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A Population-Based Longitudinal Study of Cognitive and Behavioural Impairment in ALS

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PhD

2011
Declaration

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__________________________________________

Dr Julie Phukan

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Summary

Introduction

Amyotrophic Lateral Sclerosis is the most common neurodegenerative disorder of young and middle-aged adults. Convergent research from the disciplines of neuroimaging, neuropathology, genetics and neuropsychology now points to extra-motor change in ALS and an overlap with frontotemporal dementia (FTD).

Aims

This study was designed to determine for the first time the population prevalence, evolution and impact of cognitive and behavioural impairment in ALS. It was hypothesised that cognitive decline primarily affecting the executive domain would be present in up to 50% of the Irish ALS population, that a smaller number of patients would have overt dementia, and that a proportion of patients with cognitive or behavioural impairment would progress to develop full-blown frontotemporal dementia. In addition, it was predicted that cognitive and behavioural impairment would impact upon medical decision-making capacity and psychological well being of patients with ALS.

Methods

Patient recruitment was achieved through the Irish Register of ALS, a population-based instrument that has been in operation since 1994. Diagnosis of ALS was based upon the El Escorial criteria. A comprehensive and validated neuropsychological battery was utilised for all patients and controls and over 200 home visits optimised follow-up. Cognitive and/or behavioural categorisation of patients was facilitated by the recently published consensus criteria (2009) and thus the present analysis also tested the utility of the guidelines as a research tool.

Results

18% (16 patients) of this population-based sample of ALS patients (n=87) had frontotemporal dementia at baseline, predominantly frontal variant FTD. 13 patients (15%) had ALSci affecting executive function, memory and language. 8 patients (9%) had both ALSci and ALSbi concomitantly and 37% of patients did not have cognitive or behavioural impairment.
Behavioural change, predominantly apathy, occurred in up to a third of patients. There was marked discrepancy in its prevalence depending on the consensus criteria definition used. Neither cognitive nor behavioural change inevitable progressed to dementia; a baseline diagnosis of "pure" ALS (i.e. absence of cognitive and behavioural impairment) favoured an absence of dementia at follow-up. Misclassification was observed in up to 22% of patients who had an initial diagnosis of cognitive or behavioural change but were found to have no such impairments at follow-up.

In addition, lack of medical decision-making capacity was demonstrated in one third of ALS patients. Some facets of psychological well-being were compromised in those with cognitive and behavioural impairment.

Discussion

This population-based longitudinal study is the largest of its kind. It has provided clarification regarding the population-based frequency, risk and evolution of cognitive and behavioural impairment in patients with ALS; this is crucial for patients and caregivers, for disease management, and for service development.

The utility of the recent consensus criteria for diagnosis of frontotemporal cognitive and behavioural syndromes in ALS have been tested. These guidelines facilitated categorisation of subgroups to track the evolution of cognitive and behavioural impairment over time but misclassification and discrepancies in defining behavioural impairment suggest that a more rigorous validation process is required prior to their use in clinical practice.

The recognition that other neurodegenerative conditions can overlap with ALS has been an important step in our understanding of the pathogenesis of ALS and FTD. From a genetic viewpoint, it is anticipated that this study will ultimately provide the knowledge to identify novel gene(s) that increase the risk of cognitive decline in ALS, and therefore provide further valuable insights into the pathogenesis of the neurodegenerative process.
Acknowledgements

Professor Orla Hardiman has been an ever-present supervisor and mentor. Her enthusiasm for translational research and for training of the next-generation of clinician scientists is notable.

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My family have never failed to shepherd me through all the trials and (primarily) tribulations of medical school, life as a doctor, and this PhD. Their unconditional support is wonderful.

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Chapter 1  Motor Neurone Disease (MND)

1.1 Terminology

The term MND refers to a number of progressive neurological diseases which affect motor neurones, of which ALS (Amyotrophic Lateral Sclerosis) is the most common.

MND is the standard term used in United Kingdom and Ireland whereas the term ALS is used more commonly in the United States (often interchangeably with MND). It is also known there as Lou Gehrig's disease, after the famous baseball player who succumbed to the disease at the age of 37. This thesis specifically examines ALS, a progressive neurodegenerative disease that simultaneously affects upper and lower motor neurones.

1.2 Epidemiology

Motor Neurone Disease (MND) is a rare disease. Its crude incidence ranges between 0.6 and 2.6 per 100,000 population (Chancellor 1992; Román GC 1996), leading to a lifetime risk of developing ALS of 1 per 800 (Cleveland 2001). Its most commonly reported world-wide prevalence is 5/100,000 (Traynor 1999; Leigh 1994). However three regions in the Western Pacific: Guam, the Kii Peninsula, and Western New Guinea (the Auyu and Jakai people) (Kurland 1987) differ notably. The Western Pacific form of ALS has been of interest for over 50 years because its incidence, prevalence, and mortality rates were initially 50 to 100 times those of sporadic ALS. The condition was frequently associated with a parkinsonism / dementia complex (PDC). The frequency of Western Pacific ALS has declined in recent times (Plato 2002). Putative theories involve temporary exposure to environmental risk factors such as neurotoxins in local wildlife including cycad nuts, possibly in a genetically susceptible population. However, no single genetic defect, environmental toxin, or virus has been convincingly linked to these cases.

A recent systematic review suggests that the incidence of ALS may be lower among African, Asian, and Hispanic ethnicities than among whites (Cronin 2007) although further prospective epidemiological studies are needed. Recent research suggests that ancestral origin is likely to play a role in ALS susceptibility (Zaldivar 2009).
With the exception of some familial cases, the aetiology of ALS remains unknown. Genetic susceptibility is an indisputable risk factor with familial cases accounting for about 10% of presentations. The other 90% of cases are referred to as 'sporadic'. Comparison of familial ALS (FALS) and sporadic ALS (SALS) suggests that the familial form may present at an earlier age, although this is not always the case. No clinical features can reliably distinguish FALS from SALS.

Age is the most significant predictor of MND, with the highest rate of onset occurring between 55 and 75 years of age. ALS is more common in males than females by a ratio of 1.3 to 1.6: 1, but this disparity decreases over the age of 70 (Nelson 2005). Excessive physical activity has been suggested as a risk factor for developing ALS perhaps in genetically susceptible individuals which would be in agreement with the primary hypotheses underpinning ALS pathogenesis: increased oxidative stress and glutamate excitotoxicity. However previous studies examining physical activity and the risk of developing ALS have produced conflicting results (Critchley 1962; Felmus 1976; Chancellor 1993; Longstreth 1998; Scarmeas 2002). A more recent large, case-control study found no association between physical activity and the risk of developing ALS, but it did find that increased leisure time physical activity was associated with an earlier age at onset (Veldink 2005). Some studies, however, have been plagued by methodological flaws, particularly small study numbers, multiple hypotheses testing, and inadequate consideration of confounders (Harwood 2009).

The role of environmental exposure as a trigger in ALS may be supported by a limited body of evidence that suggests an association between military service and later development of ALS. US Gulf War veterans have about a two-fold higher incidence of ALS than expected (Haley, 2003; Horner 2003). It was postulated that environmental exposures specific to Gulf War service, such as organophosphorus pesticides, chemical nerve agents or multiple vaccinations with mercury containing vaccines, may have triggered the disease in genetically susceptible individuals. However, bias could have occurred due to the small numbers of ALS cases and to potential methodological flaws including under-reporting of ALS in the non-deployed Gulf War population, an uncertain age at disease onset, and assumptions made when trying to ascertain the expected incidence of ALS in the US population during the time of the study (Armon 2004).
A large cohort study of 500,000 men (Weisskopf 2005) found that US military veterans had an increased death rate from ALS compared with non-veterans (adjusted relative risk 1.58, 95% CI 1.14-2.19). This increase appeared to be largely independent of the branch of service and the time period served. This latter result may thus provide evidence against a specific environmental trigger related to the Gulf War being a cause of ALS. Despite the limitations of such a retrospective study, the results are consistent with other reports supporting the concept of a possible correlation between ALS and military service (albeit a low increased risk).

Smoking has been found to be an independent risk factor for ALS (Armon 2003) and whilst a number of other risk factors have been suggested, including a history of strenuous physical activity, trauma, electric shock and exposure to pesticides, these associations have generally been found to be weak and inconsistent.

Putative environmental risk factors in ALS will require large case-control studies that examine the complete spectrum of known or possible exposures.

1.3 Diagnosis

This section refers specifically to the diagnosis of ALS. Other forms of motor neurone disease are discussed separately. ALS diagnosis is based upon clinical criteria that include the presence of upper motor neuron (UMN) and lower motor neuron (LMN) signs, progression of disease, and the absence of an alternative explanation. There is no single diagnostic test that can confirm or entirely exclude the diagnosis of motor neuron disease. The El Escorial criteria were developed in 1990 (revised 1998) and endorsed by the World Federation of Neurology for the diagnosis of ALS in research and clinical trials. These guidelines were introduced for research purposes to ensure uniformity and certainty in diagnosis, which is of particular importance in clinical trials (Appendix 1). These criteria, although not entirely without criticism, have been shown to be sensitive and specific and have been validated pathologically (Chaudhuri 1995).

The clinical diagnosis of ALS, without pathological confirmation, may be categorized into various levels of certainty by clinical assessment alone depending on the presence of upper motor neurone and lower motor neurone
signs together in the same topographical anatomic region in either the brainstem (bulbar cranial motor neurons), cervical, thoracic, or lumbosacral spinal cord (anterior horn motor neurons).

The clinical presentation of ALS patients is extremely variable. It classically present in an insidious, progressive fashion. The chief initial symptoms may be non-specific muscle cramping, twitching, and ill-defined weakness and fatigue. Patients may also present with gait difficulties (e.g. tripping, dragging one leg) or difficulties with fine movements e.g. fastening buttons. 25% present with bulbar symptoms such as drooling (sialorrhoea), slurred speech (dysarthria), and swallowing difficulties (dysphagia). Up to 50% of patients with ALS experience pseudobulbar affect, also known as "emotional lability" (Gallagher 1989), which consists of uncontrollable laughter or crying. Emotional lability is not specific to ALS; it also occurs in other unrelated conditions including multiple sclerosis, stroke, Parkinson’s disease and Alzheimer’s disease. Patients less frequently present with respiratory symptoms such as dyspnoea.

Of note, when making a diagnosis of ALS, there should be an absence of sphincter disturbance, ocular involvement or ptosis, prominent sensory symptoms, and involuntary movements. Up to one quarter of patients complain of minor sensory symptoms, which should not dissuade the clinician from making the diagnosis. Indeed, detailed electrophysiological evaluation of sensory and autonomic systems demonstrates involvement in up to 20% of patients (Isaacs 2007; Pugdahl 2007). However, in clinical practice significantly reduced sensory nerve action potential amplitude should prompt consideration of other diagnoses than ALS. Small, or absent sensory nerve action potentials are also a feature of other motor neuron disorders including Kennedy's syndrome and some forms of spinal muscular atrophy (Eisen 2001).

The course should not be relapsing/remitting. Cognitive dysfunction, although not recognized by the El Escorial criteria as a core feature of ALS, is not infrequent and is described below. Frontotemporal executive dysfunction can precede or follow the onset of motor symptoms and may be more common in patients with bulbar onset ALS.

The clinical hallmark of MND on neurological examination is the presence of widespread, purely motor signs of both upper and lower motor neuron dysfunction
not attributable to other causes, especially when the signs occur concomitantly at the same spinal level (e.g. brisk reflexes in a weak, fasciculating limb).

Patients in whom the diagnosis of ALS is considered on clinical grounds should have electrophysiological studies performed to confirm LMN dysfunction in clinically affected regions, to detect electrophysiological evidence of LMN dysfunction in clinically uninvolved regions, and to exclude other pathological processes including potentially treatable conditions such as multifocal motor neuropathy with conduction block.

Multifocal motor neuropathy is an acquired immune-mediated demyelinating neuropathy associated with slowly progressive weakness, fasciculations, and cramping. The condition can mimic the early stages of ALS. However symptoms can be partially or completely reversible by intravenous immunoglobulin (IVIg) therapy (Kaji 1999).

Electrophysiology may demonstrate evidence of acute and chronic denervation.

- Fibrillation and positive sharp waves in limbs and bulbar region indicate acute denervation
- Reduction in number and increase in amplitude and duration of motor unit action potentials (MUAPs) with neurogenic recruitment and a reduced interference pattern indicate chronic denervation.
- Fasciculation potentials may also appear in denervated muscles. These may also be visible to the naked eye on the muscle surface. They represent spontaneous firing of motor units that are not voluntarily recruited.
- Normal excitability and conduction velocity of sensory nerve fibres, even in affected areas (Leigh 1994).

Fasciculation potentials associated with neurogenic disease, especially ALS, show a complex morphology, and often exhibit instability. In contrast, benign fasciculations occurring in healthy muscles are simple in morphology, are stable and are always recorded in the context of normal voluntarily activated motor unit potentials. Fasciculation potentials only achieve diagnostic significance for ALS in the context of a clinically suspected diagnosis (de Carvalho 2007).
More recent studies of the neurophysiology of ALS have focused on motor evoked potentials (MEP) recorded following transcranial stimulation of motor cortex. Upper motor neuron involvement in ALS can be demonstrated through increased MEP thresholds (reflecting progressive inexcitability of central motor pathways), a reduction of the normal inhibitory cortical stimulation silent period, and a normal or modestly prolonged central motor conduction times (Komissarow 2004) In contrast, markedly slow central conduction occurs in patients with PLS (as well as increased cortical threshold requiring a strong stimulus and severely attenuated MEP amplitude) (Kuipers-Upmeijer 2001) and the D90A CuZn-SOD1 ALS mutation (recessive) (Eisen 2001). The role of transcranial magnetic stimulation in ALS has yet to be fully defined but it may be highly predictive in identifying progression to ALS in patients with probable upper motor neuron signs i.e. incongruously present or overactive tendon reflexes in weak and wasted limbs without Babinski or Hoffmann signs or clonus (Miscio 1999).

