

7.4.6. Multimodal research

Cognitive neuroimaging

As highlighted throughout Chapter Two, numerous studies have incorporated neuroimaging techniques alongside neuropsychological testing to explore the cerebral substrates of cognitive and behavioural change in ALS. Emphasis has been placed on identifying the neural correlates of executive impairment above other cognitive domains. The current study suggests a predominant pattern of executive dysfunction in the patient sample. This might seemingly justify the disproportionate focus on executive impairment in ALS cognitive neuroimaging research. However, findings of changes in socio-emotional processing and memory in non-demented ALS are mixed. In addition, language processing deficits have been suggested to be as prevalent, if not more prevalent, than executive dysfunction. Both dependence and independence of these domains from executive dysfunction has been demonstrated (see Chapter 2). Future research should therefore integrate brain imaging with extensive neuropsychological batteries encompassing all cognitive domains. This may identify distinct patterns of cerebral involvement for different cognitive subtypes (e.g. Phukan et al., 2012). Furthermore, the results of the caregiving study from the current research advise the assessment of interpersonal (e.g. empathy) and personality traits as an adjunct to cognitive and behavioural measures in neuropsychological investigations of ALS. The inclusion of these inventories in cognitive neuroimaging studies might reveal interactions between patients’ premorbid characteristics, pathological changes and cognitive–behavioural impairment (Masellis et al., 2010).

Neuropathology, genotypic variation and ‘cognitive phenotypes’

Chapter One introduced growing evidence for the influence of genetic factors on cognitive profiles in ALS (Byrne et al., 2012; Snowden et al., 2013; Wicks et al., 2009).
Although not a focus of the current thesis, the study exhorts the use of genetic and neuropathological data in future studies of cognitive–behavioural change in non-demented patients. Ideally, studies would stratify patients on the basis of genotypic information and compare subgroups on a range of neuropsychological indices. Alongside in vivo cognitive imaging, neuropathological data could then be collected from deceased patients who have donated their brain and spinal tissue. Large-scale projects of this kind might be ambitious for single MND centres and would require collaboration between numerous research sites. The advent of the MNDA Brain and DNA banks, as well as the online ALSOD genetic database (see Chapter 1, Section 1.3.2.) might enable data sharing between research groups. This necessitates the need for a standardised neuropsychological battery to be accessible to all research teams. Should distinct cognitive phenotypes continue to be associated with separate ALS genotypes this may reconcile discrepant findings between cognitive investigations of ALS or explain the heterogeneous profiles of impairment found within these studies. It may also delineate the nature of the proposed cognitive continuum between ALS and FTLD, as similar genotype–phenotype relationships which have been demonstrated in ALS had previously been found for FTD patients (Simon-Sanchez et al., 2012; Snowden et al., 2012).

7.5. 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 emotional processing and social cognition within the disease. This was achieved by using a range of socio–emotional tasks, which varied from static to more ecologically–valid measures in a large ALS sample. In addition, the study further qualified the relationship between patients’ executive functioning and performance on these measures, by using a set of standardised executive function tasks alongside assessments of behaviour, personality and empathy. The study suggests a cognitive impairment in non–demented ALS patients that is characterised by executive dysfunction rather than emotional processing or ToM. Where impaired performance on a social cognition task in ALS was reported, this appeared to be secondary to patients’ executive dysfunction.

The thesis also sought to expand understanding of caregiving perceptions in ALS. The research is the first to include objective measures of patients’ cognitive function,
alongside patients’ disease status and behaviour, in examining the impact ALS poses upon caregivers in terms of their mood, perceived strain, burden and marital satisfaction. Instead of patients’ cognitive status, the results of this study affirmed previous reports implicating the role of patients’ functional disability and behavioural dysfunction in caregivers’ responses to ALS. These results also suggested a possible specificity with which these different symptoms may impact on caregivers. Exploratory analyses revealed discordant perspectives between caregivers and patients regarding patients’ personality, empathy and behaviour, and highlighted their potential implications for caregiver outcomes.

The thesis has outlined several limitations of the current research which restrict the interpretation of its results. 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 those affected by this terrible disease.
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List of appendices

Appendix I – Approval Letters, information sheets, recruitment poster

Appendix II – Missing data

Appendix III – TASIT Task, Happé Task examples

Appendix IV – Effect size and Confidence Intervals (CI) calculations

Appendix V – Medication profiles of participants

Appendix VI – Happé Task demographics, inter–rater reliabilities, response times

Appendix VII – Patient medication subgroups demographics and analyses

Appendix VIII – FrSBe: comparison of data between studies

Appendix IX – Caregiver outcomes correlation matrix

Appendix X – NEO–FFI: carers’ premorbid vs. patients’ current ratings
Appendix I

1. Ethics approval letters
   a. Ethics approval letter for study (22/11/2011)
   b. Ethics approval letter: amendment one (2/08/2011)
   c. Ethics approval letter: amendment two (17/05/2012)

2. Addenbrookes Hospital initial invitation letter

3. Information sheets
   a. ALS participants (and control participants)
   b. Caregiver participants

4. Consent forms
   a. ALS participants (and control participants)
   b. Caregiver participants

5. Recruitment poster (control participants)
22 March 2011 (amended 9 May 2011)

Ms Tamlyn J Watermeyer
Department of Psychology, PO78
Institute of Psychiatry
De Crespigny Park
London
SE5 8AF

Dear Ms Watermeyer,

Study Title: Emotional Processing and Social Cognition in Amyotrophic Lateral Sclerosis / Motor Neuron Disease
REC reference number: 11/H0807/1
Protocol number: CSA/10/042

Thank you for your letter of 16 February 2011, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion” below).

Conditions of the favourable opinion

This favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research (“R&D approval”) should be obtained from the relevant care organisation(s) in accordance with NHS research...
A.I.1.a.: Ethics approval letter (pg. 2 of 4)
A.I.1.a.: Ethics approval letter (pg. 3 of 4)

| Advertisement | 2.0 | 06 December 2010 |
| Evidence of insurance or indemnity | | 14 February 2011 |
| Covering Letter | | 09 December 2010 |
| Covering Letter | | 16 February 2011 |
| Invitation: Letter Healthy Control | 2.0 | 06 December 2010 |
| Debrief Leaflet for People with ALS / MND | 1.0 | 06 December 2010 |
| Debrief Leaflet - Spouse | 1.0 | 01 December 2010 |
| Debrief Leaflet - Healthy Controls | 1.0 | 06 December 2010 |
| Investigator CV | 2.0 | 22 October 2010 |
| Interview schedules/Topic Guides: Schedule for Participants (Controls) | 2.0 | 06 December 2010 |
| Participant Information Sheet: Emotions in ALS / MND (Spouse / Partner) | 2.0 | 09 February 2011 |
| Participant Consent Form: Patient | 2.0 | 06 December 2010 |
| Participant Consent Form: Spouse | 2.0 | 06 December 2010 |

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

Please quote this number on all correspondence: 11/H0807/1

With the Committee’s best wishes for the success of this project.
A.I.1.a.: Ethics approval letter (pg. 4 of 4)

Yours sincerely

Mr Tony Eaton
Chair

Email: audrey.adams@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Ms Jennifer Liebacher
R&D office for NHS care organisation at lead site
02 August 2011

Ms Tamlyn J Watermeyer
Department of Psychology, PO78
Institute of Psychiatry
De Crespigny Park, London
SE5 8AF

Dear Ms Watermeyer,

Study title: Emotional Processing and Social Cognition in Amyotrophic Lateral Sclerosis / Motor Neuron Disease

REC reference: 11/H0807/1
Protocol number: CSA/10/042
Amendment number: Amendment 1
Amendment date: 20 July 2011

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

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<td>13 July 2011</td>
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<td>Amendment 1</td>
<td>20 July 2011</td>
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Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.
R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Yours sincerely

[Signature]

Mr John Richardson
Chair
E-mail: charis.bailey@oe.nhs.uk

Enc: List of names and professions of members who took part in the review

CC: Mrs Jenny Liabei
Research and Development Office,
King’s College, University of London
Institute of Psychiatry / South London and Maudsley NHS Foundation Trust
De Crespigny Park
London
SE5 8AF

Dr Zoe Harris
R&D Department
King’s College Hospital NHS Foundation Trust
1st Floor, Jennie Lee House
34 Love Walk
London
SE5 8AQ
Study title: Emotional Processing and Social Cognition in Amyotrophic Lateral Sclerosis / Motor Neuron Disease