Electrophysiological results should be evaluated in conjunction with the clinical and other ancillary findings.

Neuroimaging studies should be selected in order to exclude other conditions which may cause UMN and/or LMN signs but there are no neuroimaging tests which provide positive support for the diagnosis of ALS. Brain MRI is indicated whenever bulbar disease is present. Cervical and lumbosacral spine MRI can be used to evaluate lower motor neuron disease in the limbs. MRI findings such as hyperintensities of the corticospinal tract (CST) in the brain or in the spinal cord, hypointensities in the precentral gyrus or atrophy of the precentral gyrus/enlargement of the central sulcus have moderate to low sensitivity and specificity (Chan 2003).

Computational neuroanatomy techniques such as voxel-based morphometry (analysis of regional volume alterations of the grey or white matter) and diffusion tensor imaging (analysis of the white matter integrity) hold promise in understanding the pathophysiology of ALS and developing quantitative surrogate markers for disease progression usable in clinical trials (Reviewed in Grosskreutz 2008).

Routine blood tests should be performed to exclude other conditions. Cerebrospinal fluid analysis is not explicitly indicated for diagnosis but the presence of a significantly raised protein or cell count points to ALS mimics
including meningeal infiltration with lymphoma, or (in LMN syndromes) a motor variant of chronic inflammatory demyelinating neuropathy (CIDP).

Genetic testing is not a routine part of the ALS diagnosis at present. Familial ALS accounts for approximately 10 percent of cases. Approximately 20 percent of familial ALS is linked to superoxide dismutase type 1 gene (SOD1) mutations located on chromosome 21q22. SOD1 testing is commercially available, but it is usually only pursued if there is a clear family history of autosomal dominant disease. Since only 20% of familial ALS will test positive for this mutation, the test has limited value in genetic counselling. In addition, weak or variable penetrance is associated with some mutations, so that identification of a mutation in an unaffected individual does not imply that ALS is inevitable. Genetic counselling is required before genetic testing and must take into account the nature of the mutation and the pedigree.

Genetic testing may be utilised in diagnosis of mimic-conditions such as Kennedy syndrome and late-onset Tay Sachs disease.

Table 6 demonstrates the differential diagnosis of MND. During the early stages both false positive and false negative diagnoses are common. A review of the Scottish Motor Neuron Disease Register demonstrated that in 8% (46/552), an alternative diagnosis was made (Davenport 1996). In a study on Irish ALS patients, a percentage of 7.3% (32/437) misdiagnoses were reported (Traynor 2000).

1.4 Clinical Characteristics

MND encompasses a number of disorders, including ALS (both upper and lower motor neurone features), Progressive Muscular Atrophy (PMA; only lower motor neurone signs), Primary Lateral Sclerosis (PLS; exclusively upper motor neurone signs) and Progressive Bulbar Palsy (PBP); (Table 1). These clinically heterogeneous presentations are grouped under the unifying diagnosis of MND. It remains controversial whether these disorders do indeed represent distinct entities or if they are simply manifestations of the same disorder, in other words varying phenotypes with differential involvement of motor and CNS systems. It also remains to be seen whether each may have different aetiologies or modifying factors. Clarification of these issues will aid formulation of more stringent diagnostic criteria and perhaps targeted therapeutic strategies.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical features</th>
<th>Other comments</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS</td>
<td>Both upper and motor neurone signs in multiple spinal segments</td>
<td>Most common adult-onset form of motor neuron disease.</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Primary Lateral Sclerosis</td>
<td>Upper motor neuron signs only</td>
<td>Many patients eventually develop clinical or electrophysiological signs of LMN involvement. ALS develops in up to 77% within 3-4 years.</td>
<td>For those who remain with a diagnosis of PLS, median survival = 20 years or more</td>
</tr>
<tr>
<td>Progressive Muscular Atrophy</td>
<td>Lower motor neuron signs only</td>
<td>Variable evolution to ALS</td>
<td>5 years. A subset survive 20 years or more</td>
</tr>
<tr>
<td>Progressive Bulbar Palsy</td>
<td>Speech and swallowing affected initially due to LMN involvement of CN IX, X, XII.</td>
<td>Symptoms include dysarthria, dysphagia, and dysphonia. Aspiration pneumonia is usually the terminal event</td>
<td>2-3 years</td>
</tr>
</tbody>
</table>

**CN: Cranial Nerves**  
**UPM: Upper Motor Neuron**  
**LMN: Lower Motor Neuron**

Neuropathologically, these disorders do not lend themselves to such simple classification. For example, of 12 PMA patients studied in a case review, 75% were found to have neuropathological or clinical evidence of UMN degeneration (Ince 2003). It was also noted that most had ubiquitinated inclusions typical of ALS. The study concluded that a patient presenting with PMA with rapid clinical evolution likely has the pathology and pathophysiology of ALS whether or not upper motor neuron signs evolve.

Another study (Iwanga 1997) demonstrated loss of Betz cells in the motor cortex and myelin pallor in the corticospinal tract (both UMN signs) in two patients with long-duration PMA, conventionally believed to exclusively affect the LMNs. Conversely, evidence of LMN involvement (e.g. loss of pallor and demyelination of the corticospinal tract; electrophysiological findings) have also been seen in PLS (Le Forestier 2001; Swash 1999) alongside progression to classic ALS in half of all cases.

Nonetheless, it seems that PLS or at least UMN-dominant ALS appear to have a more benign prognosis than typical ALS. Survival is longer and disease progression is slower in patients classified as PLS compared with ALS controls (Gordon 1996). Survival for patients with UMN-dominant ALS was intermediate between that of PLS and classic ALS.
1.4.1 Amyotrophic Lateral Sclerosis (ALS)

ALS is the most common adult onset form of motor neurone disease from which approximately 6,500 individuals die each year in the United States. The presence of both UMN and LMN signs in multiple segments is required for the diagnosis of ALS.

Upper motor neurone signs include increased muscle tone, brisk reflexes, and pathologic reflexes such as crossed adductors, positive jaw jerk, or Hoffman sign. The Babinski sign (reflex great toe extension, often with fanning of the small toes, with lateral plantar stimulation) is present in about one-half of patients with ALS (Landau 1959). Such upper motor neurone signs result from degeneration of frontal motor neurons located in the motor strip (Brodman area 4) and their axons traversing the corona radiata, internal capsule, cerebral peduncles, pontine base, medullary pyramids, and the lateral corticospinal tracts of the spinal cord.

Lower motor neurone signs include decreased muscle tone, muscle wasting, and fasciculations. These result from lower motor neurone degeneration in the brainstem and spinal cord.

UMN and LMN symptoms can occur independently or simultaneously in both upper and lower limbs, as well as the bulbar region (affecting the face, mouth, tongue and throat) and trunk.

UMN loss results in slowness of movement, incoordination and stiffness with relatively little weakness. Patients may report poor dexterity, spastic gait with poor balance, or spontaneous leg flexor spasms. Hyperreflexia and clonus can cause muscle pain. Bulbar ALS is present in 20% of patients upon presentation and may manifest with dysarthria (slurred speech; UMN involvement can cause strained, slow speech), dysphagia (swallowing difficulties which can lead to coughing and choking), laryngospasm and less frequently trismus (‘lockjaw’) Emotional lability (Involuntary Emotional Expression Disorder), an affective disinhibition syndrome, is evident in up to 45% of patients. This refers to involuntary and inappropriate laughing, crying or yawning; it may be mood-incongruent and although most commonly seen in MND, it is also seen in other neurological conditions such as multiple sclerosis, brain trauma, Alzheimer’s disease and Parkinson’s disease.
LMN loss results in overt weakness, often with atrophy and fasciculations. Patients may report difficulties with fine movements (e.g. handling buttons, zips and coins). Proximal arm weakness results in difficulty elevating the arm to the level of the mouth or above the head which produces difficulty with bathing, dressing, grooming and eating. Proximal leg weakness results in difficulty rising from a chair, climbing stairs and balance problems (knee buckling with falls). Distal leg weakness results in tripping, particularly on uneven surfaces, and a slapping gait secondary to foot drop.

LMN damage can also result in dysphagia and dysarthria. Tongue or pharyngeal constrictor weakness results in dysphagia. Coughing and choking can occur whilst eating or drinking but can occur even during swallowing of secretions, potentially resulting in aspiration. Sialorrhoea (excess secretions) combined with dysphagia and facial weakness can lead to drooling. LMN weakness of the masseter muscle can result in chewing difficulties and similar weakness of the pterygoids can cause weakness of mouth opening. Severe weakness of these two muscles may produce temporomandibular joint dislocation.

Dysarthria may result from weakness of the tongue, lips or palate. The speech is usually slurred and may have a nasal quality. Hoarseness may be caused by associated vocal cord weakness.

LMN weakness affecting the trunk and spine may manifest by head drop or truncal extension weakness as well as abdominal protuberance.

Respiratory muscle weakness is present in most patients with ALS at diagnosis (Bourke 2001; Schiffman 1993) even if it is not always clinically prominent. It is a strong independent predictor of quality of life (Bourke, 2001) and results in breathlessness and thus hypoventilation and sleep disruption, morning headache, unrefreshing sleep, daytime somnolence, lethargy, fatigue, poor concentration, and poor appetite. Lower motor neurone diaphragm weakness may also cause orthopnoea.

Weight loss occurs frequently in motor neurone disease; the extent of this weight loss is disproportionate to the degree of muscle atrophy or nutritional difficulties.

Autonomic symptoms may occur in ALS as the disease progresses. Constipation occurs frequently but is likely multifactorial. Delayed colonic
motility has been demonstrated as has delayed gastric emptying (early satiety, bloating). Urinary urgency without incontinence is common, but incontinence itself is uncommon.

Patients with ALS often experience fear, anxiety and depression. Cognitive difficulties in ALS are described in the literature review section.

Despite the widespread involvement described in this relentlessly progressive disease, certain functions remain preserved in ALS including extraocular muscle movement (cranial nerve III, IV and VI nuclei are spared until very late in the disease course), bladder and bowel control, sensory function and skin integrity.

Death occurs in most patients within five years of disease onset although survival may be longer in some juvenile-onset forms (Leigh 1994; Chancellor 1992). Respiratory failure is usually the terminal event responsible. Approximately ten percent of ALS patients can live 10 years or more. Survival beyond 20 years is rare and partly depends on treatment decisions made by patients, their families and physicians.

1.4.2 Progressive Muscular Atrophy (PMA).

This progressive LMN disorder is usually described as a disease characterized by slow progression and long duration with survival from onset ranging from 43 to 407 months (mean 159.2 months) (Norris 1992). It accounts for about 5% of all MND cases.

PMA shows variable degrees of progression. Some individuals never develop clinical UMN signs. Most, however, do develop UMN signs later in their clinical course, at which point the disease is called LMN-onset ALS. Ince et al demonstrated that half of PMA cases in their series showed corticospinal tract degeneration (by CD68 immunocytochemistry) although not all develop clinically apparent UMN signs (Ince 2003). Asymmetric distal upper limb weakness is the most common initial presentation. Bulbar involvement is often mild and occurs late in the disease (Swank 1943; Chio 1985).

1.4.3 Primary Lateral Sclerosis (PLS)

This is classically defined as a progressive isolated UMN disorder accounting for about 4% of MND cases. It is a clinical diagnosis. Commonly used criteria
are adult onset, negative family history, gradual progression, spasticity with paresis of the legs for more than 3 years, and dysfunction clinically limited to the corticospinal tracts (Pringle 1992).

However, a retrospective study (Gordon 2006) followed 39 patients initially presenting with a PLS-like syndrome, 29 fulfilling criteria for PLS. Over a mean 8.7 years of follow-up, 16 continued to show a pure UMN syndrome compatible with PLS (and had long survival), while electromyographic or clinical evidence of denervation and LMN disease developed in 13 patients who were initially classified as UMN-dominant ALS. Recognition of pure PLS was reliable after 4 years observation, including repeat EMG evaluation. Development of LMN signs later in their clinical course is thus referred to as UMN-onset ALS.

The UPM signs in limbs and/or the bulbar region are similar to those described in ALS above, including muscle spasticity (but only slight lower limb weakness) and pseudobulbar affect (Le Forestier 2001). In contrast to ALS however, PLS has a longer duration and more insidious course, with extensive cortical atrophy (Kuipers-Upmeijer 2001).

1.4.4 Progressive Bulbar Palsy

This is a progressive UMN and LMN disorder of cranial nerve motor nuclei resulting in bilateral atrophy of the ninth through twelfth cranial nerves, resulting in bulbar symptoms such as dysarthria, dysphagia, dysphonia, poor cough and associated respiratory problems, tongue atrophy & fasciculations, abnormal corticobulbar reflexes as well as emotional lability (if there is involvement of the corticobulbar tract). Patients may subsequently develop UMN and LMN limb signs and the condition is then referred to as bulbar-onset ALS. 25% of MND patients have this bulbar-onset from.