REC reference: 11/H0807/1

Protocol number: CSA/10/042

Amendment number: Amendment Two 27/04/2012

Amendment date: 08 May 2012

Amendment detail: 1. We are modifying one criterion, psychoactive medication use, in our exclusion criteria, as we have found that this measure is preventing otherwise eligible and suitable participants from taking part in the study. Patients are often prescribed psychoactive medication for disease symptoms (such as hyper salivation, discomfort/pain) and not necessarily mood disorder. For that reason, we will not recruit anyone who is experiencing...
mood disturbance (in keeping with our existing exclusion criteria) and/or receiving a dose of psychoactive medication that would usually be prescribed to treat mood disorder. Therefore, patients who are prescribed this medication solely for the treatment of disease symptoms will be eligible. 2. We will continue to recruit patients through the research centres associated with our study as stipulated in the protocol and the original REC application. In addition, we would like to allow patients whose care falls outside of the NHS Trusts from which this study operates but who have contacted us directly to volunteer their participation. These patients will be screened with the same criteria as the patients recruited from the centres and receive the same informed consent procedure. Screening will be conducted through liaison with the patient. We will not access these patients' medical information unless they consent for us to do so and if it is relevant to their participation. We will also not invite the patient’s spousal caregiver to the study without the patient’s consent. Only with the patient's consent, we will inform their GP of their participation in the study or report any relevant information (such as depressed mood, anxiety, etc.) to their GP or MND Care Team (please see attached Consent form: pwMND_Self-Referrers Version1.0 27/04/2012). These patients will receive the same treatment and ethical protection (i.e. informed consent, data protection / confidentiality, etc.) as stipulated in the approved ethical opinion letter (dated 22/03/2011). 3. We would like to advertise this study to the MND community, such as the Motor Neurone Disease Association (MNDA), MND conferences or academic talks. Please see the advert attached (Recruitment_Poster_pwMND_Version1.0_27/04/2012). Patients will be able to enquire about the study by contacting the chief investigator (telephone number and email provided on the advert). After screening for eligibility (through liaison with the patient and applying the same criteria as above) and a discussion about the research, the patient will be sent a PIS and consent form, for them to read. Testing sessions will only be arranged once the patient has read the PIS and agrees to take part. Again, we will not access these patients' medical information unless they consent for us to do so and if it is relevant to their participation. We will also not invite the patient's spousal caregiver to the study without the patient’s consent. Only with the patient's consent, we will inform their GP of their participation in the study or report any relevant information (such as depressed mood, anxiety, etc.) to their GP or MND Care Team (please see attached Consent form: pwMND_Self-Referrers Version1.0 27/04/2012). These patients will receive the same treatment and ethical protection (i.e. informed consent, data protection / confidentiality, etc.) as stipulated in the approved ethical opinion letter (dated 22/03/2011).
The above amendment was reviewed by the Sub-Committee in correspondence at the meeting of the Sub-Committee held on 15 May 2012.

**Ethical opinion**

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

**Approved documents**

The documents reviewed and approved at the meeting were:

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<tr>
<td>Confirmation of approval from sponsor</td>
<td>e-mail from Jennifer Liebscher, R&amp;D, SLaM/IoP 09 May 2012</td>
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**Membership of the Committee**

The members of the Committee who took part in the review are listed on the attached sheet.

**R&D approval**

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

**Statement of compliance**
The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/H0807/1: Please quote this number on all correspondence

Yours sincerely

Mr John Richardson
Chair

E-mail: peter.drew@oe.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: Dr Zoe Harris, Kings College Research and Development Office
Ms. Jennifer Liebscher
DATE

Dear <name>,

The clinical team at Addenbrookes’ has become aware of a research study in MND that might be of interest to you. The study is concerned with thinking patterns and behaviour; it does not entail a trial of medication.

If you are interested in being contacted with more information about this study, please contact the researcher Tamlyn Watermeyer:

Ms Tamlyn Watermeyer
PO78
Institute of Psychiatry
De Crespigny Park
SE5 8AF

Email: tamlyn.watermeyer@kcl.ac.uk

Phone: 020 7848 5715

You are under no obligation to take part in this study. Should you not wish to take part, the care you receive at the clinic currently or in future, will not be affected.

Yours sincerely,

Dr Chris Allen
Consultant Neurologist, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust

Joanna Sasson & Helen Copsey

MND clinic co-ordinators
Following your clinic appointment at the Motor Nerve Clinic at King’s College Hospital I would like to invite you to take part in a research study.

The study is part of a PhD project looking at how thinking patterns, behaviour and responding to emotional material might change in some people with motor neuron disease. A PhD student at the Institute of Psychiatry, Ms Tamlyn Watermeyer, is carrying out the project, which involves questionnaires, interviews, puzzles and tasks that will be done on a laptop computer. The assessment would be done in your own home at your convenience. You would not have to travel to King’s unless you would prefer to.

I have enclosed information about the project outlining the purpose of the study and what to do if you would like to take part. If, after reading the information, you would like to ask any further questions or let us know that you would like to take part please contact Tamlyn Watermeyer by email on tamlyn.watermeyer@kcl.ac.uk or by phone on 020 7848 5715. Alternatively you can contact the project supervisor Professor Laura Goldstein on 020 7848 0218 or laura.goldstein@kcl.ac.uk.

Please contact me if you do not wish to be involved. If I do not hear from you, Tamlyn will contact you by telephone within two weeks to determine if you wish to be involved. If you do not want to take part this will not affect your current or future medical care in any way.

Yours sincerely,

Ammar Al-Chalabi MB ChB PhD FRCP DipStat,

Professor of Neurology and Complex Disease Genetics
Director, King’s MND Care and Research Centre
Tel: 020 7848 5187
Participant Information Sheet for People with Amyotrophic Lateral Sclerosis / Motor Neuron Disease

(REC 11/H0807/1)

You are invited to take part in a research study on Motor Neuron Disease at the Institute of Psychiatry, King’s College London. This study is being conducted as part of a student’s PhD research project and is funded by the Medical Research Council. Please find below all information relevant to participation in this study. Please ask us if you have any questions. Thank you for reading this.

1. Study title: Emotion in Amyotrophic Lateral Sclerosis/ Motor Neuron Disease (ALS/MND)

2. The purpose of the study: The main purpose of this study is to investigate changes in emotional, social and everyday behaviour that may occur in some, but not all, people with MND and how these relate to thinking, personality and mood. We will compare our results to those obtained from people who do not have MND. We also aim to investigate the perceptions of such changes from the perspective of the carers of people with MND.

3. Why have I been invited? We believe that this study may be suitable for you, if you would like to take part. You are being invited to take part on the basis of your recent visit to the Motor Nerve Clinic at King’s College Hospital. We will be seeing a total of 55 people with MND and we will also be seeing a total of 55 healthy volunteers.

4. Do I have to take part? No. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive now or at any later date.

5. Description of the study: Testing can take place at your home at a time of your convenience or at the King’s MND Care & Research Centre if you prefer. If you decide to take part we will start by asking you some questions about the duration of your symptoms and how you have been feeling in the recent weeks. Then we will move on to a series of tests, similar to word games and puzzles, some of which will take place on a laptop computer. Please see the enclosed ‘Schedule for Participants’, for a description of each task.
The completion of the tests will take approximately 6 ½ hours. This comprises about 10-30 mins of gaining your consent to participate; 2 ½ – 3 hrs of interview questions and 2 ½ - 3 hrs of the experimental tasks. This is a long time but this can be split into two shorter sessions on separate days, if you prefer, and if you need to take a break at any time you are free to do so. If you prefer to travel to the King’s MND Care & Research Centre to take part in the study, we will reimburse you and your carer for any travel expenses incurred.

If you agree to take part, we will arrange the study days to suit you as much as possible. You will not have to come off medication or undergo any invasive procedure whatsoever, although we would prefer you not to consume any alcohol 24 hours before any of the tests. Most of the thinking and behaviour tests are in the form of interviews, questionnaires or puzzle-like tests. If you are unable to write we will assist you in filling out the questionnaires.

Some of the tests will require you to view videos and other information on a laptop computer (such as faces or words) and cartoons. We would, however, like to conduct both test sessions fairly close together in time (preferably within two weeks of each other).

As part of the study, we would separately like to ask your carer some questions. We are interviewing carers to try and get different perspectives about possible changes in behaviour that may, or may not, occur in people with MND. This will consist of them having an interview that will enquire about any changes that may have occurred since the onset of your MND, in areas of your everyday life such as how interested you are in things going on around you, how easily you control your emotions and how well you are able to organise and plan everyday events. In connection with this they will be asked to complete some questionnaires. This will take about 45 minutes – 1 hour, which can also be conducted on two separate occasions lasting 25 -30 mins each. Any responses given to us by your carer will remain confidential and we will not reveal them to you. We will also not tell your carer how you responded to any of the tests or interviews.

6. Advantages of the study: There are no immediate benefits of this study to you. However, we expect that the study will shed new light on the possible emotional, social and behavioural consequences of MND, leading to better interventions to assist people with MND and their carers.

7. Possible risks and disadvantages of the study:

Whilst we do not anticipate any health risks from taking part in this study, you and your carer may find some of the questions uncomfortable. If you feel upset we will be happy to discuss this with you at the time and we will also telephone you the following day to see if there are outstanding issues you would like to discuss. All people taking part will be given some information about sources of support after the interview is finished. If you are upset by any of the issues covered in the interviews we would encourage you to contact your GP for advice or we can pass on a request to your MND Care team with your permission.

Due to the length of time it will take to go through and complete the various tests and questionnaires you may find testing to be tiring. Therefore we recommend splitting the
testing into at least two shorter sessions at your convenience, morning or afternoon or even on separate days.

8. Confidentiality and publication of data: Your data will be stored under an anonymised code available only to the investigators associated with this study. You will not be identified in our computers or publications by name, but by ID number, and all information will be kept strictly confidential. We expect that the data collected in this study will be published in scientific articles, but you will not be personally identifiable in any such publications. No personal information will be released to third parties without your written approval. The data will be stored without any personal identifying information in password-locked computers at the Institute of Psychiatry for 10 years after completing the study. If you would like to receive a summary of the research we can arrange for this to be sent to you but it will not be until the study has been completed.

9. Will my GP know about my participation in the study? We will only contact your GP with your consent. Should you agree, your GP will receive a letter from us informing them of your participation and an outline of the study.

10. Discontinuation of the study by the investigators: At any time during the testing, the investigators have the right to terminate your participation in the study for any reason. If later on in the study it is concluded that you no longer have capacity to consent to participating we would like to continue to be able to use any data that we have already collected, in an anonymised form.