The dysarthria resulting from this disease, which usually develops into a mixed spastic-flaccid type, can be rapidly progressive. Speech may be effortful and slow with short phrases, inappropriate pauses, imprecise consonants, hypernasality, strain-strangled voice, as well as decreased pitch and loudness range (Duffy 1995).

This subtype seems to have a more rapidly progressive disease pattern compared to corticospinal subgroups. Respiratory complications due to
aspiration frequently result in death within 1 to 3 years. There have been no reports of specific pathology in PBP.

1.4.5 Familial MND/ALS (FALS) vs. Sporadic MND/ALS (SALS)

1.4.5.1 Familial MND

5-10% of MND cases are termed familial (inherited) whilst the remainder are labelled sporadic in origin. In most individual cases, it may be difficult to determine on clinical grounds alone if ALS is familial or sporadic, especially at the onset of disease.

Familial ALS demonstrates phenotypic and genetic heterogeneity. Comparison of familial ALS (FALS) and sporadic ALS (SALS) suggests that the familial form may present at an earlier age, although this is not always the case. There are no clinical features that can reliably distinguish FALS from SALS.

Numerous genetic loci, with dominant, recessive, and X-linked patterns of inheritance, have been associated with familial ALS (see Table 2; (reviewed in Beleza-Meireles 2008). Mutations in the gene encoding copper-zinc superoxide dismutase 1 gene (SOD1) account for 20 percent of cases of familial ALS. SOD-1 mutations were first described in 1993 (Rosen). The SOD-1 protein is involved in detoxification of superoxide free radicals. The exact mechanism of SOD1-mediated pathogenesis remains uncertain but it may be that mutations cause a toxic gain of function that is deleterious to motor neurones. Putative mechanisms include oxidative stress resulting from aberrant enzymatic specificity, copper toxicity, and abnormal protein aggregation.

Table 2. Familial ALS Loci

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type Inheritance</th>
<th>Gene</th>
<th>Onset</th>
<th>Chromosome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS 1</td>
<td>Dominant and recessive (D90A)</td>
<td>SOD 1</td>
<td>Adult</td>
<td>21q22.1</td>
<td>Rosen et al. 1993; Al-Chalabi et al. 1998</td>
</tr>
<tr>
<td>ALS 2</td>
<td>Recessive</td>
<td>Alsin</td>
<td>Juvenile</td>
<td>2q33</td>
<td>Hadano et al. 2001; Yang et al. 2001</td>
</tr>
<tr>
<td>ALS 3</td>
<td>Dominant</td>
<td></td>
<td>Adult</td>
<td>18q21</td>
<td>Hand et al. 2002; Sapp et al. 2003</td>
</tr>
<tr>
<td>ALS 4</td>
<td>Dominant</td>
<td>Senataxin</td>
<td>Juvenile</td>
<td>9q34</td>
<td>Chen et al. 2004</td>
</tr>
<tr>
<td>ALS 5</td>
<td>Recessive</td>
<td></td>
<td>Juvenile</td>
<td>15q15.1-q21.1</td>
<td>Hetnati et al. 1998</td>
</tr>
<tr>
<td>ALS 6</td>
<td>Dominant</td>
<td></td>
<td>Adult</td>
<td>16q12</td>
<td>Abalkhail et al. 2003; Ruddy et al. 2003; Sapp et al. 2003</td>
</tr>
</tbody>
</table>

13
SOD mutations have also been described in 5% of patients with apparently sporadic disease. Of the 100 or more SOD mutations reported the most common is the substitution of valine for alanine at position 4 (A4V) (Anderson 2003). All SOD1 mutations are dominant, except for the substitution of alanine for aspartate at position 90 (D90A), which can be either recessive or dominant. MND patients with different SOD1 mutations, also known as FALS-1, demonstrate heterogeneity with respect to clinical presentation (spinal or bulbar), age of onset, penetrance, rate of decline, survival (survival ranges from 1 to 20 years), and histopathology. For example, patients with the A4V mutation generally exhibit sparing of corticospinal tracts but pathological involvement of extra-motor neuronal systems are more common (Cudkowicz 1998). Rapid progression is typically evident with an average life expectancy of 1.5 years after the onset of symptoms (Ratovitski 1999). Conversely, the rare A89V SOD1 mutation is characterized by incomplete penetrance, variable age of onset, and an associated painful sensory neuropathy (Rezania 2003). Aside from SOD1, researchers have attempted to identify other genes in familial ALS. Genetic loci associated with ALS-like human motor neuron disease have been designated ALS1 through ALS8, ALS with frontotemporal dementia (ALS-FTD) and ALS-FTD with Parkinson's disease (ALS-FTDP). Mutations in genes encoding angiogenin (ANG) and sequence variants in neurofilament genes have also been reported. However, only ALS1, ALS3, ALS6, ALS7, mutations in angiogenin, and some cases of ALS8 represent the classic neurodegenerative condition with mixed upper and lower motor neurone signs. Genes that cause familial ALS include dynactin 1 (Puls 2003),
alsin (Hadano 2001), senataxin (Chen 2004), vesicle-associated protein B (Nishimura 2004), and angiogenin (Greenway 2004, 2006). Identifying the genes causing the remainder of familial cases will be challenging, since many of the remaining loci appear to segregate in individual families (Kunst 2004).

Most recently, mutations in the FUS gene, located on chromosome 16q12, have been reported as a cause of FALS (Vance 2009; Kwiatkowski 2009). These variants are inherited in an autosomal-dominant pattern and the resulting phenotype is clinically and pathologically consistent with typical ALS; cognitive changes were absent in patients from both studies. The FUS gene bears functional similarity to TARDBP, another gene implicated in familial ALS (Van Deerlin 2008; Sreedharan 2008; discussed further in Chapter Two).

The occurrence of mutations in two or three genes that are together required to cause an ALS phenotype could account for the large proportion of supposedly familial disease with reduced penetrance, as well as a substantial proportion of sporadic cases (Valdmanis 2008). However, recent whole genome association studies have demonstrated that there is no single gene of large effect that accounts for the majority of sporadic ALS (Cronin 2008).

Loci linked to familial MND include 9q34 (Chance 1998), which codes for senataxin. These patients present early (before the age of 25), initially with distal weakness, and demonstrate slow progression. Autosomal recessive juvenile-onset ALS has been linked to chromosomes 2q33 (Hentati, 1994) and 15q15–22 (Hentati, 1998). An X-linked dominant form of FALS (Xp11-q12) has also been reported (Figlewicz, 2003). These individuals have adult onset with prominent bulbar features and a slowly progressive course.

The genetics of MND associated with frontotemporal dementia will be discussed in the next chapter.

1.4.5.2 Sporadic MND

90% of MND cases occur in the absence of a family history of the disease. However, familial aggregation studies, twin studies and epidemiological observations have suggested a substantial genetic contribution to disease risk (Chio 2009). It seems that genetic factors are involved in the sporadic form of this disease and that these may interact with environmental factors. If this is the case, it is not clear if sporadic ALS is monogenic (i.e. a single-gene
disorder) or polygenic (i.e. multiple interacting genes). Statistical and genealogical evidence suggest that quite a number of diagnosed sporadic cases may in fact be familial cases in pedigrees with very low disease penetrance (Andersen 2001).

Several association studies have searched for possible genetic risk factors. Putative susceptibility genes include VEGF (Lambrechts 2003), ANG (Greenway 2006), HFE (Goodall 2005), SMN (Corcia 2006, Veldink 2005), PON (Slowik 2006), although not all have been replicated. Patients with homozygote ciliary neurotrophic factor (CNTF) gene deletions show earlier onset of disease (Giess, 2002).

Vascular endothelial growth factor (VEGF) is an important angiogenesis factor upregulated in hypoxic conditions. Its role in sporadic MND is supported by the discovery of two VEGF haplotypes in a case-control meta-analysis of ALS in four European populations (Lambrechts, 2003). Subsequent studies have demonstrated conflicting results with a lack of association of the VEGF polymorphisms with SALS in Dutch and North American populations; this may however be a population-based effect and does not exclude a role for VEGF in the pathogenesis of ALS (Van Vught 2005; Chen 2006).

Genome-wide association (GWA) studies are ongoing (2006) to investigate the genetics of sporadic MND (Dunckley 2007; van Es 2007; Schymick 2007; Cronin 2008; Chio 2009). Challenges for GWA studies include the need to collect several thousand well-phenotyped samples, the high false positive rate when several hundred thousand tests are performed on the same data set, the genetically heterogeneous nature of sporadic ALS (multiple genes and multiple alleles may be responsible thus limiting the power of GWAs), difficulty in finding the best statistical method of correcting for multiple testing and the need for replication in large heterogeneous cohorts (Schymick 2007). These studies have however provided publicly accessible data and may ultimately help identify novel genes involved in the pathogenesis of sporadic MND. To date, no single locus has definitively been associated with increased risk of developing disease, although potentially associated candidate single-nucleotide polymorphisms (SNPs) have been identified. These act as proxy markers for neighbouring genetic variation and may prove to be important in further understanding the genetics of sporadic ALS; however it must be
established whether these individual SNPs are pathogenic and whether these findings are replicable in large independent cohorts.

1.5 Treatment

Whereas there are limited pharmacological options in MND, the mainstay of management is symptomatic treatment. MND remains an incurable condition. MND patients who received care at a multidisciplinary clinic have a better prognosis than patients attending a general neurology clinic (Table 3). Median survival was 7.5 months longer for the former group (Traynor, 2003; Chio 2006) and was roughly two months more for patients with bulbar dysfunction. The data suggest that active and aggressive management enhances survival.

Table 3. Roles of the Multidisciplinary Team

<table>
<thead>
<tr>
<th>Role</th>
<th>Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologist</td>
<td>Diagnosis, disclosure of diagnosis, treatment and symptom management, initiation of respiratory and nutritional interventions, unbiased information regarding research developments</td>
</tr>
<tr>
<td>Family Doctor</td>
<td>Symptom control, drug monitoring, liaison with other teams</td>
</tr>
<tr>
<td>MND Specialist Nurse</td>
<td>Liaison with medical team and coordination of care, home visits, practical advice re accessing support services, patient advocacy</td>
</tr>
<tr>
<td>Speech &amp; Language Therapist</td>
<td>Evaluation and monitoring of dysphagia and aspiration, speech therapy and counselling re communication devices.</td>
</tr>
<tr>
<td>Occupational Therapist</td>
<td>Optimisation of the patient's environment. Advice re safety awareness, adaptive and splinting devices, activity modification, driving, energy conservation, home modification.</td>
</tr>
<tr>
<td>Dietitian / Nutritionist</td>
<td>Evaluation of nutritional status and the need for tube feeding, management of dysphagia, management if enteral feeding</td>
</tr>
<tr>
<td>Physiotherapist</td>
<td>Evaluation of muscle strength and function, advice re walking aids and orthoses, safety awareness</td>
</tr>
<tr>
<td>Social Worker</td>
<td>Advice and counselling re employment, change in lifestyle and financial issues, support for carers</td>
</tr>
<tr>
<td>Palliative Care</td>
<td>Symptom control, pain management, maintenance of quality of life, preservation of dignity</td>
</tr>
<tr>
<td>Psychiatry and Neuropsychology</td>
<td>Evaluation and management of cognitive impairment/dementia, adjustment disorders, anxiety and depression</td>
</tr>
<tr>
<td>Respiratory Physician</td>
<td>Assessment of respiratory dysfunction, initiation of non-invasive ventilation</td>
</tr>
</tbody>
</table>

ALS is a terminal condition, and optimal management should include early access to palliative care services. Initiation of discussion of advance directives
well in advance of the terminal phase should occur with re-evaluation at least every 6 months (Miller 1999). The patient's role in the decision-making process is cardinal. In the event of evolving cognitive impairment, a power of attorney for health care should also be obtained and/or healthcare proxy identified by the patient and family.

1.5.1 Breaking the diagnosis

The average delay from onset of symptoms to diagnosis is about 14 months. The patient may already suspect the diagnosis and may have visited internet sites or have watched television programmes about people with MND choking to death or demanding the right to assisted suicide. Patients with a suspected diagnosis of MND should be "fast-tracked" through the health system to expedite the diagnosis, address their fears, and initiate care. The recommendations of the European and AAN Practice Parameters (Andersen 2005; Miller 1999) make intuitive sense to most clinicians and includes the advice that diagnosis always be given in person and never by telephone, and that implications of the diagnosis should be discussed (see Table 4 below).

The disclosure should be planned so that family members of friends are present as well as, if possible, a nurse specialist. Many patients do not want all the details at once, and follow-up appointments should be arranged soon afterwards to resolve outstanding concerns. Referral to a specialist voluntary support group may be beneficial to some patients.