11. Withdrawal from the study: Your participation in this study is entirely voluntary. You have the right to withdraw from the study at any time without penalty of any kind. In the event of a future loss in capacity, any data already collected, under your consent, may continue to be used, confidentially, in connection with this study.

12. Compensation: You will receive Marks & Spencer vouchers of the value of £30 as a token of our gratitude for giving up your time in completing the study investigations. We will also reimburse any travel expenses incurred during transport to and from the Institute of Psychiatry, should you prefer to travel to King’s MND Care & Research Centre for the study.

13. Who is organising and funding the research? The study is being undertaken as part of a student’s PhD project and is funded by the Medical Research Council. It is being organized in collaboration with Professor Laura Goldstein, Professor Richard Brown and Professor Ammar Al-Chalabi.

14. Who has reviewed the study? The study has been reviewed and granted ethics approval by South East London Research Ethics Committee 4 (REC 11/H0807/1)

15. Contact details for any other inquiries concerning the study: If you have any inquiries concerning this study, please refer to the contact details below:
Ms. Tamlyn Watermeyer  
Department of Psychology, PO78  
Institute of Psychiatry  
King’s College London  
De Crespigny Park  
London SE5 8AF  
Phone: **020 7848 5715** Email: tamlyn.watermeyer@kcl.ac.uk

You can also contact  
Professor Laura Goldstein tel. 020 7848 0218 ([laura.goldstein@iop.kcl.ac.uk](mailto:laura.goldstein@iop.kcl.ac.uk));  
Professor Richard Brown tel. 020 7848 0773 ([richard.g.brown@iop.kcl.ac.uk](mailto:richard.g.brown@iop.kcl.ac.uk)) or  
Professor Ammar Al-Chalabi tel. 020 7848 5187 ([ammar.al-chalabi@kcl.ac.uk](mailto:ammar.al-chalabi@kcl.ac.uk)) if you require more information about the study.

For independent and general advice on taking part in research please contact:

Dr. Angela Grainger  
Assistant Director of Nursing - Nursing Education & Research Lead  
020 3299 1695
Dear,

Research Study Entitled “Emotion in Amyotrophic Lateral Sclerosis/ Motor Neuron Disease”
(REC 11/H0807/1)

Following your partner’s/spouse’s agreement to take part in a research study at The Institute of Psychiatry, I would like to invite you to also participate in a part of the study. The study is part of a student’s PhD project and is funded by the Medical Research Council. The research project will examine the nature and extent of emotional, social and behavioural change that *sometimes* occurs in people with MND and the perceptions and impact of these changes, if they occur, from the perspective of the carer of the individual with MND. It is hoped that this research may increase our understanding of any behavioural and emotional change that may occur in MND as well as improve clinical management for people with MND and their carers.

Participation in this part of the study involves asking you a number of questions and asking you to fill in some questionnaires, which will be conducted in private; at a time that is convenient for you. This is expected to take approximately 45mins – 1 hr, but can be split into two shorter sessions of 25 – 30mins, if you prefer. Should you need a break or tend to your spouse/partner, you would be free to do so, at any time. Some of the questionnaires can be completed in your own time and returned to me at the your spouse’s/partner’s second testing session, if you prefer.

Please refer to the ‘Participant Information Sheet’ and ‘Schedule for participants’, enclosed, for details about the types of issues that we would discuss with you. We would like to stress that any information you provide us with, will be treated with the strictest confidence and will not be relayed to your spouse under any circumstance.

If, after reading the enclosed information, you would like to ask any further questions or inform us that you would like to take part please contact me by email on tamlyn.watermeyer@kcl.ac.uk or by phone on 020 7848 5715. Alternatively please contact the project supervisor Professor Laura Goldstein on 020 7848 0218 or laura.goldstein@kcl.ac.uk.

If you do not wish to participate in the project it would be very helpful if you could let us know. If we have not heard from you within two weeks after sending the letter, I will contact you to ask if you have any queries about the project.

You are under no obligation to participate and your decision will not affect your spouse’s/partner’s current or future medical care in any way.

Yours sincerely,

Ms. Tamlyn Watermeyer
PhD Student
Psychology Dept, PO 78, Institute of Psychiatry,
4 Windsor Walk
De Crespigny Park,
London SE5 8AF Tel : 020 7848 5715 Email: tamlyn.watermeyer@kcl.ac.uk
Participant Information Sheet for Spouse/Partners of People with Amyotrophic Lateral Sclerosis / Motor Neuron Disease

(REC 11/H0807/1)

You are invited to take part in a research study on Motor Neuron Disease at the Institute of Psychiatry, King’s College London. This study is being conducted as part of a student’s PhD research project and is funded by the Medical Research Council. Please find below all the information relevant to your participation in this study. Please ask us if you have any questions. Thank you for reading this.

1. Study title: Emotion in Amyotrophic Lateral Sclerosis / Motor Neuron Disease (ALS/MND)

2. The purpose of the study: The main purpose of this study is to investigate changes in emotional, social and everyday behaviour that may occur in some, but not all, people with MND and how these relate to thinking, personality and mood. We will compare our results to those obtained from people who do not have MND. We also aim to investigate the perceptions of such changes from the perspective of the carers of people with MND.

3. Why have I been invited? We believe that this study may be suitable for you if you would like to take part. You are being invited to take part because your spouse or partner, who recently visited the Motor Nerve Clinic at King’s College Hospital, has agreed for us to contact you. We will be seeing a total of 55 people with MND and we will also be seeing a total of 55 healthy volunteers. As part of the study we are hoping, wherever possible, to interview the spouse / partner carer of the person with MND. We hope to get different perspectives about possible changes in behaviour that may, or may not occur, in people with MND, before and after the onset of their disease. We will also be asking carers about their experiences of caring for a spouse / partner with MND.

4. Do I have to take part? No. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care your spouse / partner receives now or at any later date.

5. What does my participation involve? If you decide to take part, the study is in the form of an interview and involves the completion of some questionnaires. We will arrange to visit you at your home for this at a time of your convenience. Alternatively we can undertake this at the King’s MND Care & Research Centre, if you prefer. Should you prefer to travel to the centre, we will reimburse you and, if they come with you, your partner/spouse for any travel expenses incurred. If you agree to take part we will arrange the study days to suit you and your partner/spouse as much as possible.

If you decide to take part we would like to spend approximately 45 minutes – 1 hour with you. In addition to spending about 10 - 15 minutes going through the study with you and gaining your consent to participate we will ask you to complete some questionnaires. These ask about changes that you may have noticed in your spouse since the onset of their illness in terms of their everyday behaviour, interest in what is going on around them and their ability to organise and plan things, as well as their ability to understand other people’s feelings. We will also ask you some questions about their personality, before and after their MND started. We will also ask you some questions about your mood and any strain you feel as part of caring for your spouse as well as how you currently view the relationship between the two of you. Please see the enclosed ‘Schedule for Participants’, for a description of the different questionnaires we will ask you to complete. You do not have to complete these all
in one go. The interview can be split into two shorter sessions of approximately 25-30 mins on separate days if you prefer. If you need to take a break or need to tend to your relative at any time during the interview, you are free to do so. Some of the questions can be completed in your own time in between your spouse/partner’s testing sessions, if you prefer. Your responses to the interview will remain confidential within the research team and we will not reveal them to your partner/spouse, under any circumstance.

6. **Advantages of the study:** There are no immediate benefits of this study to you. However, we expect that the study will shed new light on the possible emotional, social and behavioural consequences of MND, leading to better interventions to assist people with MND and their carers.

7. **Possible risks and disadvantages of the study:**
   While we do not anticipate any health risks from taking part in this study, you may find some of the questions uncomfortable. If you feel upset we will be happy to discuss this with you at the time and we will also telephone you the following day to see if there are outstanding issues you would like to discuss. All people taking part will be given some information about sources of support after the interview is finished. If you are upset by any of the issues covered in the interviews we would encourage you to contact your GP for advice or we can pass on a request to the MND Care team with your permission.

8. **Confidentiality and publication of data:**
   Your data will be stored under an anonymised code available only to the researchers associated with this study. You will not be identified in our computers or publications by name, but by number, and all information will be kept strictly confidential. We expect that the data collected in this study will be published in scientific articles, but you will not be personally identifiable in any such publications. No personal information will be released to third parties without your written approval. The data will be stored without any personal identifying information in password-locked computers at the Institute of Psychiatry for 10 years after completing the study. If you would like to receive a summary of the research we can arrange for this to be sent to you but it will not be until the study has been completed.

9. **Withdrawal from the study:** Your participation in this study is entirely voluntary. You have the right to withdraw from the study at any time without penalty of any kind.

10. **Who is organising and funding the research?**
    The study is being undertaken as part of a student’s PhD project and is funded by the Medical Research Council. It is being organized in collaboration with Professor Laura Goldstein, Professor Richard Brown and Professor Ammar Al-Chalabi.

11. **Who has reviewed the study?** The study has been reviewed and granted ethics approval by South East London Research Committee 4 (REC 11/H0807/1)

12. **Contact details for any other inquiries concerning the study:** If you have any inquiries concerning this study, please refer to below contact details:

    **Ms. Tamlyn Watermeyer**
    Department of Psychology, PO78
    Institute of Psychiatry
    King’s College London
    De Crespigny Park
    London SE5 8AF
    Phone: 020 7848 5715       Email: tamlyn.watermeyer@kcl.ac.uk

    You can also contact:
    Professor Laura Goldstein tel. 020 7848 0218 (laura.goldstein@iop.kcl.ac.uk);
    Professor Richard Brown tel. 020 7848 0773 (richard.g.brown@iop.kcl.ac.uk) or
    Professor Ammar Al-Chalabi tel. 020 7848 5187 (ammar.al-chalabi@kcl.ac.uk) if you require more information about the study.
Consent Form for People with Amyotrophic Lateral Sclerosis / Motor Neuron Disease

Emotion in Amyotrophic Lateral Sclerosis / Motor Neuron Disease (ALS/MND)

(REC 11/H0807/1)

Please tick each box if you agree to the statement

☐ I, __________________________________________, have read the description of the study called “Emotion in Amyotrophic Lateral Sclerosis/Motor Neuron Disease”. I have had the opportunity to ask questions and all my queries have been met.

☐ Further, I understand that I may ask for more information about each test either before or after it is given.

☐ I understand that I am free to withdraw from the testing at any time if I desire without giving a reason; without my medical care or legal rights being affected.

☐ I understand that my personal information will be kept confidential.

☐ I consent to you contacting my GP to inform them of my participation in this study.

☐ I consent to members of the research team for this study, who are either from King’s College Hospital, London or the Institute of Psychiatry having access to my medical records, when this is relevant to my taking part in research.

☐ I consent to you contacting the MND Research and Care Team, should you find any new information about me (e.g. depressed mood, anxiety) that may inform the existing care and support they provide me.

☐ I consent that in the event of a future loss in capacity, any data already collected may continue to be used, confidentially, in connection with this study.
I consent to you asking my spouse/partner to provide some information about me. I understand that the information he/she provides will be treated confidentially between my spouse/partner and the research worker.

I would like to receive a summary of the results of the study

I agree to take part in the study

_____________________________  _______________________
Signature of participant          Date

_____________________________
Name of participant (in capitals)

I confirm that I have explained the study to

_____________________________
(name of participant)

and have answered questions honestly and fully.

_____________________________  _______________________
Signature of investigator          Date

_____________________________
Name of investigator (in capitals)
Consent Form for Spouse/Partner Carers of
Patients with Amyotrophic Lateral Sclerosis / Motor Neuron Disease (ALS/MND)

Emotion in Amyotrophic Lateral Sclerosis / Motor Neuron Disease

(REC 11/H0807/1)

Please tick each box if you agree to the statement

☐ I,__________________________________________, have read the description of the study called “Emotion in Amyotrophic Lateral Sclerosis / Motor Neuron Disease”. I have had the opportunity to ask questions and all my queries have been met.

☐ Further, I understand that I may ask for more information about each set of questions either before or after it is given.

☐ I understand that I am free to withdraw from the interview at any time if I desire, without giving a reason and without my legal rights and the care of my spouse/partner with ALS/MND being affected.

☐ I understand that the information I provide regarding my spouse/partner will be treated as confidential between myself and the research worker, and that under no circumstance will any information I provide be relayed to my spouse/partner.

☐ I understand that all my personal information will be kept confidential.
I would like to receive a summary of the results of the study

I agree to take part in the study

_____________________________ ________________________
Signature of participant Date

Name of participant (in capitals)

I confirm that I have explained the study to ________________________________
(name of participant) and have answered questions honestly and fully.

_____________________________ ________________________
Signature of investigator Date

Name of investigator (in capitals)
A.I.5.: Recruitment poster for control participants

Participants wanted for research study

We are conducting a study into emotion and behaviour in Motor Neuron Disease (MND) and require healthy control participants (REC 11/H0807/1)

WHERE?
You will be invited to the Institute of Psychiatry in Camberwell to complete assessments. We will reimburse your travel expenses and you will receive an equivalent of £30 in Marks & Spencer vouchers for your time.

WHAT DOES THE STUDY INVOLVE?
The study will involve a maximum of two sessions (of 2 – 3 ½ hrs each) where we will give you a series of questionnaires and puzzle-like tests. You will also be shown videos, cartoons and other stimuli and asked to comment on them. The tasks will take about 6 ½ hours in total. You will be given generous breaks between tasks.

WHO CAN APPLY?
If you are:
- Under the age of 75
- Have English as your first language
- Have no history of diabetes or a neurological or psychiatric disorder
- Are not taking any drugs or medication that might affect your mood or concentration

Then you may be suitable for this study.

If you would like to take part then please contact:

Tamlyn Watermeyer
tamlyn.watermeyer@kcl.ac.uk
Or on 020 7848 5715
to request more information.
Appendix II

a. Missing data: patients and controls

b. Missing data: caregivers
## A.II.a.: Missing data: patient and control groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>ALS N</th>
<th>Missing count ALS (%)</th>
<th>HC N</th>
<th>Missing count HC (%)</th>
</tr>
</thead>
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<td>TASIT</td>
<td>55</td>
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<td>49</td>
<td>0 (0)</td>
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<tr>
<td>Reading Mind in the Eyes (RME)</td>
<td>54</td>
<td>1 (1.8)</td>
<td>49</td>
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<td>Happé Cartoon Task</td>
<td>45</td>
<td>10 (18.2)</td>
<td>48</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Happé Scenario Task</td>
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<td>17 (30.9)</td>
<td>45</td>
<td>4 (8.2)</td>
</tr>
<tr>
<td>D–KEFS Card Sorting Task</td>
<td>53</td>
<td>2 (3.6)</td>
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<td>0 (0)</td>
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<tr>
<td>Written/ Verbal Fluency Task</td>
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<td>49</td>
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<tr>
<td>Brixton Task</td>
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<td>49</td>
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<td>Hayling Sentence Completion Task</td>
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<td>Graded Naming Test (GNT)</td>
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<td>49</td>
<td>0 (0)</td>
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<tr>
<td>California Verbal Learning Test (CVLT)</td>
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<td>4 (7.3)</td>
<td>49</td>
<td>0 (0)</td>
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<tr>
<td>Weschler Test of Adult Reading (WTAR)</td>
<td>51</td>
<td>4 (7.3)</td>
<td>49</td>
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<tr>
<td>Weschler Abbreviated Scale of Intelligence (WASI)</td>
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<td>7 (12.7)</td>
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<tr>
<td>Interpersonal Reactivity Index (IRI)</td>
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<td>49</td>
<td>0 (0)</td>
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<tr>
<td>Emotional Lability Questionnaire (ELQ)</td>
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<td>49</td>
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<tr>
<td>NEO–FFI</td>
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<td>48</td>
<td>1 (2)</td>
</tr>
<tr>
<td>FrSBe</td>
<td>51</td>
<td>4 (7.3)</td>
<td>48</td>
<td>1 (2)</td>
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<td>ALSFRS–R</td>
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### A.II.b.: Missing data: Caregivers

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<tr>
<th>Questionnaire</th>
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<th>Missing Count (%)</th>
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<td>HADS</td>
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<tr>
<td>Morris Strain Scale (MSS)</td>
<td>35</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Zarit Burden Interview (ZBI)</td>
<td>34</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Marital Intimacy Scale (MIS)</td>
<td>32</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>NEO–FFI</td>
<td>30</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Interpersonal Reactivity Scale (IRI)</td>
<td>29</td>
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<tr>
<td>Emotional Lability Questionnaire (ELQ)</td>
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<td>1 (2.9)</td>
</tr>
<tr>
<td>FrSBe</td>
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<td>2 (5.7)</td>
</tr>
<tr>
<td>Age</td>
<td>31</td>
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<tr>
<td>Education</td>
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</tr>
<tr>
<td>Relationship years</td>
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</tr>
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</table>

HADS, Hospital Anxiety and Depression Scale; NEO–FFI, NEO Five–Factor Personality Inventory; FrSBe, Frontal Systems Behavioural Scale
Appendix III

c. TASIT Task dialogue and prompt questions

d. Happe Task examples of cartoon stimuli

e. Happe Task examples of written scenarios/stories
A.III.a: The TASIT Task: examples of dialogue and question prompts

Social Inference Minimal – sarcastic exchange

“Date”

Michael: “Well congratulate me. I’ve got a date with Anne”
Gary: “With Anne?! You must be joking?!”
Michael: “Now, don’t be jealous”
Gary: (rolls eyes and says in sarcastic tone) “Sure, I’m jealous…who wouldn’t be?”
Michael walks away upset.

Questions:

a) Is Gary criticising Michael for dating Anne?
b) Is Gary trying to say it’s a mistake to date Anne?
c) Does Gary think Anne is a good date?
d) Is Gary openly impressed that Michael is dating Anne?

Social Inference Enriched – deceptive exchange

“Boyfriend”

Geoff: “What did you think of Annie’s new boyfriend…isn’t he terrible?”
Jane: (laughing) “He was ghastly! I don’t know what she sees in him. Argh, he was such a pain and so boring!”
Geoff: (laughing) “I know, I thought I’d fallen asleep while he was talking…”
Jane: “I only listened to him for five minutes, he went on and on about some rubbish…”
Annie: (interrupts) “Well, what do think of the love of my life? Isn’t he great?”
Jane: (hiding a laugh) “Hmm, he’s a real catch… I don’t know where you find them!”
Annie: “I think he’s so interesting”
Jane: “Yeah…he’s really interesting…I could sit and talk to him all day”

Questions:

a) Is Jane trying to reassure Annie that she like her new boyfriend?
b) Is Jane trying to say that she thinks Annie’s boyfriend is great?
c) Does Annie believe that Jane likes her new boyfriend?
d) Does Jane dislike Annie’s new boyfriend?
A.III.b.: The Happé Task: examples of cartoon stimuli

*Cartoon Inference subtask*

‘Physical’ condition | ‘Mental’ condition

*Forced-Choice Cartoon Abstraction (Cartoon Pairs)*

‘Physical’ condition | ‘Mental’ condition
A.III.c.: The Happé Task: examples of written scenarios/stories

‘Physical condition’

Example 1: Two enemy powers are at war. Their forces are equally matched. However, the Blue army is stronger in foot soldiers, while the Yellow army is stronger in air power. On the day of the deciding battle, there is dense fog over the battlefield. The Blue army wins the battle.