Table 4. Recommendation for Breaking the News. AAN Practice Parameter

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 The physician should give the diagnosis to the patient and discuss its implications.</td>
<td>Respect the cultural and social background of the patient in the communication process by asking whether the patient wishes to receive information or prefers that the information be communicated to a family member. (Guideline)</td>
</tr>
<tr>
<td>2 The diagnosis should always be given in person and never by telephone.</td>
<td>(Guideline)</td>
</tr>
<tr>
<td>3 Provide printed materials about the disease and about support and advocacy organizations (Guideline), and a letter or audiotape summarizing what the physician has discussed.</td>
<td>(Option)</td>
</tr>
<tr>
<td>4 Avoid the following: withholding the diagnosis, providing insufficient information, delivering information callously, or taking away or not providing hope.</td>
<td>(Guideline)</td>
</tr>
</tbody>
</table>
Pharmacological Treatment

Riluzole (2-amino-6-(trifluoromethoxy) benzothiazole, RP 54274), an anti-glutamate agent is the only drug licensed to treat MND. Although the drug reduces glutamate-induced excitotoxicity, its precise mechanism in ALS is unknown. The first randomised prospective, double-blind placebo trial of the drug in 155 patients (Bensimon 1994) found increased survival at 12 month follow-up (74% versus 58%, relative risk 0.43, CI 0.24-0.77), particularly for patients with a bulbar onset (73% versus 35%). Towards the end of the study the improvement was less noticeable suggesting the drug may help patients to stay in earlier phases of the disease for longer. Recent meta-analysis (including 3 double-blind randomised placebo controlled trials) from the Cochrane Library (Miller 2002) suggests that the drug provides a 9% gain in the probability of surviving one year and adds approximately 2 months to patient survival.

Recommended dosage is 50mg twice daily. Riluzole is well absorbed orally with a bioavailability of 60% and an elimination half-life of 12 hours. It is generally well tolerated although gastrointestinal adverse effect can occur as well as liver enzyme abnormalities.

The American Academy of Neurology's practice advisory (1997) states that the patients most likely to benefit from treatment include those who have:

- Definite or probable ALS by El-Escorial criteria, in whom other causes of progressive muscle atrophy have been ruled out
- Symptoms present for less than five years
- Vital capacity (VC) greater than 60 percent of predicted
- No tracheostomy

Other glutamate antagonists, neurotrophic factors, antioxidants and immunomodulatory agents have not been proven to be effective in human clinical trials but trials are ongoing. The most recent study involved 16 patients treated with lithium (Fornai 2008). The drug, which has known neuroprotective effects, seemed to slow ALS disease course. However this small non-blinded pilot study was heavily criticised (Meininger 2008); a larger, randomized controlled trial is planned to verify whether these pilot data can be replicated. Most neurologists retain a healthy degree of scepticism about this potential new treatment at present, especially given the recent events
surrounding minocycline. The latter was another therapy that generated excitement in the ALS community. The animal data was promising but it demonstrated no beneficial effect, and for some patients, worsened measurable outcomes (Gordon 2007). A detailed analysis of clinical trials in ALS has been published recently (Lanka 2008). Clinical trials that are currently recruiting patients are outlined in Table 5.

**Table 5. Current clinical trials in ALS**

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Recruitment pending</th>
</tr>
</thead>
<tbody>
<tr>
<td>Far infrared radiation</td>
<td>Growth Hormone</td>
<td>MCI-186</td>
<td>ONO-2506PO Phase II</td>
</tr>
<tr>
<td>Ceftriaxone (compassionate use)</td>
<td>E0302</td>
<td>Memantine</td>
<td>Arimoclomol Phase II</td>
</tr>
<tr>
<td>Na phenyl-butyrate</td>
<td>Tretinoin and Pioglitazone HCL Combination Therapy</td>
<td>Creatine Monohydrate</td>
<td>Talampanel Phase II</td>
</tr>
<tr>
<td>R(+) pramipexole dihydrochloride monohydrate</td>
<td>MCI-186</td>
<td>Sodium phenylbutyrate</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td></td>
<td>Memantine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KNS-760704</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>R(+) pramipexole dihydrochloride monohydrate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: http://clinicaltrials.gov/ct2/results?term=als&recr=Open&cond=%22Amyotrophic+Lateral+Sclerosis%22. This table does not include completed trials.

1.5.2.1 Symptomatic treatment

Quinine sulphate 325 mg twice a day is the most effective treatment option for muscle spasms and cramps (Borasio 2001). Baclofen and tizanidine are used for excess muscle spasticity that causes incoordination and discomfort. Sialorrhea (excess salivation) may respond to amitriptyline, atropine, botulinum toxin injection, glycopyrronium or hyoscyamine. Insomnia should be tackled by addressing underlying problems e.g. depression, dyspnoea, dysphagia and pain. This may obviate the need to use sedatives. Pain management includes the use of non steroidal anti-inflammatory agents, anti-convulsants e.g. carbamazepine, and later opiates if / when the former treatments fail.

Emotional lability is frequently treated with amitriptyline (Schiffer 1985) or fluvoxamine. However, a combination of dextromethorphan and quinidine
(30mg/30mg) was assessed in a randomized, double-blind, controlled trial (Brooks 2004) and was effective in reducing the frequency and severity of pathologic laughter and crying compared with either drug alone. The combination also resulted in improved quality of life. Longer-term studies regarding side effects of this combination are awaited.

1.5.3 Respiratory Insufficiency

Management of respiratory complications is an issue that should be broached early on in patient consultations and be considered as part of the overall care plan. Although, respiratory muscle weakness may not be initially evident, options for ventilatory support should be discussed long before the development of respiratory insufficiency.

Symptoms of respiratory insufficiency often develop insidiously and may be subtle. Patients may report dyspnoea, orthopnoea, disturbed sleep (sleep fragmentation due to hypoventilation), morning headaches, daytime somnolence and fatigue. Others may be asymptomatic. Respiratory muscle weakness, an independent predictor of quality of life (Bourke 2001), can lead to cognitive dysfunction. Respiratory failure is the most common cause of death in ALS patients. Assessment of respiratory insufficiency includes history and examination, early morning arterial blood gas, and overnight pulse oximetry.

Vital capacity is widely used in the assessment of respiratory insufficiency in MND but limitations include insensitivity to significant changes in respiratory function partly because the shape of the lung pressure-volume curve (Lyall 2000), patient difficulty in performing the test due to muscle weakness or apraxia, and finally weak correlation with survival.

Thus sniff nasal inspiratory nasal pressure (SNIP) is a useful tool on deciding whether a patient needs assisted ventilation. It is particularly useful in patients with bulbar involvement since a face mask is not required. The SNIP correlates well with diaphragm strength (Lyall 2000), and it is sensitive to changes in respiratory muscle strength (Stefanutti 2000).

A prospective observational study of 98 ALS patients (Morgan 2005) highlighted the clinical usefulness of SNIP. A higher proportion of patients could still perform the SNIP at the last clinic visit (before death or study completion) compared with the FVC or MIP (94 versus 84 versus 79 percent).
The study found that a SNIP of <40 cm H2O had a higher sensitivity for predicting six-month mortality compared with a FVC of <50 percent maximum (97% versus 58%), but a slightly lower specificity (79% versus 96%). Further studies are awaited regarding the prognostic value of SNIP.

Transcutaneous carbon dioxide / oxygen sensor can be useful during home visits as it avoids the need for regular arterial blood gases. Whilst not used as a primary tool in the assessment of the need for non-invasive ventilation, it can be a useful adjunct.

Management of respiratory insufficiency in ALS is guided by the American Academy Practice Parameter. Deciding when to initiate non-invasive mechanical ventilation is critical because of the risk of either sudden death or ventilator dependence without proper advance planning (Miller 1999). The recommendations are as follows:

• Be vigilant for symptoms indicating hypoventilation. Serial measures of pulmonary function (especially vital capacity) are recommended to guide management and to determine prognosis with the understanding that no single test can detect hypoventilation reliably.
• Offer non-invasive ventilatory support as an effective initial therapy for symptomatic chronic hypoventilation and to prolong survival in patients with amyotrophic lateral sclerosis.
• When long-term survival is the goal, offer invasive ventilation and fully inform patient and family of burdens and benefits.
• In accordance with the principle of patient autonomy, physicians should respect the right of the patient with amyotrophic lateral sclerosis to refuse or withdraw any treatment, including mechanical ventilation.
• When withdrawing ventilation, use adequate opiates and anxiolytics to relieve dyspnea and anxiety.

Non-invasive positive pressure ventilation (NIPPV) is particularly useful if patients have nocturnal respiratory symptoms but also can be used during waking hours as the disease progresses. Current recommendations are that NIPPV should be offered to any patient with respiratory symptoms and vital capacity less than 50 percent of predicted; a SNIP of less than 40cm H2O, or
where symptoms of respiratory insufficiency are associated with nocturnal hypoxemia. An elevated early morning blood CO2 level is an absolute indication.

NIPPV has been shown to extend survival, particularly in those who are compliant with 4 hours each day and those without severe bulbar dysfunction (Lo Coco 2006). It also improves quality of life in patients without increasing caregiver burden or stress (Mustfa 2006; Le Coco 2006) and in some studies it improves cognitive impairment due to sleep disruption (Newsom-Davis 2001). Those with early respiratory muscle involvement, sleep related symptoms, orthopnoea, and fewer bulbar problems are most likely to benefit from NIPPV (Aboussouan 1997).

Patients with bulbar-onset disease have an increased risk of aspiration and physicians should consider that difficulties may arise in clearing secretions related to abnormal vocal cord function.

The use of NIPPV is not a substitute for permanent assisted ventilation, and discussions regarding tracheostomy and permanent ventilation must be ongoing, regardless of whether NIPPV is utilised.

Long term ventilatory support in ALS usually requires tracheostomy ventilation (Gelinas 2000). This is currently used in less than 10% of MND patients in Europe (Borasio 1998), somewhat more frequently in part of North America (Gelinas 2000) and in up to 25% in Japan. This variability appears to be due to different cultural attitudes towards ALS as well as financial and structural variations in health care systems. Patient concerns regarding reduced quality of life and physicians’ attitudes towards mechanical ventilation are likely to differ from country to country. The fact that mechanical ventilation may cost $15,000/month, and the need for 24-hour support, perhaps from a family member, may also explain the disparity in tracheostomy uptake between nations.

An unfortunate situation may develop if tracheostomy ventilation is performed inadvertently as an emergency procedure. This poses complex ethical and clinical problems, as neither the patient nor the family have had the opportunity and time to make an informed choice about end of life issues (Leigh 2003). Patients may be maintained on tracheostomy ventilation until
they become "locked in" and unable to communicate by any means. One study showed that when a patient with MND is ventilated acutely, independence from the ventilator is rarely achieved (Bradley 2002). Almost all of the patients need long term ventilatory support and the degree of respiratory support increases with time as the underlying disease progresses. The aim of management of these patients should be weaning the patient onto the minimum support compatible with symptomatic relief and comfort.

Expiratory muscle weakness leads to difficulty clearing secretions, plugging of bronchi, and increased risk of infection in patients with ALS (Polkey 1999; Mustfa 2001). Techniques to assist expiratory movement include physiotherapy manoeuvres (e.g. manual abdominal thrust), mechanical insufflators-exsufflator, and cough assist devices. Suction can also be assisted by using a portable home suction device. Carbocisteine is helpful in loosening tenacious secretions and adequate hydration is important. Mucolytics, expectorants, theophylline, antibiotics, annual influenza immunisation and oxygen can contribute to respiratory management.

It is worth bearing in mind that the symptomatic relief and prognostic benefits provided by respiratory support should be balanced against iatrogenic difficulties, patient adherence, demands on carers and relatives, increasing dependence on ventilatory support, and distressing and unwanted prolongation of life. It is best to address these possibilities early in patient consultations, respect patient autonomy and regularly revisit discussion of advance directives.

1.5.4 Nutrition

Nutritional status and weight loss are predictors of survival (Stambler 1998). Malnutrition and weight loss can occur due to dysphagia, longer time to finish meals due to arm weakness, and in some cases occurs due to hypermetabolism in those with respiratory compromise. Dysphagia increases the risk for insufficient calorie intake, aspiration and choking. This can be evaluated by clinical, videofluoroscopic and fibreoptic examination. Input from a dietician and speech and language therapist in diagnosis and management is key.
Management of dysphagia includes modification of food and fluid consistency, postural advice (e.g. chin tuck: flexing the neck forward on swallowing to protect the airway), and parenteral feeding.

A PEG (Percutaneous Endoscopic Gastrostomy) placement is indicated for those who have symptomatic dysphagia or significant weight loss (Miller 1999). Advantages include improved nutrition, increased BMI, decreased weight loss, and improved survival, although the latter survival effect is likely to be marginal (Mazzini 1995; Forbes 2004). Morbidity relating to PEG placement increases with worsening respiratory function. The overall 30 day mortality of PEG in a retrospective review of the BDNF study was 9.6%, but this was mainly related to the high risk of death in patients with VC < 50%. The 30 day mortality of patients with VC >50% was 0% (Kasaskis 1999).

Thus, for optimal safety and efficacy, PEG should be placed before the forced vital capacity falls to 50 percent of predicted, and before SNIP falls below 40cm H2O (Miller 1999). A RIG (Radiologically Inserted Gastrostomy) is preferred in patients with pronounced bulbar symptoms and/or respiratory compromise. Indeed, in some centres RIG is the preferred method for gastrostomy in all MND patients as insertion does not require sedation and patients can remain upright during the procedure without having to swallow an endoscopic tube. If there is evidence of respiratory insufficiency, non-invasive ventilation should be considered before gastrostomy.

Once parenteral feeding is established, oral feeding may be maintained to enhance quality of life as long as there is no risk of aspiration. Calorie supplementation may be required and weight and anthropometric measures should be regularly monitored.

1.5.5 Communication

Dysarthria can make verbal communication increasingly difficult. Speech and Language therapists can advise on strategies such as:

Enhancing the intelligibility of speech by methods such as facing the listener, slowing the rate of speech and reducing background noise.