Question prompt: Why did the blue army win?

Example 2: Paul is very rich, and today he is going to buy an expensive new car. If he pays in monthly instalments, the dealer will charge 5% interest on the loan. His bank currently gives him 8% interest on the money in his account. Even though he has easily enough money to pay the full amount, he decides to pay by monthly instalments.

Question prompt: Why does Paul pay in instalments?

‘Mental condition’

Example 1: A burglar who has just robbed a shop is making his getaway. As he is running away, a policeman sees him drop a glove. He wants to tell him he dropped his glove. When the policeman shouts out to the burglar "Hey, you! Stop!", the burglar turns round, sees the policeman and gives himself up.

Question prompt: Why did the burglar give himself up?

Example 2: During a war, a soldier is taken prisoner by the enemy. The enemy asks the prisoner where his army's tanks are. They think he will lie to them, and they know they are either by the sea or in the mountains. The tanks are really in the mountains. When the enemy asks him where his tanks are, he says, "They are in the mountains".

Question prompt: Why did the prisoner say that the tanks were in the mountains?
Appendix IV: Effect size and Confidence Intervals (CI) calculations

Cohen’s d: \[ d = \frac{M_1 - M_2}{\sqrt{\frac{(SD_1)^2 + (SD_2)^2}{2}}} \]

Where \( M_1 \) = Mean of Group 1; \( M_2 \) = Mean Group 2; \( SD_1 \) = Standard Deviation for Group 1; \( SD_2 \) = Standard Deviation for Group 2.

Pearson’s \( r \) correlation coefficient (Mann–Whitney \( U \) tests): \[ r = \frac{z}{\sqrt{N}} \]

Where \( z \) = test statistic; \( N \) = total observations

Cramer’s V: \[ \sqrt{\frac{X^2}{N(k-1)}} \]

Where \( X^2 \) = chi–square statistic; \( N \) = total observations; \( k \) = the number of rows or columns, whichever is smaller in the variable matrix.

Partial–eta squared\(^7\): \[ \eta^2 = \frac{SS_{effect}}{SS_{effect} + SS_{error}} \]

Where \( SS_{effect} \) = Sums of Squares for the effect of interest; the denominator is the Total Sums of Squares (effect of interest including error).

\(^7\) For a one-way design; for more complicated designs, please consult Cohen (1988).
Appendix V

a. Medication profile: patients and controls

b. Patients receiving psychoactive medication
### A.V.a.: Participant medication profile

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Drug</th>
<th>ALS</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease Management</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baclofen</td>
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<tr>
<td></td>
<td>Fentanyl</td>
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<tr>
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<td>Diclofen</td>
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<tr>
<td></td>
<td>Gabapentin</td>
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<td>0</td>
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<tr>
<td></td>
<td>Pregablin</td>
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<td>0</td>
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<tr>
<td></td>
<td>Tramadol</td>
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<td>Naproxen</td>
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<td>1</td>
</tr>
<tr>
<td></td>
<td>Quinine Sulphate</td>
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<td>Generic painkillers (e.g. Aspirin) (on request)</td>
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<td>2</td>
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<td>Glycopuronium bromide</td>
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</tr>
<tr>
<td></td>
<td>Diazepam</td>
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<td>0</td>
</tr>
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<td></td>
<td>Temazepam (on request)</td>
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<td>0</td>
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<td></td>
<td>Tizanidine (one patient used only on request)</td>
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<td><strong>Hyocine (Scopolamine) patches</strong></td>
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<td>0</td>
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<tr>
<td></td>
<td>Carbocisteine</td>
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HC, Healthy controls. Psychoactive medication in **bold**.
### A.V.b. Patients receiving psychoactive medication

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n=15.
Appendix VI

1. Happé subtasks demographics
   a. Cartoon subtasks
   b. Scenarios subtask

2. Happé subtasks inter–rater reliabilities
   a. Inter–rater agreement for response accuracy scores
   b. Inter–rater agreement for error responses

3. Happé subtask response times: comparisons between groups
A.VI.1.a.: Happé cartoon subtests demographics

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† WTAR and demographic predicted premorbid FSIQ; * Predicted premorbid FSIQ: ALS (n=44); WASI Full Scale IQ: ALS (n=41).
### A.VI.1.b: Happé scenarios subtest demographics

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† WTAR and demographic predicted premorbid FSIQ; * Predicted premorbid FSIQ: ALS (n=38); WASI Full Scale IQ: ALS (n=35).

---

⁸ Not significant following Bonferroni correction (adjusted p<.03); Pearson’s product correlation r=-.2. This effect size estimate is small according to Cohen (1988) conventions.
**A.VI.2.a: Inter-rater agreement for response accuracy scores**

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**A.VI.2.b.: Inter-rater agreement for error responses**

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<tr>
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<td>.67</td>
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<tr>
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<td>86.7</td>
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<td>Mental 8</td>
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### Task: A.VI.3.: Happe Cartoon and Scenarios response times

<table>
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<tr>
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<th>Mean RT (SD)</th>
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<td></td>
<td>ALS (n=45)</td>
<td>HC (n=48)</td>
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<tr>
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</tr>
<tr>
<td>Cartoon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>inference</td>
<td>Physical $\propto$</td>
<td>49.8 (18.78)</td>
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<tr>
<td></td>
<td>Mental $\propto$</td>
<td>51.56 (21.6)</td>
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<tr>
<td>Cartoon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pairs</td>
<td>ALS (n=45)</td>
<td>HC (n=48)</td>
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<tr>
<td></td>
<td>Physical</td>
<td>81.42 (42.86)</td>
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<td></td>
<td>Mental</td>
<td>76.73 (49.85)</td>
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<tr>
<td>Scenarios</td>
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</tr>
<tr>
<td></td>
<td>ALS (n=38)</td>
<td>HC (n=45)</td>
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<tr>
<td></td>
<td>Physical</td>
<td>170.42 (62.04)</td>
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<tr>
<td></td>
<td>Mental</td>
<td>164.24 (58.55)</td>
</tr>
</tbody>
</table>

$p$–values from ANOVAs. $\propto$ Naperian log transformation applied: original means (SDs) are shown. RT, Response Times (in seconds)
Appendix VII

a. Demographic and disease characteristics of patient medicine subgroups

b. Patient subgroups MANOVA: medicated versus non–medicated patients

c. Patient subgroups comparisons for Executive function components & Hayling Task scores

d. Single–case analysis – Executive function composite components and Hayling Task scores: patient medication subgroups

e. Patient subgroups comparisons for EMOSOC components

f. Patient subgroups comparisons for EMOSOC components

g. Patient subgroups comparisons for GNT and CVLT performance

h. Patient subgroups comparisons for IRI ratings

i. Patient subgroups comparisons for FrSBe T–scores

j. Patient subgroups comparisons for ELQ ratings

k. Patient subgroups comparisons for NEO–FFI T–scores
### A.VII.a.: Demographic and disease characteristics of patient medicine subgroups

<table>
<thead>
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<th>p</th>
<th>d</th>
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<tr>
<td><strong>NM (n=40)</strong></td>
<td><strong>Med (n=15)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>59.9 (8.2)</td>
<td>61.3 (9.3)</td>
<td>-0.53 (53)</td>
<td>.6</td>
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<tr>
<td><strong>Education (yrs)</strong></td>
<td>14.8 (3.6)</td>
<td>13.7 (3.4)</td>
<td>1.06 (53)</td>
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<tr>
<td><strong>Months since onset</strong></td>
<td>33.1 (20.5)</td>
<td>28.47 (11.5)</td>
<td>0.82 (53)</td>
<td>.42</td>
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<tr>
<td><strong>Months since diagnosis</strong></td>
<td>16.1 (18)</td>
<td>16.8 (11.58)</td>
<td>-0.14 (53)</td>
<td>.89</td>
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<tr>
<td><strong>Age at symptom onset</strong></td>
<td>57.3 (8.7)</td>
<td>59.2 (9)</td>
<td>-0.71 (53)</td>
<td>.48</td>
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<tr>
<td><strong>Epworth Scale</strong></td>
<td>3.2 (2.8)</td>
<td>4.3 (3.3)</td>
<td>-1.20 (53)</td>
<td>.22</td>
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<tr>
<td><strong>ALSFRS–R Tot</strong></td>
<td>35.1 (7.1)</td>
<td>31.4 (9.2)</td>
<td>1.60 (53)</td>
<td>.12</td>
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<tr>
<td><strong>ALSFRS–R Limb</strong></td>
<td>14.6 (6.3)</td>
<td>13.2 (6.9)</td>
<td>1.50 (17.6)</td>
<td>.15</td>
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<tr>
<td><strong>ALSFRS–R Bulbar</strong></td>
<td>9.5 (2.4)</td>
<td>7.8 (4.1)</td>
<td>0.70 (53)</td>
<td>.49</td>
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<tr>
<td><strong>ALSFRS–R Respiratory</strong></td>
<td>11 (1.2)</td>
<td>10.4 (2.7)</td>
<td>0.79 (16.2)</td>
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**Median (MAD/IQR)**

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<th>r</th>
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<td><strong>Med (n=15)</strong></td>
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<tr>
<td><strong>Disease progression rate</strong></td>
<td>0.5 (0/0.3)</td>
<td>0.6 (0/0.3)</td>
<td>228 (-1.4)</td>
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<tr>
<td><strong>HADS Anxiety†</strong></td>
<td>4 (0/4)</td>
<td>4 (0/6)</td>
<td>235 (-1.3)</td>
</tr>
<tr>
<td><strong>HADS Depression†</strong></td>
<td>2 (0/3)</td>
<td>3 (0/4)</td>
<td>255 (-0.8)</td>
</tr>
<tr>
<td><strong>WASI FS IQ†</strong></td>
<td>117 (0/14)</td>
<td>111 (0/17)</td>
<td>164 (-0.9)</td>
</tr>
<tr>
<td><strong>WTAR predicted FSIQ†</strong></td>
<td>113 (0/7)</td>
<td>111 (0/15)</td>
<td>224 (-0.2)</td>
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**N (%)**

<table>
<thead>
<tr>
<th></th>
<th><strong>χ2(df)</strong></th>
<th>p</th>
<th>φc</th>
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<td><strong>NM (n=40)</strong></td>
<td><strong>Med (n=15)</strong></td>
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<td></td>
</tr>
<tr>
<td><em><em>Gender</em> Men</em>*</td>
<td>31 (77.5)</td>
<td>9 (60)</td>
<td>1.68 (1)</td>
</tr>
<tr>
<td>Women</td>
<td>9 (22.5)</td>
<td>6 (40)</td>
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<tr>
<td><em><em>Onset Location</em> Limb</em>*</td>
<td>31 (77.5)</td>
<td>11 (73.3)</td>
<td>0.11 (1)</td>
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<tr>
<td>Bulbar</td>
<td>9 (22.5)</td>
<td>4 (26.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Mental Health</strong></td>
<td>7 (17.5)</td>
<td>4 (26.7)</td>
<td>0.57 (1)</td>
</tr>
<tr>
<td><strong>Riluzole</strong>*</td>
<td>30 (75)</td>
<td>13 (86.7)</td>
<td>0.87 (1)</td>
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</table>

NM, No medication; d, Cohen’s d; r, Pearson’s correlation coefficient; φc, Cramer’s V p–values from two–tailed t–tests except † Mann–Whitney U test; * Pearson’s χ2 test and **Mental health = previous contact with a GP or psychiatrist regarding mental health.
### A.VII.b: Patient subgroups MANOVA: medicated versus non–medicated patients

<table>
<thead>
<tr>
<th>Composite</th>
<th>NM (n=40)</th>
<th>Med (n=15)</th>
<th>F(df)</th>
<th>p</th>
<th>ηp²</th>
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<td>Mean (SD)</td>
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<tr>
<td>Executive†</td>
<td>0.45 (1)</td>
<td>0.46 (1)</td>
<td>0.002 (1.53)</td>
<td>.97</td>
<td>&lt;.01</td>
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<tr>
<td>EMOSOC†</td>
<td>0.31 (0.8)</td>
<td>0.44 (0.9)</td>
<td>0.27 (1.53)</td>
<td>.61</td>
<td>.01</td>
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</table>

<table>
<thead>
<tr>
<th>Composite</th>
<th>Back transformed Mean (CI)</th>
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<tr>
<td>Mean (CI)</td>
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</tr>
<tr>
<td>Executive††</td>
<td>0.8 (0.73; 0.89)</td>
<td>0.79 (0.65; 0.97)</td>
<td>0.002 (1.53)</td>
<td>.89</td>
<td>&lt;.01</td>
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<tr>
<td>EMOSOC††</td>
<td>0.3 (0.27; 0.33)</td>
<td>0.31 (0.25; 0.38)</td>
<td>0.14 (1.53)</td>
<td>.71</td>
<td>&lt;.01</td>
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*p–values are from ANOVAs. † Untransformed original data. ††Back transformed data. NM, No Medication; Med, Medicated patient; ηp², partial–eta squared.

### A.VII.c: Patient subgroups comparisons for Executive function components & Hayling Task scores

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<tr>
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<th>Mean (SD)</th>
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<th>p</th>
<th>d</th>
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<td>Med</td>
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<tr>
<td>D–KEFS sorting</td>
<td>6.2 (2)</td>
<td>5.7 (2.3)</td>
<td>.8 (51)</td>
<td>.43</td>
<td>0.28 (-0.8; 1.9)</td>
</tr>
<tr>
<td>D–KEFS description</td>
<td>26.3 (10.3)</td>
<td>27.3 (12.1)</td>
<td>-0.29 (51)</td>
<td>.77</td>
<td>-0.09 (-7.9; 5.9)</td>
</tr>
<tr>
<td>VFI–S words</td>
<td>5.3 (3.4)</td>
<td>4.9 (3)</td>
<td>.33 (53)</td>
<td>.74</td>
<td>0.10 (-1.7; 2.3)</td>
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<td>VFI–C words</td>
<td>16.7 (12.5)</td>
<td>14.3 (9.7)</td>
<td>0.65 (53)</td>
<td>.52</td>
<td>0.21 (-4.9; 9.5)</td>
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<tr>
<td>Brixton Errors</td>
<td>17.7 (5.4)</td>
<td>20.1 (6.7)</td>
<td>-1.39 (53)</td>
<td>.17</td>
<td>-0.40 (-5.9; 1.1)</td>
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<tr>
<td>Hayling Error A</td>
<td>3 (2.4)</td>
<td>2.9 (2.6)</td>
<td>.19 (52)</td>
<td>.85</td>
<td>0.21 (-1.4; 1.7)</td>
</tr>
<tr>
<td>Hayling Error B</td>
<td>3.4 (2.4)</td>
<td>3.1 (2.5)</td>
<td>.31 (52)</td>
<td>.76</td>
<td>0.10 (-1.3; 1.7)</td>
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<tr>
<td>Hayling Latency†</td>
<td>37.3 (32.8)</td>
<td>50.4 (40.1)</td>
<td>-1.22 (52)</td>
<td>.23</td>
<td>-0.36 (-34.8; 8.5)</td>
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*p–values from two–tailed t–tests; NM, Non–medicated patients; Med, medicated patients; d, Cohen’s d; 95% CI for difference between means. Note: higher scores indicate worse performance.
A.VII.d.: Single–case analysis – Executive function composite components and Hayling Task scores: Patient medication subgroups

<table>
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<th>Composite</th>
<th>N (%)</th>
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<th>p</th>
<th>φc</th>
<th>95% CI</th>
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<td>Med</td>
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<td></td>
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<td>D–KEFS sorting</td>
<td>4 (10)</td>
<td>0 (0)</td>
<td>—</td>
<td>.53</td>
<td>.16; -0.1; 0.2</td>
</tr>
<tr>
<td>D–KEFS description</td>
<td>7 (17.5)</td>
<td>3 (23.1)</td>
<td>—</td>
<td>.61</td>
<td>.06; -0.2; 0.3</td>
</tr>
<tr>
<td>VFI–S words</td>
<td>9 (22.5)</td>
<td>2 (13.3)</td>
<td>—</td>
<td>.62</td>
<td>.10; -0.2; 0.3</td>
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<tr>
<td>VFI–C words</td>
<td>8 (20)</td>
<td>3 (20)</td>
<td>—</td>
<td>&gt;.99</td>
<td>&lt;.01; -0.3; 0.2</td>
</tr>
<tr>
<td>Brixton errors</td>
<td>2 (5)</td>
<td>3 (20)</td>
<td>—</td>
<td>.09</td>
<td>.23; -0.0; 0.4</td>
</tr>
<tr>
<td>Hayling Errors A</td>
<td>9 (22.5)</td>
<td>3 (21.4)</td>
<td>—</td>
<td>&gt;.99</td>
<td>0.01; -0.3; 0.2</td>
</tr>
<tr>
<td>Hayling Errors B</td>
<td>10 (25)</td>
<td>2 (14.2)</td>
<td>—</td>
<td>.65</td>
<td>.11; -0.2; 0.3</td>
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<td>Hayling Latency†</td>
<td>22 (55)</td>
<td>8 (57.1)</td>
<td>0.19</td>
<td>.89</td>
<td>.02; -0.3; 0.3</td>
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</table>

*p*-values from two–tailed Fisher–Boschloo exact test except † Pearson’s χ2 test. φc, Cramer’s V. 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions. NM, Non–medicated patients; M, Medicated patients.