Use of voice amplifiers for patients with good articulation but a weak voice due to respiratory muscle weakness.
Choice of appropriate alternative communication methods. Augmentative alternative communication (AAC) range from pen and paper and alphabet boards to electronic communication devices which can be adapted for use with either hand or eye controls. The Lightwriter (Toby Churchill Ltd) is a widely used "type to speech" output device, which is commonly used in the Ireland and the UK.

Gaze communication systems use eye tracking to allow communication for those with very limited mobility who cannot manually use a mouse or keyboard. Such systems generally feature a camera mounted at the bottom of the screen that "tracks" the eyes as they move across the screen. The viewer's precise gaze-point at an onscreen keyboard is detected, allowing the user to spell a message for speech or text output. Software also allows the user to switch lights and appliances on and off, and dial telephone numbers. The systems are compatible with personal computers or AAC devices.

Although costs are currently high, about €20,000 for a top-of-the-range system, the aim is to introduce provide more portable systems with sufficient resolution at a reasonable cost.

1.5.6 Mobility and functional decline

Progressive muscle weakness and functional decline can be ameliorated by physiotherapy and occupational therapy (OT) input.

OT provides tailored assistive devices such as ankle foot orthoses, crutches, canes, and walking frames to maximise function. Eventually, most patients will require a wheelchair. Adaptations in the house include higher toilet seats and bath tub lifts that help to maintain toileting and bathing as well as specialised eating utensils, grips, and holders.

Physical therapy can be adapted to the patient's needs throughout the course of the disease. This may begin with exercises to promote strength, range of motion, and endurance. Heat, massage, or transcutaneous electrical nerve stimulation may be added later to relieve pain. Range of motion and stretching exercises are important to prevent spasticity and muscle contractures. A randomized controlled trial demonstrated that resistance exercise three times a week resulted in significantly better function, as measured by total ALS Functional Rating Scale and upper and lower extremity subscale scores, and
improved quality of life without adverse effects as compared with patients receiving usual care (Bello-Haas 2007).

1.5.7 Psychiatric, Psychosocial and other issues

Studies of depression in MND have been inconsistent. A recent longitudinal study (Rabkin 2005) that assessed 80 hospice-eligible ALS patients at monthly intervals until death or tracheostomy demonstrated that major depression in people with late-stage MND is rare (<10%), although transient depressive symptoms may occur. The authors conclude that picture of resiliency rather than despair is seen in MND patients. Nonetheless, the combined rate of 19 percent for both major and minor depression was higher than the 2 to 9 percent prevalence rate reported for depression in the general population. The presence of depression does not appear to be associated with a desire to hasten dying in patients with end-stage ALS (Albert 2005). Depression in carers also merits attention (see Chapter Five).

Psychological status is strongly related to outcome in ALS, and psychological distress renders patients with a greater risk of mortality (McDonald 1994). Supportive counselling is a first-line approach. Pharmacological agents include tricyclic antidepressants such as amitriptyline (particularly useful if the patient has other troublesome symptoms that may respond to this agent such as insomnia, drooling or pseudobulbar affect), or selective serotonin reuptake inhibitors.

Links should be made to hospice care early in the illness. Palliative care should not be reserved for the last weeks of care. The aim of palliative care is instead to ensure a whole-person approach to care that is local and supplements primary care with expertise in symptom control and (later on) end-of-life care. Ideally, palliative care continues after death through bereavement support (Radunovic 2007).

Cognitive and behavioural symptoms have been described in MND for over a century. A recognizable phenotype of cognitive decline has been described in ALS characterized by personality change, irritability, obsessions, poor insight and pervasive deficits on frontal executive tests (Phukan 2007). This presentation is consistent with the character change, altered social conduct and executive deficits seen in FTD.
Cognitive impairment in MND ranges from mild impairment with subtle executive deficits, which is the case for the majority of patients, to overt frontotemporal dementia (FTD) in 5% or more (Lomen Hoerth 2003, Barson 2000). The presence of cognitive impairment (including judgement, attention, and response inhibition/generation) has major clinical implications. Compliance with interventions such as non-invasive ventilation, the ability to competently engage in end of life decisions and the mental capacity to make decisions in relation to healthcare or financial circumstances may be affected. Therapists may also note a lack of initiative and compliance in occupational and physical therapy. Patients with ALS-FTD are twice as likely to be noncompliant with interventions such as NIV and those with bulbar onset ALS-FTD are more than twice as likely to die at any interval after disease onset as compared with patients with bulbar onset classic ALS (OIney 2005). Safety awareness (falls, choking) may also be compromised due to cognitive impairment.

Clinicians should be aware of the character or behavioural change, as reported by a spouse or relative, which may provide the most useful clue to a diagnosis of ALS-FTD. Brief batteries can be performed in the clinic such as word generation test to evaluate verbal fluency or the Addenbrooke’s Cognitive Examination (ACE), which incorporates the MMSE with additional testing to evaluate orientation, attention, memory, verbal fluency, language and visuospatial ability (Mathuranath 2000). However, referral to a neuropsychologist is recommended for a definitive diagnosis. The Second International Research Workshop on frontotemporal dementia in ALS (London, Ontario, 2007) has issued a consensus document (Strong 2009) which will has helped to further define the role and optimum methodology of neuropsychological testing (Chapter Two). Consensus guidelines have also helped to define the role of neuroimaging in ALS with cognitive impairment.

It is also important to be aware of reversible causes of impaired cognition such as nocturnal hypoventilation and sleep disturbance, depression and other psychosocial causes may also account for impaired cognition.

Treatment of overt frontotemporal dementia continues to evolve; since most studies to date are small and uncontrolled, evidence is sparse. The management of intellectual decline thus often entails off-label use of
medications more commonly used in Alzheimer’s disease despite the fact that there is no consistent evidence of cholinergic deficit in FTD. These include donepezil, rivastigmine (class III evidence), galantamine and memantine.

SSRIs are commonly used for aggression, agitation, disinhibition and depression in FTD. In one randomised controlled study, patients treated with paroxetine showed significant improvements in behavioural symptoms at 14 months, reflected by a reduction of caregiver stress (Moretti 2003).

In one study subjects with FTD were administered an SSRI and evaluated for a change in behavioural symptoms after three months (Swartz 1997). Disinhibition improved in six of nine subjects, carbohydrate craving improved in five of nine, and compulsions in four of seven. Treatment with SSRI is well tolerated, and they are currently the drugs of choice for behavioural control in FTD (Perry 2001).

Benzodiazepines and high-dose neuroleptics for psychosis and agitation carry the risk of extrapyramidal and other side effects and should generally be avoided. Behavioural changes unresponsive to SSRIs can be managed with low dose atypical neuroleptics such as olanzapine or risperidone however. Anticonvulsants, for instance, carbamazepine and valproate are also useful. Lifestyle changes (evaluation re fitness to drive, assisted living, avoidance of financial responsibility) and behavioural/environmental modifications play a cardinal role in the management of FTD.

1.5.8 Caregiver Support

Significant burden and depression may occur in caregivers of patients with ALS (Gauthier 2007, Hecht 2003). Caregiver burden may be even higher if the patient has cognitive impairment or dementia (Phukan 2007) and increases with functional impairment (Hecht 2003). It has also been found that the greatest carer burden subscore is time dependence (Chio 2005), indicating that caregivers are mostly affected by time restrictions due to their caring duty.

Recognising and managing caregiver burden and depression is not only vital for caregivers; it only ensures optimal management of ALS. Rabkin et al (2005) reported that concordance between patient and caregiver distress is high, suggesting that attention to the mental health needs of caregivers may alleviate the patient’s distress as well. Hence the importance of offering
caregiver support through respite, counselling, caregiver support groups, information on financial assistance and maintaining hope.

1.6 MND-Differential Diagnosis and Mimic Disorders

MND must be differentiated from numerous other conditions (Table 6).

Table 6. Differential Diagnosis of MND.

<table>
<thead>
<tr>
<th>Differential Diagnosis of MND</th>
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<tbody>
<tr>
<td>Other motor neuron diseases: primary lateral sclerosis, progressive muscular atrophy, spinal muscular atrophy, spinobulbar muscular atrophy (Kennedy's disease)</td>
</tr>
<tr>
<td>Structural: cervical spondylotic myelopathy, Arnold-Chiari malformation, syringomyelia/bulbia, CNS irradiation, tumour, stroke</td>
</tr>
<tr>
<td>Metabolic/toxic: hyperthyroidism, hyperparathyroidism, heavy metal intoxication, lathyism</td>
</tr>
<tr>
<td>Immune/inflammatory: multifocal motor neuropathy with conduction block, chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, myasthenia gravis, inclusion body myositis, polymyositis, paraneoplastic syndromes</td>
</tr>
<tr>
<td>Hereditary: hexosaminidase A deficiency, hereditary spastic paraparesis with amyotrophy, spinocerebellar ataxias, oculopharyngeal muscular dystrophy, adrenomyeloneuropathy, acid maltase deficiency</td>
</tr>
<tr>
<td>Infectious: HIV, HTLV-1, Creutzfeldt-Jakob disease, syphilis</td>
</tr>
<tr>
<td>Other degenerative disorders affecting the CNS: corticobasal degeneration, dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, Parkinson's disease</td>
</tr>
<tr>
<td>Benign fasciculations</td>
</tr>
<tr>
<td>Monomelic amyotrophy (&quot;Hirayama disease&quot;)</td>
</tr>
</tbody>
</table>

Adapted with permission from William S Baek and Nayan P Desai. ALS: Pitfalls in the Diagnosis. Practical Neurology 2007;7:74-81

Diagnostic work is described above and helps in differential diagnosis. In one study, 8 percent of participants were given an erroneous diagnosis of ALS, and half of those patients had treatable conditions (Wokke 1996). The absence of a specific diagnostic test on occasion makes it difficult to separate ALS from other motor neuron diseases. The application of the El Escorial diagnostic criteria may facilitate early recognition of non-ALS cases as demonstrated by a study by Traynor et al (2000). Twenty-seven (84%) of patients with an ALS-Mimic syndrome fulfilled the El Escorial criteria for either "suspected" or "possible" ALS, 4 (13%) met the criteria for probable ALS, and 1 (3%) had definite ALS.

ALS-Mimic syndromes occur as a consequence of other, non-ALS pathogenic processes, and do not represent other forms of ALS. Such syndromes include the post-polio myelitis syndrome; multifocal motor neuropathy with or without conduction block; endocrinopathies - especially hyperparathyroid or
hyperthyroid states; lead intoxication; infections; and paraneoplastic syndromes. Four of these are discussed below.

1.6.1 **Multifocal Motor Neuropathy (MMN)**

MMN is an acquired, immune-mediated, demyelinating motor neuropathy. This slowly progressive condition is dominated by lower motor neuron signs (but active tendon reflexes), especially in the upper limbs. Unlike ALS, it is frequently characterized by multiple motor-conduction blocks on electrophysiology testing, the presence of antibodies against GM1 ganglioside in up to 84% of patients, and response to treatment with cyclophosphamide or intravenous immune globulin. It accounts for 2% of patients seen in ALS centres. Autopsy findings have described the loss of motor neurons and in some cases intraneuronal inclusions called Bunina bodies, which may be pathognomonic of motor neuron disease.

1.6.2 **Kennedy's Disease**

Spinobulbar muscular atrophy (Kennedy's Disease) is an X-linked genetic disorder (involving the androgen receptor gene) affecting almost exclusively males. It is characterised by degeneration of both motor and sensory neurons. Onset is typically between the ages of 40 and 60, and is characterised by progressive weakness of the limb and bulbar musculature. Additional neurologic features include sensory abnormalities, tremor of the upper extremities, and a quivering chin. Patients may also have various endocrinologic abnormalities, such as diabetes, testicular atrophy, gynaecomastia, oligospermia, and erectile dysfunction. Differentiators from MND include postural tremor of the upper limbs, sensory impairment in the lower limbs and prominent endocrine abnormalities. Creatine kinase levels are frequently raised. Genetic testing for CAG repeat expansion in the androgen receptor in SBMA can confirm the diagnosis. Testing for this mutation in a recent study (Parboosingh 1997) revealed that ALS was clinically misdiagnosed in 2% of sporadic cases and in two of the 100 FALS kindreds. Hence the importance of genetic testing in male patients with atypical ALS. No curative therapy exists for Kennedy's disease.
1.6.3 Monomelic Amyotrophy
This lower motor neurone condition of unknown aetiology is most commonly reported in Japan and India, typically occurring in young males (15-25 years) as a sporadic condition. It is characterized by insidious onset of weakness and wasting of the muscles of the hand and forearm, often asymmetric. It follows a relatively benign course after a few years of progression, hence differentiating it from the relentless progression seen in many forms of MND. Treatment is symptomatic.

1.6.4 Post-polioymelitis syndrome
Post-polioymelitis syndrome (PPS) occurs in up to 10% of individuals who have recovered from the paralytic form of polioymelitis. The syndrome is ill-defined and encompasses a constellation of new symptoms, generalised and muscle fatigability, cold intolerance and pain, and in a small percentage, a progressive decline of function in a previously recovered limb. The latency to development of PPS is by definition at least fifteen years. The precise mechanism of PPS is unknown but is most likely to be multifactorial, including degenerative changes in ligaments and joints of affected limbs. The progressive form of PPS, which leads to the development of new muscle weakness and wasting, is thought to be due in part to distal degeneration of enlarged post-polio motor units as a result of terminal axon sprouting.