A.VII.e.: Patient subgroups comparisons for EMOSOC components

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<th>95% CI</th>
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<td>Med</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TASIT EET</td>
<td>5.5 (2.5)</td>
<td>7.1 (2.4)</td>
<td>-2.2 (53)</td>
<td>0.03</td>
<td>-0.65; -3.1; -0.1</td>
</tr>
<tr>
<td>TASIT SIM</td>
<td>10.7 (6.6)</td>
<td>10.1 (7.2)</td>
<td>0.28 (53)</td>
<td>0.78</td>
<td>0.09; -3.5; 4.7</td>
</tr>
<tr>
<td>TASIT SIE</td>
<td>12.9 (6.2)</td>
<td>12.3 (7.7)</td>
<td>0.29 (53)</td>
<td>0.78</td>
<td>0.09; -3.4; 4.6</td>
</tr>
<tr>
<td>RME</td>
<td>10.8 (4.6)</td>
<td>9.8 (5.6)</td>
<td>0.66 (52)</td>
<td>0.52</td>
<td>0.19; -2; 3.9</td>
</tr>
<tr>
<td>C–Inference</td>
<td>11.8 (5.0)</td>
<td>12.5 (6.2)</td>
<td>-0.39 (43)</td>
<td>0.70</td>
<td>-0.12; -4.4; 3</td>
</tr>
<tr>
<td>C–Pairs</td>
<td>11.2 (4.6)</td>
<td>12.5 (4.7)</td>
<td>-0.82 (43)</td>
<td>0.42</td>
<td>-0.28; -4.5; 1.9</td>
</tr>
<tr>
<td>Scenarios</td>
<td>9.5 (3.9)</td>
<td>10.1 (4.6)</td>
<td>-0.41 (36)</td>
<td>0.68</td>
<td>-0.14; -3.9; 2.6</td>
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</tbody>
</table>

*p*-values from two–tailed *t*-tests; NM, Non–medicated patients; Med, medicated patients; *d*, Cohen’s *d*; 95% CI for difference between means. Uncorrected significant results shown in **bold**-*p*<.05. *Note:* higher scores indicate worse performance.
### A.VII.f.: Single–case analysis – EMOSOC composite components: patient medication subgroups

<table>
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<th>Composite</th>
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<th></th>
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<td>Med</td>
<td>p</td>
<td>$\phi_c$</td>
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<tr>
<td>RME</td>
<td>4 (10)</td>
<td>2 (13.3)</td>
<td>&gt;.99</td>
<td>.04</td>
</tr>
<tr>
<td>TASIT EET</td>
<td>2 (5)</td>
<td>1 (6.7)</td>
<td>&gt;.99</td>
<td>.03</td>
</tr>
<tr>
<td>TASIT SIM</td>
<td>2 (5)</td>
<td>1 (6.7)</td>
<td>&gt;.99</td>
<td>.03</td>
</tr>
<tr>
<td>TASIT SIE</td>
<td>3 (7.5)</td>
<td>1 (6.7)</td>
<td>&gt;.99</td>
<td>.01</td>
</tr>
<tr>
<td>C–Inference</td>
<td>11 (33.3)</td>
<td>3 (33.3)</td>
<td>&gt;.99</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>C–Pairs</td>
<td>5 (14.7)</td>
<td>1 (9.1)</td>
<td>&gt;.99</td>
<td>.07</td>
</tr>
<tr>
<td>Scenarios</td>
<td>4 (13.3)</td>
<td>1 (12.5)</td>
<td>&gt;.99</td>
<td>.01</td>
</tr>
</tbody>
</table>

NM, Non–medicated patients; Med, Medicated patients. $p$–values from two–tailed Fisher–Boschloo exact test. $\phi_c$, Cramer’s V. 95% CI, Newcombe–Wilson hybrid confidence interval for difference between proportions.

### A.VII.g.: Patient subgroups comparisons for GNT and CVLT performance

<table>
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<th>d</th>
<th>95% CI</th>
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</thead>
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<td>NM</td>
<td>Med</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GNT †</td>
<td>7.4 (3.4)</td>
<td>6.7 (3.4)</td>
<td>0.69 (53)</td>
<td>.50</td>
<td>0.21</td>
</tr>
<tr>
<td>Immediate free recall</td>
<td>26.0 (4.3)</td>
<td>28.1 (3.5)</td>
<td>-1.49 (49)</td>
<td>.14</td>
<td>-0.54</td>
</tr>
<tr>
<td>Short delay free recall</td>
<td>6.8 (1.8)</td>
<td>7.5 (1.1)</td>
<td>-1.25 (49)</td>
<td>.22</td>
<td>-0.47</td>
</tr>
<tr>
<td>Long delay free recall †</td>
<td>6.4 (1.9)</td>
<td>6.9 (1.8)</td>
<td>-0.74 (49)</td>
<td>.47</td>
<td>-0.26</td>
</tr>
<tr>
<td>Long delay cued recall</td>
<td>6.4 (1.9)</td>
<td>7.6 (1.1)</td>
<td>-2.08 (49)</td>
<td>.04</td>
<td>-0.77</td>
</tr>
</tbody>
</table>

$p$–values from two–tailed $t$–tests; $d$, Cohen’s d; 95% CI for difference between means. Uncorrected significant results shown in **bold** – $p<.05$. †Sensitivity analysis using non–parametric tests found same non–significant results. Note: higher scores indicate superior performance for CVLT but worse performance for GNT.
A.VII.h.: Patient subgroups comparisons for IRI ratings

<table>
<thead>
<tr>
<th>IRI domains</th>
<th>Mean (SD)</th>
<th>(t(df))</th>
<th>(p)</th>
<th>(d)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NM (n=40)</td>
<td>Med (n=15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perspective</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking</td>
<td>16.8 (5)</td>
<td>17.5 (6)</td>
<td>-0.44 (53)</td>
<td>.66</td>
<td>-0.13</td>
</tr>
<tr>
<td>Fantasy</td>
<td>11.8 (4.9)</td>
<td>11.1 (4.6)</td>
<td>0.50 (53)</td>
<td>.62</td>
<td>0.15</td>
</tr>
<tr>
<td>Thinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empathic</td>
<td>19.1 (5.6)</td>
<td>19.8 (4.6)</td>
<td>-0.43 (53)</td>
<td>.67</td>
<td>-0.14</td>
</tr>
<tr>
<td>Concern</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal</td>
<td>8.3 (4.8)</td>
<td>10.3 (4.6)</td>
<td>-1.37 (53)</td>
<td>.18</td>
<td>-0.42</td>
</tr>
<tr>
<td>Distress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(p\)-values from two–tailed paired–sample \(t\)-tests. NM, Non–medicated patients; Med, Medicated patients; Conscien., Conscientiousness; \(d\), Cohen’s \(d\) for paired samples; 95% CI, confidence interval for difference between means.

A.VII.i.: Patient subgroups comparisons for FrSBe \(T\)-scores

<table>
<thead>
<tr>
<th>FrSBe</th>
<th>Mean (SD)</th>
<th>(t(df))</th>
<th>(p)</th>
<th>(d)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(T)-score</td>
<td>NM (n=38)</td>
<td>Med (n=13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (pre.)</td>
<td>51.4 (11.2)</td>
<td>51.4 (15.7)</td>
<td>-0.00 (49)</td>
<td>.99</td>
<td>-0.00</td>
</tr>
<tr>
<td>Total (cur.)</td>
<td>59.8 (12.8)</td>
<td>61.1 (19.1)</td>
<td>-0.27 (49)</td>
<td>.79</td>
<td>-0.08</td>
</tr>
<tr>
<td>Apathy (pre.)</td>
<td>47 (10.9)</td>
<td>49.3 (12.8)</td>
<td>-0.62 (49)</td>
<td>.54</td>
<td>-0.19</td>
</tr>
<tr>
<td>Apathy (cur.)</td>
<td>59.5 (14.4)</td>
<td>65.9 (17.3)</td>
<td>-1.31 (49)</td>
<td>.20</td>
<td>-0.40</td>
</tr>
<tr>
<td>Disinhib. (pre.)</td>
<td>55.9 (12.7)</td>
<td>53.6 (15.4)</td>
<td>0.54 (49)</td>
<td>.59</td>
<td>0.16</td>
</tr>
<tr>
<td>Disinhib. (cur.)</td>
<td>57.8 (12)</td>
<td>56 (14.1)</td>
<td>0.44 (49)</td>
<td>.66</td>
<td>0.13</td>
</tr>
<tr>
<td>Exec. Dys. (pre.)</td>
<td>51.3 (10.9)</td>
<td>50.8 (16.2)</td>
<td>0.13 (49)</td>
<td>.90</td>
<td>0.02</td>
</tr>
<tr>
<td>Exec. Dys. (cur.)</td>
<td>56.3 (11.5)</td>
<td>54.5 (16.1)</td>
<td>0.44 (49)</td>
<td>.66</td>
<td>0.13</td>
</tr>
</tbody>
</table>

\(p\)-values are from two–tailed \(t\)-tests. NM, Non–medicated patients; Med, Medicated patients; Disinhib., Disinhibition; Exec.Dys., Executive Dysfunction; pre., premorbid; cur., current; \(d\), Cohen’s \(d\); 95% CI, confidence interval for difference between means.

Note. Participants were asked to rate their behaviour at present time and approximately 2 years prior; \(p\)-values are from two–tailed \(t\)-tests. NM, Non–medicated patients; Med, Medicated patients; Disinhib., Disinhibition; Exec.Dys., Executive Dysfunction; pre., premorbid; cur., current; \(d\), Cohen’s \(d\); 95% CI, confidence interval for difference between means.
### A.VII.j.: Patient subgroups comparisons for ELQ ratings

<table>
<thead>
<tr>
<th></th>
<th>Median (MAD/IQR)</th>
<th>$U(z)$</th>
<th>$p$</th>
<th>$r$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NM (n=40)</td>
<td>Med (n=15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELQ Total</td>
<td>6.5 (0/20)</td>
<td>9 (0/22)</td>
<td>249.00 (-0.9)</td>
<td>.32</td>
<td>-.12</td>
</tr>
<tr>
<td>ELQ Laugh</td>
<td>0 (0/9)</td>
<td>0 (0/18)</td>
<td>299.00 (-0.2)</td>
<td>.98</td>
<td>-.03</td>
</tr>
<tr>
<td>ELQ Cry</td>
<td>0 (0/12)</td>
<td>7 (0/13)</td>
<td>256.50 (-0.9)</td>
<td>.38</td>
<td>-.12</td>
</tr>
<tr>
<td>ELQ Smile</td>
<td>0 (0/3)</td>
<td>0 (0/1)</td>
<td>295.50 (-0.1)</td>
<td>.91</td>
<td>-.01</td>
</tr>
</tbody>
</table>

$p$–values from Mann–Whitney $U$ tests. NM, Non–medicated patients; Med, medicated patients; $r$, Pearson’s correlation coefficient; 95% CI, Hodges–Lehmann confidence interval for difference between medians.

### A.VII.k.: Patient subgroups comparisons for NEO–FFI $T$–scores

<table>
<thead>
<tr>
<th>NEO–FFI $T$–scores</th>
<th>Mean (SD)</th>
<th>$t(df)$</th>
<th>$p$</th>
<th>$d$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NM (n=39)</td>
<td>Med (n=13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroticism</td>
<td>42.7 (8.6)</td>
<td>49 (8.7)</td>
<td>-2.3 (50)</td>
<td><strong>.03</strong></td>
<td>-0.73</td>
</tr>
<tr>
<td>Extraversion</td>
<td>54.3 (10)</td>
<td>53.5 (6.3)</td>
<td>0.33 (33.1)</td>
<td>.74</td>
<td>0.09</td>
</tr>
<tr>
<td>Openness</td>
<td>51.4 (11.9)</td>
<td>49 (11.5)</td>
<td>0.64 (50)</td>
<td>.52</td>
<td>0.21</td>
</tr>
<tr>
<td>Agreeableness</td>
<td>47.5 (10.3)</td>
<td>53.6 (10)</td>
<td>-1.86 (50)</td>
<td>.07</td>
<td>-0.60</td>
</tr>
<tr>
<td>Conscien.</td>
<td>49.7 (9.4)</td>
<td>52.4 (10.4)</td>
<td>-0.88 (50)</td>
<td>.38</td>
<td>-0.27</td>
</tr>
</tbody>
</table>

$p$–values from two–tailed paired–sample $t$–tests. NM, Non–medicated patients; Med, Medicated patients; Conscien., Conscientiousness; $d$, Cohen’s $d$ for paired samples; 95% CI, confidence interval for difference between means.

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9 When overall mood (HADS $T$ scores) was entered as a covariate in an ANCOVA, the difference between groups was no longer significant, $F(1,49)=3.37$, $p=.07$, $\eta^2=.06$. 

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Appendix VIII

a. Comparison of the patients’ self-rated mean FrSBe domain scores with those of previous studies

b. Proportions of patients satisfying FrSBe ‘caseness’ criteria across studies
A.VIII.a.: Comparison of the patients’ self-rated mean FrSBe domain scores with those of previous studies

<table>
<thead>
<tr>
<th>FrSBe Mean T–scores</th>
<th>Study</th>
<th>ALS n</th>
<th>Chio et al, 2005</th>
<th>Woolley et al, 2010</th>
<th>Girardi et al, 2011 (Study A)</th>
<th>Current study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>ALS n</td>
<td>35</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Total (pre.)</td>
<td></td>
<td></td>
<td>44.7 (10.5)</td>
<td>—</td>
<td>—</td>
<td>51.4 (12.3)</td>
</tr>
<tr>
<td>Total (cur.)</td>
<td></td>
<td></td>
<td>53.1 (11.7)</td>
<td>64 (-)</td>
<td>56.5 (14.7)</td>
<td>60.1 (14.4)</td>
</tr>
<tr>
<td>Apathy (pre.)</td>
<td></td>
<td></td>
<td>43.0 (9.7)</td>
<td>—</td>
<td>—</td>
<td>47.6 (11.3)</td>
</tr>
<tr>
<td>Apathy (cur.)</td>
<td></td>
<td></td>
<td>50.9 (13.1)</td>
<td>67 (-)</td>
<td>57.1 (16.2)</td>
<td>61.1 (15.3)</td>
</tr>
<tr>
<td>Disinhib. (pre.)</td>
<td></td>
<td></td>
<td>45.8 (10.8)</td>
<td>—</td>
<td>—</td>
<td>55.3 (13.3)</td>
</tr>
<tr>
<td>Disinhib. (cur.)</td>
<td></td>
<td></td>
<td>49.7 (11.1)</td>
<td>59 (-)</td>
<td>54.8 (13.9)</td>
<td>57.3 (12.4)</td>
</tr>
<tr>
<td>Exec. Dys. (pre.)</td>
<td></td>
<td></td>
<td>47.6 (10.0)</td>
<td>—</td>
<td>—</td>
<td>51.2 (12.3)</td>
</tr>
<tr>
<td>Exec. Dys. (cur.)</td>
<td></td>
<td></td>
<td>55.9 (11.6)</td>
<td>60 (-)</td>
<td>54.8 (14.1)</td>
<td>55.8 (12.7)</td>
</tr>
</tbody>
</table>

FrSBe, Frontal Systems Behavioural Scale; Disinhib., Disinhibition; Exec. Dys., Executive Dysfunction; pre., premorbid; cur., current; — or (-), not provided.

A.VIII.b.: Proportions of patients satisfying FrSBe ‘caseness’ criteria across studies

<table>
<thead>
<tr>
<th>FrSBe</th>
<th>Study N (%)</th>
</tr>
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<tbody>
<tr>
<td>T ≥ 65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Witgert et al 2010</td>
</tr>
<tr>
<td></td>
<td>(n=225)</td>
</tr>
<tr>
<td></td>
<td>(proxy–rated)</td>
</tr>
<tr>
<td></td>
<td>Current study</td>
</tr>
<tr>
<td></td>
<td>(n=51)</td>
</tr>
<tr>
<td></td>
<td>(self–rated)</td>
</tr>
<tr>
<td>Total (pre.)</td>
<td>—</td>
</tr>
<tr>
<td>Total (cur.)</td>
<td>55 (24.4)</td>
</tr>
<tr>
<td>Apathy (pre.)</td>
<td>—</td>
</tr>
<tr>
<td>Apathy (cur.)</td>
<td>70 (31.1)</td>
</tr>
<tr>
<td>Disinhibition (pre.)</td>
<td>—</td>
</tr>
<tr>
<td>Disinhibition (cur.)</td>
<td>38 (16.9)</td>
</tr>
<tr>
<td>Exec. Dys. (pre.)</td>
<td>—</td>
</tr>
<tr>
<td>Exec. Dys. (cur.)</td>
<td>44 (19.6)</td>
</tr>
</tbody>
</table>

FrSBe, Frontal Systems Behavioural Scale; Exec. Dys., Executive Dysfunction; pre., premorbid; cur., current; —; not provided.
### Appendix IX.: Intercorrelations of caregiver outcome measures

<table>
<thead>
<tr>
<th></th>
<th>HADS A</th>
<th>HADS D</th>
<th>MSS</th>
<th>ZBI</th>
<th>MIS premorbid</th>
<th>MIS current</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>r</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>(p-values)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS A</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS D</td>
<td></td>
<td>.42 (.01)</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSS</td>
<td></td>
<td>.66 (&lt;.001)</td>
<td>.56 (&lt;.001)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZBI</td>
<td></td>
<td>.37 (.03)</td>
<td>.57 (&lt;.001)</td>
<td>.56 (.001)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>MIS premorbid</td>
<td>.30 (.13)</td>
<td>.24 (.19)</td>
<td>.26 (.15)</td>
<td>-.03 (.89)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>MIS current</td>
<td>.10 (.63)</td>
<td>-.06 (.77)</td>
<td>-.10 (.60)</td>
<td>-.45 (.009)</td>
<td>.81 (&lt;.001)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

\(r=\)Pearson’s correlation coefficient. Significant correlations shown in **bold**-\(p<.01\). HADS T, Hospital Anxiety and Depression Scale scores (n=35); MSS, Morris Strain Scale (n=35); ZBI, Zarit Burden Interview (n=34); MIS, Marital Intimacy Scale (n=32).
### Appendix X: Comparison of carers’ premorbid and patients’ current ratings of patients’ personality

<table>
<thead>
<tr>
<th>NEO–FFI–I T–scores</th>
<th>Mean (SD)</th>
<th>t(df)</th>
<th>p</th>
<th>d</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carer Premorbid (n=29)</td>
<td>Patient Current (n=29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroticism</td>
<td>39.2 (12.6)</td>
<td>40.9 (10.6)</td>
<td>-0.57 (28)</td>
<td>0.57</td>
<td>0.23</td>
</tr>
<tr>
<td>Extraversion</td>
<td>55.6 (12.4)</td>
<td>54.1 (11.3)</td>
<td>0.50 (28)</td>
<td>0.62</td>
<td>0.13</td>
</tr>
<tr>
<td>Openness</td>
<td>48.5 (12.9)</td>
<td>51.3 (12.1)</td>
<td>-1.09 (28)</td>
<td>0.29</td>
<td>0.22</td>
</tr>
<tr>
<td>Agreeableness</td>
<td>51.3 (14.8)</td>
<td>47.8 (11.1)</td>
<td>1.61 (28)</td>
<td>0.12</td>
<td>0.27</td>
</tr>
<tr>
<td>Conscien.</td>
<td>50.1 (12.5)</td>
<td>49.8 (11.1)</td>
<td>0.12 (28)</td>
<td>0.91</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*p*–values from two–tailed paired–sample *t*–tests. Conscien., Conscientiousness; *d*, Cohen’s *d* for paired samples; 95% CI, confidence interval for difference between means.
“...the sea's only gifts are harsh blows and, occasionally, the chance to feel strong. Now, I don't know much about the sea, but I do know that that's the way it is here. And I also know how important it is in life not necessarily to be strong but to feel strong, to measure yourself at least once, to find yourself at least once in the most ancient of human conditions, facing blind, deaf stone alone, with nothing to help you but your own hands and your own head...”

Primo Levi

Bear Meat