Electrophysiological features of acute denervation are superimposed on chronic denervation-reinnervation. Features that distinguish PPS from ALS include the earlier age of onset of PPMA, higher prevalence amongst females, motor involvement that is usually focal or multifocal and asymmetric, sparse frequency and distribution of fasciculations, absence of corticospinal tract signs, absence of bulbar and respiratory involvement (except in survivors of bulbar cases) and slower progression. Fatality is rare.

1.7 Summary
ALS, the most common subtype of motor neurone disease, is a rare disease. This chapter outlined the possible aetiologies, methods of clinical diagnosis and treatment. The remainder of this thesis focuses on the more recently discovered cognitive and behavioural changes that occur in ALS.

32
2.1 Introduction

ALS was traditionally believed to spare cognitive functions, but is now known to involve a range of cognitive impairments. Most patients with ALS have mild cognitive impairment with subtle executive deficits and up to 15% have a clinical subtype of frontotemporal lobar degeneration (FTLD) called frontotemporal dementia (Lomen-Hoerth 2003; Barson 2000). FTLD, which was originally described as Pick's disease, is the second most common cause of progressive cognitive impairment after Alzheimer's disease. The three forms of FTLD were defined by consensus criteria in 1998 (Table 7, Neary 1998) The form most frequently described in patients with ALS is frontal variant frontotemporal dementia (fvFTD); the other two forms are non-fluent progressive aphasia, which is characterised by language impairment, and semantic dementia, which is characterised by loss of conceptual knowledge.

Table 7. FTLD Syndromes as defined by Neary criteria

<table>
<thead>
<tr>
<th>FTLD Syndrome</th>
<th>Neuropathological topography</th>
<th>Cognitive symptoms</th>
<th>Behavioural changes</th>
<th>Neurological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal variant frontotemporal dementia</td>
<td>Frontal atrophy more severe than temporal atrophy, Particularly affected: right dorsolateral and prefrontal cortex, left premotor cortex.</td>
<td>Executive dysfunction (e.g. verbal fluency and attention).</td>
<td>Distractibility, disinhibition, decline in personal hygiene, hyperorality, compulsions, perseveration, apathy, and submissiveness.</td>
<td>Frontal release signs and primitive reflexes, motor neuron disease. Possible extrapyramidal features (PSPS or CBD).</td>
</tr>
</tbody>
</table>
Temporal atrophy more severe than frontal atrophy. Particularly affected: insula, amygdala, anterior hippocampus.

Impairment of word meaning and object identity. Fluent, empty spontaneous speech, semantic paraphasias, long-term memory loss and perceptual disorder (e.g. prosopagnosia, associative agnosia, or both).

Emotional withdrawal, depression, mental rigidity and compulsions.

Neurological findings emerge late in the course of this illness.

The behavioural changes associated with fvFTD differ according to which neuroanatomical pathways are most severely affected (Snowden 2001). Some patients become disinhibited, fatuous, purposelessly overactive, and easily distracted, with socially inappropriate behaviour and little concern for others. Pathological changes in these patients are confined to orbitomedial frontal and anterior temporal regions. Other patients become bland, apathetic, inert, mentally rigid, and perseverative, and lack volition and mental effort. In these patients, pathological changes extend throughout the frontal lobes, including the dorsolateral frontal cortex. A third group of patients presents with stereotyped, ritualistic behaviour that is associated with substantial changes to the striatum. These patients also have variable cortical involvement, often with pathology of the temporal lobe rather than the frontal lobe. In ALS, the most common recognised form of cognitive impairment is a frontal dysexecutive syndrome. This syndrome refers most closely to the second of the three aforementioned groups (Phukan 2007).

2.2 Overlap of ALS and dementia

Although ALS is predominantly a disease of motor system degeneration, cognitive and behavioural symptoms have been described for over a century, and an association between ALS and frontal lobe dementia was postulated as early as 1932 (Von Braunmuhl 1932).

Many authors have since suggested that ALS and frontotemporal dementia form a clinical and pathological spectrum. This idea remains controversial, but
there is no doubt that ALS and frontotemporal dementia have clinical, radiological, pathological, and genetic overlap.

A clinical phenotype of cognitive decline in ALS has been characterised by personality change, irritability, obsessions, poor insight, and pervasive deficits on frontal executive tests (Bak 2001). This presentation is consistent with the character change, altered social conduct, and executive deficits in patients with frontotemporal dementia. Some patients with ALS show more subtle frontal executive deficits that involve verbal fluency, attention, and working memory.

Convergent research from the disciplines of neuroimaging, neuropathology, genetics and neuropsychology is described below and demonstrates how evidence now points to extra-motor change in ALS.

### 2.2.1 Neuroimaging studies

Neuroimaging techniques have provided evidence to support a biological basis for cognitive change. Imaging correlates of cognitive decline in ALS include atrophy of the frontal lobe and hypometabolism in the cortex, particularly in frontotemporal regions and the anterior cingulate gyrus (Ludolph 1992; Talbot 1995; Jeong 2005). These findings suggest that neurons other than motor neurons, particularly those along the thalamofrontal association pathway, are affected in some patients who have ALS without dementia.

Imaging studies have also implicated dysfunction of the dorsolateral prefrontal cortex in some patients with ALS who have associated cognitive impairments (Abe 1993; Kew 1993; Kew 1993(b).

A recent voxel-based morphometry study of patterns of brain atrophy in ALS and ALS/FTLD (Chang 2005) noted a common pattern of grey matter atrophy in both ALS and ALS/FTLD patients when compared to controls. This atrophy involved the bilateral motor/premotor cortices, the left middle and inferior frontal gyri, the anterior portion of the superior frontal gyri, the superior temporal gyri, the temporal poles and left posterior thalamus. Most of the frontal regions were significantly more atrophied in the ALS/FTLD group than in the ALS group in accordance with the hypothesis of an anatomic continuum between the two syndromes (Grosskreutz 2008). No significant differences were found in white matter volumes. In another voxel-based morphometry
study (Whitwell 2006) patterns of brain atrophy were compared between pathologically confirmed ALS/FTLD (n=7) and FTLD-U with ubiquitin-only-immunoreactive neuronal changes (n=11). The ALS/FTLD group demonstrated a localized pattern of frontal lobe atrophy (mainly in the frontal lobes with minor temporal lobe atrophy) whilst a more widespread pattern of grey matter atrophy affecting the bilateral frontal and temporal lobes was seen in FTLD-U. These findings are consistent with hypometabolic patterns in a previous PET study (Jeong 2005). Mezzapesa et al (2007) also described grey matter reductions in extra-motor areas (VBM study) including the bilateral frontal and temporal lobes compared to controls. This mild atrophy correlated with cognitive impairment. All of these reports support the concept of ALS as a multisystem disease with frontotemporal involvement irrespective of the presence or absence of clinical dementia.

2.2.2 Neuropathological studies

Studies with neuropathological correlates from well-characterized clinical cohorts of ALS patients with cognitive decline are more limited. Findings from such studies include frontal and temporal lobar atrophy with neuronal loss, superficial linear spongiosis, and ubiquitinated tau-negative and synuclein-negative intraneuronal inclusions (Gallassi 1985; Anderson 1995; Strong 2001). These findings are similar to those seen in patients with frontotemporal dementia who have ubiquitin-positive, tau negative and synuclein negative pathology, also known as FTLD-U. Ubiquitinated inclusions in both ALS and FTLDU contain deposits of TAR DNA-binding protein (TARDBP, also known as TDP43) (Neumann 2006).

It is increasingly recognised that clinical and pathological findings of anterior horn degeneration may be found in some patients with typical clinical features of FTD (Neary 1998; Lomen-Hoerth 2002). Conversely, post-mortem studies show that cells in the anterior horn degenerate and have typical ALS inclusions in some patients with frontotemporal dementia who had no apparent clinical features of ALS during life (Jackson 1996).

These changes are distinct from those found in Alzheimer’s disease, a condition characterised by neurofibrillary tangles and senile plaques and unlike the diffuse spongiform changes found in variant Creutzfeldt-Jakob Disease.
2.2.3 Genetic studies

The link between frontotemporal dementia and ALS is also supported by accumulating genetic evidence of mechanistic overlaps between ALS and other types of neurodegeneration (Table 8). The recent observation that mutations in progranulin gene (GRN) cause dementia in patients with non-tau, chromosome 17-linked ALS-FTD (Baker 2006), coupled with the new locus for ALS-FTD on chromosome 9p (Morita 2006; Vance 2006) and the discovery of mutations in specific genes such as CHMP2B and DCN1 (Munch 2004; Parkinson 2006) in families with ALS and FTD have supported the notion that the clinical presentations of ALS and FTD may be two points along a spectrum of neurodegeneration although not all evidence points in this direction.

The pathogenesis of ALS and FTD are unknown, but the functional similarities between some of the known causative genes including progranulin and angiogenin (ANG) might provide some clues. Both angiogenin and progranulin promote angiogenesis; angiogenin is part of a larger RNAse superfamily, and progranulin is an important signal for cell survival. These families of angiogenic and hypoxia-responsive proteins might be interesting from both a mechanistic and potentially therapeutic perspective.

Angiogenin, the 14.1-kDa product of the hypoxia responsive gene ANG on chromosome 14, is expressed in a wide variety of normal tissues including the brain and spinal cord. In the endothelium, angiogenin regulates vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF1) (Kisomoto 2005), both of which have neuroprotective properties (Oosthuyse 2001; Storkebaum 2004). Recent studies have suggested that angiogenin is an important neurodevelopmental protein with neuroprotective properties, and that mutant ANG impairs neurite outgrowth, pathfinding and survival of motor-neurons (Subramanian 2007; Wu 2007; Gellera 2008; Kieran 2008). There is thus evolving evidence to suggest that angiogenin is an important neuromodulatory peptide.

Angiogenin and progranulin share significant structural and functional similarities. Progranulin is likewise a growth factor, and is implicated in wound healing, tumour growth, inflammation, and brain development in mice (He 1999; Zhu 2002; Daniel 2003; van Swieten 2008). Progranulin is, like angiogenin, regulated by an siRNA (small interfering RNA), at an allelic site.
that is associated with an increased risk for frontotemporal dementia. Mutations in the progranulin (PGRN) gene were recently described as the cause of ubiquitin positive frontotemporal dementia (FTD) (Baker 2006; Cruts 2006). Although PGRN mutations may not be a common cause of motor neuron degeneration (Gass 2006; Schymick 2007) this may reflect incomplete pathogenic overlap of ALS and FTD which means that each individual FTD or ALS causing gene will display its own phenotype pattern (Schymick 2007). Given the clear relationship between ALS and FTD, there is still a strong rationale for continued research into progranulin. Indeed, immunexpression of PGRN in a recent small study of ALS patients (n=8) using immunohistochemical analysis of post-mortem tissue found a pattern of increased PGRN expression in areas of active degeneration in ALS. (Irwin 2008). In addition associations may be population-specific (Schymick 2007; Del Bo 2009).

Angiogenin is also functionally similar to VEGF, altered regulation of which has also been associated with ALS (Oosthuyse 2001; Nygren 2002; Lambrechts 2003; Distler 2003; Devos 2004; Ilzecka 2004; Rosenstein 2004; Subramanian 2007). 'At risk' promoter haplotypes in VEGF, which predict reduced expression of bioavailable isoforms, have been described in some European ALS populations (Lambrechts 2003) and combined with evidence from animal models, the data suggest that VEGF isoforms have a neuromodulatory and neuroprotective role in the CNS.

Mutations in the ANG gene coding for angiogenin, including loss-of-function mutations, have been associated with classical ALS in populations that include Irish, Scottish, Scandinavian, US, Italian and German patients (Greenway 2006; Wu 2007; Conforti 2008; Gellera 2008; Paubel 2008; Fernández-Santiago 2009; van Es 2009). At the time of writing, 15 different ANG missense variants have been identified in patients with ALS but not in controls. ANG mutations predict loss of RNAse and angiogenic function (Greenway 2006). A number of at risk haplotypes have been identified, one of which has been replicated in the Swedish population (Phukan 2009).

A recent study reported the K171 mutation in the ANG gene segregating with disease in a large pedigree of 29 unrelated FALS patients negative for SOD mutations (van Es 2009). The authors reported this segregation with familial
ALS, frontotemporal dementia and Parkinsonism. Another study identified a sporadic ALS patient with angiogenin mutation and frontal lobe dysfunction (Gellera 2008) suggesting a link between ANG and cognitive impairment.

Previous research has demonstrated that serum angiogenin levels in ALS differ from controls (Cronin 2006; Phukan 2007). However, the biological implications of this finding remain to be determined. Furthermore, the patterns of plasma and cerebrospinal fluid angiogenin expression have not been investigated to date, and there have been a paucity of studies that have explored whether ANG haplotypes modulate protein expression (these issues are investigated in Chapter Nine).

Furthermore the identification of pathological 43-kDa transactivating responsive sequence DNA-binding protein, also known as TDP-43, as the major component of ubiquinated inclusions in certain forms of FTLD and in ALS (Arai 2006; Neumann 2006) emphasises similar pathology in both disorders which may result in the progressive degeneration of different selectively vulnerable neurons. This ubiquitously expressed nuclear protein is normally a regulator of messenger RNA transcription and splicing. The accumulation of hyperphosphorylated and misfolded TDP-43 fragments in the perikaryon of neurons in FTLD-U and ALS is accompanied by a substantial loss of TDP-43 from the nucleus. However it is now clear that pathological TDP-43 processing may not be specific to FTLD-U and ALS. “Pathological TDP-43” aggregation has now been identified in other conditions of neurodegeneration including the Guamanian ALS-PD complex, corticobasal degeneration and approximately 70% of cases with hippocampal sclerosis. It also localizes to neurofibrillary tangles in approximately 20% of Alzheimer’s disease cases, and with alpha-synuclein inclusions in diffuse Lewy body disease.

Immunohistochemistry and whole-central nervous system scans have demonstrated the presence of neuronal and glial TDP-43 in multiple areas of the central nervous systems of ALS patients, including in the nigro-striatal system, the neocortical and allocortical areas, and the cerebellum, but not in those of controls (Geser 2008). This lends further evidence to the emerging recognition that ALS is a multisystem disorder.

The pathophysiological link between TDP-43 and ALS has now been firmly supported by the identification of thirty dominantly inherited (mainly
missense) mutations specific to sporadic and familial ALS (Daoud 2008; Van Deerlin 2008; Gitcho 2008; Kabashi 2008; Sreedharan 2008; Corrado 2009). This aberrant form of TDP-43 is likely to directly trigger neurodegeneration (Lagier-Tourenne 2009). However only one patient carrying a TDP-43 mutation has been reported to develop cognitive deficits (Corrado 2009).

The common pathogenic mechanisms of neuronal cytoplasmic protein aggregation and defective RNA metabolism have been identified in mutations of another gene encoding a DNA / RNA binding protein. The fused in sarcoma / translated in liposarcoma (FUS/TLS) protein is usually predominantly located in the nucleus and is concerned with regulation of gene expression i.e. DNA repair, regulation of transcription, RNA splicing, and transport to the cytoplasm.

Kwiatkowski et al (2009) reported 13 homozygous missense mutations in the FUS / TLS gene on chromosome 16 that were specific to familial ALS. This study involved an ALS family originating from the Cape Verde islands in which disease transmission was compatible with an autosomal recessive inheritance pattern. Similarly Vance et al (2009) reported missense mutations in FUS in large dominant British kindreds with FUS-immunoreactive cytoplasmic inclusions, absence of TDP-43 inclusions, and predominantly lower motor neuron degeneration. These two studies cumulatively suggest that FUS/TLS mutations exist in approximately 4% of familial ALS i.e. 0.4% of all ALS cases (Lagier-Tourenne 2009) and are not associated with cognitive impairment. FUS/TLS involvement has also been reported in spinal cerebellar ataxia type 3 and Huntington’s disease (Doi 2008) suggesting that disturbances in gene expression regulation are crucial to the course of neurodegeneration.

On the basis of genetic evidence, both ALS and frontotemporal dementia seem to be clinically heterogeneous. Accordingly, there might be a clinical pathological spectrum of neurodegeneration in only a subset of both conditions. For example, there is emerging pathological evidence that motor neuron degeneration associated with deposition of TARDBP is linked to a different pathogenic mechanism from that associated with mutations in SOD1 (Mackenzie 2007) particularly in mice (Robertson 2007). Although subject to further clarification, this result is consistent with the finding that dementia is uncommon in families with ALS who have mutations in SOD1 (Mase 2001;
Strong 2003b; Wicks 2009). However, whether all patients who have ALS with frontotemporal dementia have a distinct pathological signature remains to be determined.

The exciting developments in the sphere of ALS-dementia bear relevance elsewhere. Since a subset of ALS patients has cognitive impairment or dementia, and relatives of ALS patients have an increased risk of developing Parkinson’s disease, genes involved in ALS are also considered candidate genes for other neurodegenerative disorders (Van Es 2009).

**Table 8. Familial ALS and Cognitive Impairment**

<table>
<thead>
<tr>
<th>Genetic association (Locus/gene)</th>
<th>Study</th>
<th>Population</th>
<th>Clinical manifestations</th>
<th>Neuropathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome 17q 21-22; MAPT gene</td>
<td>Wilhelmsen 1994</td>
<td>1 large family in North America</td>
<td>Disinhibition-dementia-Parkinson-amyotrophy complex (DDPAC).</td>
<td>Tau pathology</td>
</tr>
<tr>
<td>Chromosome 17q21.32; progranulin gene</td>
<td>Baker 2006, Cruts, 2006, Snowden, 2006</td>
<td>North America and Scandinavia</td>
<td>Progressive change in personality, behaviour, language (e.g. PNFA) in 6th/7th decades of life followed by impairment of executive function, memory retrieval deficit +/- MND, rigidity, bradykinesia and semantic language abnormalities.</td>
<td>FTD-U type cytoplasmic inclusions of combined with intranuclear pathology</td>
</tr>
<tr>
<td>Chromosome 9p 13.2-21.3</td>
<td>Vance 2006</td>
<td>1 large family in the Netherlands</td>
<td>Motor symptoms followed by personality and behavioural abnormalities between 4th to 7th decades of life.</td>
<td>UMN and LMN degeneration and ubiquinated inclusions in anterior horn cells and granular layer of hippocampus</td>
</tr>
<tr>
<td>Chromosome 9p</td>
<td>Morita 2006</td>
<td>1 family in Scandinavia</td>
<td>5 died of ALS with mild or minimal cognitive impairment, 9 had FTD without motor neuron involvement</td>
<td>Ubiquitin pathology only; cytoplasmic and nuclear</td>
</tr>
<tr>
<td>9q21-q22</td>
<td>Hosler 2000</td>
<td>16 families in USA</td>
<td>ALS, FTD or both</td>
<td>Undefined</td>
</tr>
<tr>
<td>Genetic association (Locus/gene)</td>
<td>Study</td>
<td>Population</td>
<td>Clinical manifestations</td>
<td>Neuropathology</td>
</tr>
<tr>
<td>---------------------------------</td>
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<td>---------------</td>
</tr>
<tr>
<td>9p13.3-12, valosin-containing protein</td>
<td>Watts, 2004, Kovach 2001</td>
<td>Occurs mainly in North America due to founder effect</td>
<td>Autosomal dominant inclusion body myopathy, Paget’s disease of bone, FTD.</td>
<td>Ubiquitin pathology; cytoplasmic and nuclear</td>
</tr>
<tr>
<td>3p12, CHMP2B</td>
<td>Brown 1995</td>
<td>1 large family in Denmark</td>
<td>FTD and later motor syndrome (not typical ALS)</td>
<td>No distinctive features (tau negative, ubiquitin negative)</td>
</tr>
<tr>
<td>2p13, dynactin</td>
<td>Puls 2003</td>
<td>Large Northern American kindred</td>
<td>LMN disease with vocal cord paralysis. Normal cognition.</td>
<td>Undefined</td>
</tr>
<tr>
<td>Point mutation (R1101K) in the DCTN1 gene</td>
<td>Munch 2004</td>
<td>2 family members with classical ALS, 2 with FTD</td>
<td>FTD and ALS segregate as separate traits.</td>
<td>Undefined</td>
</tr>
</tbody>
</table>

MAPT: the microtubule-associated protein tau gene  
DDPA: Disinhibiton-dementia-Parkinson-amyotrophy complex  
FTD: Frontotemporal dementia  
CHMP2B: the chromatin-modifying protein 2B gene  
VCP: the valosin-containing protein  
DCTN1: the dynactin gene  
LMN: Lower motor neuron  
PNFA: Progressive non fluent aphasia  
FTDU: frontotemporal dementia with ubiquitin only (i.e. tau-negative and synuclein-negative) pathology  
UMN: Upper motor neuron

2.2.4 Neuropsychology

Cases combining the clinical picture of MND with mental symptoms, personality change or dementia have been reported regularly since the nineteenth century, and a possible association between MND and frontal lobe dementia was postulated as early as an 1932 case report (Braunmuhl 1932).

From the 1960's onwards an increasing number of case studies were published where ALS appeared to be associated with presenile dementia (Staal 1969; Reed 1975; Hudson 1981).

While there is a clear link between ALS and FTD, the frequency, severity and progression of cognitive impairment in otherwise “classical” ALS remains unclear.
The most consistently reported cognitive changes in ALS relate to dysfunction on components of the executive system (e.g. verbal fluency and attention), while abnormalities in memory and language are not as well characterised.

As predicted from diagnostic criteria for FTD (Neary 1998) patients demonstrate cognitive deficits on tests commonly associated with function of the frontal lobes such as tests of verbal fluency, yet show little or no impairment on tasks of memory such as the Weschler Memory Scale or tasks of delayed recall. Table 9 summarises some of these findings.

Table 9. Neuropsychological test performance in ALS

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Patients (n)</th>
<th>Neuropsychological test performance showing impairment</th>
<th>Neuropsychological test performance in the normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallassi (1985)</td>
<td>22</td>
<td>Verbal fluency (COWA) Verbal reasoning Visual attention (Barrage Test) Short-term visual recall Short-term verbal memory (Rey's)</td>
<td>Long-term verbal memory Long-term spatial memory</td>
</tr>
<tr>
<td>Neary (1990)</td>
<td>4</td>
<td>Verbal Fluency (letter and category) Set Shifting (WCST) and Weigl's Block Task Intelligence (WAIS-R) Interpretation of Proverbs, Episodic memory (VPAL),</td>
<td>Visuoperception (Money Road Map) Intelligence (KBF) Memory (Warrington Memory Test) Delayed Verbal Recall</td>
</tr>
<tr>
<td>Kew et al. (1993, 1993b)</td>
<td>12, 16</td>
<td>Verbal fluency (written), Free picture recall, Recall memory (KOLT)</td>
<td>Cognitive Inhibition (Stroop) Recognition Memory Visuoperceptual battery Set shifting (WCST) Episodic memory (VPAL)</td>
</tr>
<tr>
<td>Ludolph et al. (1992)</td>
<td>18</td>
<td>Verbal Fluency</td>
<td>Set shifting (WCST) Cognitive Inhibition (Stroop) Visual recall (RCFT) Attention (Digit span) Naming (modified test) Visual concentration (d2 test)</td>
</tr>
<tr>
<td>Author (year)</td>
<td>Patients (n)</td>
<td>Neuropsychological test performance showing impairment</td>
<td>Neuropsychological test performance in the normal range</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Massman et al.</td>
<td>146</td>
<td>Verbal Fluency (COWA), Immediate free recall (CVLT), Recognition memory (major deficiency in some patients), Attention (VSAT), Set Shifting (WCST)</td>
<td>Delayed verbal recognition memory (CVLT) Visuoperception (Benton JOL) Confrontation naming (BNT)</td>
</tr>
<tr>
<td>Abrahams et al.</td>
<td>52</td>
<td>Verbal Fluency (written), Executive function/ intrinsic generation (Random movement joystick test; noted in pseudobulbar palsy only), Planning and working memory (Computerised Tower of Hanoi), Set Shifting (WCST), Word Recognition Memory Test, Stroop Negative priming: trend towards significance</td>
<td>Episodic memory (VPAL) Recall memory (KOLT)</td>
</tr>
<tr>
<td>Rakowicz et al.</td>
<td>18</td>
<td>Verbal Fluency, Attention (Reverse Digit Span), Conceptual semantic processing (Pyramids and palm trees test), Syntactic comprehension (TROG), MMSE, Graded naming test (confrontation naming)</td>
<td>Attention (forward digit span) Picture naming Word-picture matching</td>
</tr>
<tr>
<td>Moretti et al.</td>
<td>14</td>
<td>Verbal Fluency (letter), Set Shifting (WCST), Cognitive inhibition (Stroop), Attention (PASAT), Interpretation of Proverbs, Bilingual Aphasia Test – B, MMSE</td>
<td>Intellectual ability (RSPM, WAIS-R, KBF) Attention (digit span) Story Retrieval, Past Events Retrieval, Visuoperception (JLO)</td>
</tr>
<tr>
<td>Author (year)</td>
<td>Patients (n)</td>
<td>Neuropsychological test performance showing impairment</td>
<td>Neuropsychological test performance in the normal range</td>
</tr>
<tr>
<td>--------------</td>
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<td>-------------------------------------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>Abrahams et al, (2005)</td>
<td>20</td>
<td>Verbal fluency Test (written and spoken) Computerised Sentence Completion Task</td>
<td>Confrontation Naming (Graded Naming Test), Fluency (Category and Design) Attention (PASAT, letter span) Set Shifting (WCST) Episodic memory (VPAL) Recognition Memory Test, Recall memory (KOLT) Visuoperception (Benton JOL), Object Decision, Position Discrimination.</td>
</tr>
<tr>
<td>Ringholz et al. (2005)</td>
<td>279</td>
<td>Verbal fluency VSAT Visual Recall Logical Memory (Verbal Recall) Confrontation naming (BNT)</td>
<td>Visuoperceptual ability (Benton Facial recognition Test) MMSE (except severely impaired patients) Cognitive inhibition (Stroop)</td>
</tr>
</tbody>
</table>

*BNT: Boston Naming Test*
*COWA: Controlled Oral Word Association Test*
*CRTL=continuous recognition memory test.*
*CTH=computerised Tower of Hanoi test.*
*CVLT=California verbal learning test.*
*JLO: Judgment of Line Orientation*
*KBF=Koh’s block figures.*
*KOLT: Kendrick Object Learning Task*
*MMSE: Mini Mental State Examination*
*NPI: Neuropsychiatric Inventory*
*PASAT: Paced Auditory Serial Addition Test*
*RCFT: Rey complex Figure Test*
*RMJT=Random movement joystick test.*
*RSPM=Raven’s standard progressive matrices.*
*TROG: Test for the Reception of Grammar*
*WAIS-R: Weschler Adult Intelligence Scale*
*WBT=Weigl’s block task.*
*WCST=Wisconsin Card Sorting Test*
*VPAL: Verbal Paired Associate Learning*
*VSAT: Verbal Series Attention Test*
2.3 Patterns of cognitive impairment in ALS

2.3.1 Executive dysfunction

Executive functions are traditionally thought of as higher-level mental processes that enable the control and organisation of other cognitive processes (Shallice 1988). They are a heterogeneous set of skills that facilitate problem solving and responses to novelty. The frontal striatal systems are also implicated in non-executive behavioural regulation, response initiation, motivation, and elements of memory functioning (Cummings 2007).

2.3.1.1 Verbal Fluency

Impaired verbal fluency, a sensitive indicator of frontal or striato-frontal areas that are involved in intrinsic response initiation, has been reported in almost all studies of cognitive impairment in ALS (Ludolph 1992; Massman 1996; Abrahams 1997; Frank 1997). Disturbances of both letter and category fluency which require rapid word generation (written or oral) have been reported.

With respect to letter fluency, subjects are asked to produce as many novel words as possible excluding proper names, within one minute beginning with a given letter (e.g. F, A, and S).

For category fluency, subjects are asked to generate words from given categories e.g. four categories of mandate items (household items, vehicles, musical instruments, and boats).

Simultaneous effects on both category and letter based fluency suggest that the deficit is explained by dysfunction in components of the executive system since a disproportionate reduction in category fluency is suggestive of broader semantic impairment.

Tests of verbal fluency are sensitive, but they depend on verbal or written responses and the results can be confounded by motor impairments in ALS. However, modifications to control for the speed of response can allow patients with upper limb disabilities, and consequent writing disabilities to be assessed meaningfully.

In one study comparing different versions of the test, ALS patients were found to be impaired on a written version, but not in an oral version which controlled for dysarthria (Abrahams 2000). The authors suggested that previous studies (Gallassi 1989; Ludolph 1992; Massman 1996; Frank 1997) using an oral version of the test may have exaggerated the severity of any impairment by failing to account for speech disabilities in ALS patients.

The mechanisms underlying the fluency deficit in ALS were examined in the light of some underlying cognitive processes e.g. intrinsic response generation, phonological loop functions and simple word retrieval (Abrahams 2000). 22 ALS patients were compared with 25 matched controls. ALS patients were significantly slower in generating written words that were four letters long and started with the letter 'c', as well as naming different types of animals. However, they were not significantly slower in the generation of written words beginning with the letter 's', nor on the generation of words from the semantic categories of 'colours', 'fruits', or 'towns'. No significant deficit was found on the oral version of the verbal fluency task.

The findings indicate that verbal fluency impairments in ALS patients result from a higher order dysfunction, implicating deficits in the supervisory attentional system or central executive component of working memory. The results also suggest the intact functioning of the phonological loop, simple word retrieval, and articulatory control processes, although there were some deficits found on tests of working memory.

The authors conclude that deficits on tasks of fluency in ALS are not caused by low level impairments in the phonological loop or in linguistic abilities but by higher order dysfunction in executive systems such as the Supervisory Attention System (SAS) (Shallice 1988). The SAS is theorized to modulate non-routine cognitive selection as opposed to automatic processes and is thought to be involved in novel tasks, decision making, and overcoming temptation.

Although verbal fluency is most commonly believed to result from executive dysfunction, it has recently been suggested that a true language dysfunction
may partially contribute to deficits in verbal fluency. An fMRI study (Abrahams 2004) showed abnormal activation of inferior frontal gyrus and Broca’s area during verbal fluency and naming tasks is sporadic ALS patients without aphasia or dementia. Cerebral structures involved in language seemed to be affected before clinically significant naming deficits had become apparent. Further investigations of the executive system are needed to identify clearly the nature and range of deficits in patients who have sporadic ALS without aphasia or dementia.

2.3.1.2 Set Shifting and the Wisconsin card sorting test

Set shifting refers to the ability to conceptualise abstract categories and switch cognitive sets according to contingencies of reward and punishment i.e. to move back and forth between tasks, operations, or sets. The Wisconsin card sorting test is an established measure of set shifting and mental flexibility in ALS. This test is often used to measure executive function, but it can be less reliable than tests of verbal fluency in ALS since set shifting also includes components of working memory, attention, and abstract reasoning.

The test involves matching a target card to one of four decks of cards on the basis of three dimensions: number, colour, or shape (Grant 1948). The only feedback given to the participant is the word “right” or “wrong” after each sorting. When the participant successfully matches ten cards to the correct deck on the basis of one dimension (e.g. colour), the participant is required to shift to another dimension (e.g. shape). A number of outcome variables can be recorded, such as the number of cards taken to reach the first dimension shift, the number of categories achieved, the number of perseverative errors, and the number of overall errors.

A positron emissions topography study Berman (1995) confirmed that performance of the WCST engages the frontal cortex and in particular the dorsolateral prefrontal cortex (DLPFC) It also produces activation of a complex network of regions consistently including the inferior parietal lobule but additionally involving the visual association and inferior temporal cortices as well as portions of the cerebellum.

Impairment in ALS on the Wisconsin Card Sorting Test was found in some studies (David 1986; Gallasi 1989), but has not been confirmed in others.
(Ludolph 1992; Kew 1993; Talbot 1995). However some of the latter studies used a modified version of the test which may lack sensitivity in ALS patients.

2.3.1.3  The Computerised Tower of Hanoi

This test is used to measure the executive functions of planning and working memory (a complex component of the executive system that also involves many other cognitive processes). It is closely based on the three dimensional Tower of London (TOL) tests in which subjects must move coloured balls on a computer screen to match a specified arrangement in the minimum number of moves possible. The complexity depends on the minimum number of moves needed to arrive at the correct solution.

H215O-PET-activation studies have shown that the TOL activates the frontal association cortex (dorsolateral prefrontal, premotor, anterior cingulate and frontopolar cortex) and basal ganglia, as well as posterior parietal areas (Baker 1996; Owen 1996). The areas other than the frontally activated areas are probably activated not only by the planning process itself but also by the motor and visual processes needed to perform this planning.

Patients with pseudobulbar palsy display shorter planning times on complex trials in the Computerised Tower of Hanoi than controls, with a tendency to fail to solve these trials as effectively (Abrahams 1997).

2.3.1.4  Attention

Impairments in the attentional system are often associated with frontal lobe damage. Attention also seems to be affected in ALS (Chari 1996; Massman 1996). Evaluation of attention is important because disinhibited-type patients might have near-normal results in traditional tests of frontal executive function, but show impaired responses in tests of selective attention (Neary 2000).

Visual attention was examined in an early study using the Barrage test (Gallassi 1989). This test requires participants to cross out 100 lines as quickly as possible. The authors found that patients with ALS took twice as long on average to complete the test compared to healthy controls or patients with progressive muscular atrophy.
Digit span is a commonly used test of attention, alertness, and mental processing capacity in which the examiner reads aloud a series of number sequences. The patient must repeat strings of numbers forward and backwards. The number sequences become progressively more difficult, the last being nine digits read aloud. A consistent and significant reduction in reverse digit span has been observed in patients with ALS (Rakowicz 1998). Poor reverse digit span often indicates impaired working memory rather than pure attentional impairments. Working memory is a complex component of the executive system which not only involves attention but also many other cognitive processes.

Massman et al (1996) examined attention through the use of the Verbal Series Attention Test and other tests. The former requires participants to count backwards from 100 in threes and recite sequences such as the alphabet in as specific order. Patients with ALS scored in only the 38th percentile with respect to time to complete the test. This was despite the fact that this group had above-average premorbid IQ as measured by the American National Adult Reading Test. It is worth noting however, that previous neuropsychological batteries did not make the same adaptations for motor disability and dysarthria that we are familiar with today (see below).

2.3.1.5 Cognitive Inhibition

The Stroop is one of the most widely utilised paradigms in the domain of cognitive inhibition. It is held to assess verbal working memory and executive function.

The subject is first asked to name the colour of matching colour words (e.g. the word 'blue' written in blue ink). In this 'congruous' example, usually only a short time is needed to identify the colour in which the word is printed.

The subject is then asked then to name the colour of incongruent colour words e.g. the word 'blue' written in red ink. Identification time for the ink colour is increased significantly since this requires the subject to inhibit an over-learned automatic response (reading the word) in favour of an unusual one. Ravnikilde (2002) conducted a PET study of brain activation during the Stroop test and showed activation of the prefrontal cortex and left anterior cingulate cortex.
The disproportionately impaired performance in this incongruent aspect has been examined in several groups. Results have been conflicting in ALS but may reflect heterogeneous study design.

2.3.2 Memory

There has been disagreement about memory deficits in ALS.

Studies have demonstrated that where memory is affected, immediate recall is usually involved, while the deficits in delayed recall are highly variable, suggesting difficulties in encoding rather than abnormal speed of forgetting (Bak 2001).

These results are consistent with current theories that encoding is an executive component of memory and involves a neuronal circuit that arises in the left frontal lobe (Tulving 2000).

Two studies (David 1986; Kew 1993) have reported that free picture recall is affected in ALS patients. Immediate recall, as judged by the registration component of the MMSE, was not affected in one study (Rakowicz 1998). It is acknowledged, however, that the MMSE is not a very sensitive test of memory.

2.3.3 Visuoperceptual function

Visual-perceptual functions are a heterogeneous set of processes that include attention, object identification, and object recognition processes. These processes are largely preserved in many patients with ALS, as measured by tests such as the Benton Judgement of Line Orientation Test and Object Decision and Position Discrimination from the Visual Object and Space Perception Battery (David 1986; Talbot 1996; Robinson 2006).

Patients with ALS with fronttemporal dementia are often noted to have little difficulty in navigating their way around their home environment, in location of objects, in copying of non-representational hand postures, and in identification of their home town on a map (Barber 1995).

2.3.4 Language assessment

Whilst focus in ALS has primarily been on the frontal dysexecutive syndrome, literature on the contribution of the non-fluent progressive aphasia and semantic dementia to ALS is scarce.
Language networks appear to be involved in MRI and PET studies of ALS patients (Abrahams 2000) which lends support to aforementioned findings described that ALS affects extramotor pathways.

Language deficits noted in studies of ALS have included reduced verbal output (Strong 1999; Bak 2004), deficits in naming of objects (Massman 1996; Abrahams 1997; Robinson 2006), perseverations, echolalia (repetition of words said by other people), stereotypic expressions (Rakowicz 1998) and semantic paraphasias (substitution of words that relate closely to one another, e.g., sock for glove, or rabbit for squirrel (Rakowicz 1998; Strong 1999). Patients with ALS can have features of progressive non-fluent aphasia, semantic dementia that is often atypical, or both (Caseeli 1993; Doran 1995; Davies 2005).

Rakowicz and Hodges (1998) reported significant language deficits in patients with ALS particularly on tests of naming and syntactic comprehension. Patients with ALS who did not have dementia had a language output disorder characterised by difficulties with word finding and naming, with a tendency to make category-coordinate semantic errors or circumlocutions. Both groups performed well on tests of non-verbal semantic knowledge and grammar.

Naming deficits have also been reported in other ALS studies (Massman 1996, Rakowicz 1998; Robinson 2006) which suggests that language dysfunction underlies basic word-finding processes. However in some patients, confrontation naming ability is intact (Kew 1993; Abrahams 2000). Processing of verbs has been reported to be greater than that of nouns in patients who have primary progressive aphasia (Hillis 2004) or ALS with dementia (Bak 2004). Hillis and colleagues (2004) suggest that such differences in the patterns of language deterioration might relate to degeneration of different brain areas, which implicates the posterior inferior frontal cortex and insula in motor speech and naming actions.

Results from other studies have suggested that language deficits such as progressive slowing of word retrieval speed form a continuum with aphasia in ALS (Doran 1995; Bak 2001; Abrahams 2005). The possibility that deficits in executive functions, such as verbal fluency, are related to language deficits merits further scrutiny.
Whether aphasia represents an early stage of an aphasic-dementing process is unclear. Another possibility is that language deficits occur independently from cognitive impairment and that patients with such deficits have a distinct separate subtype of ALS-related dementia. However, consistent with the idea that some subtypes of ALS and frontotemporal dementia form a continuum, mutations in \textit{GRN} have been associated with ALS, typical frontotemporal dementia, and a non-fluent progressive aphasia within a single family (Snowden 2006).

Language dysfunction in frontotemporal dementia might also form clinical subtypes. For example, the language deficits of patients with frontotemporal dementia who have mutations in \textit{GRN} might differ from those in patients with mutations in the microtubule-associated protein tau gene (\textit{MAPT}). People with mutations in \textit{GRN} have been reported to show phonological deficits, whereas patients with mutations in \textit{MAPT} demonstrated language abnormalities in the form of semantic disturbance. These findings further support the link between frontotemporal dementia and non-fluent progressive aphasia, and suggest that patients with FTLD who have mutations in \textit{MAPT} are clinically different to those who have mutations in \textit{GRN} (Snowden 2006).

2.3.5 Social cognition, emotional processing and behaviour

Social cognition, which is crucial for human interaction has been found to be impaired in various studies of frontotemporal dementia. Lough et al (2006) showed that patients with frontal variant FTD had impaired recognition of all emotions, and particularly anger and disgust, which may partly explain the difficulty these patients have with identification of social violations. Empathy, as rated by carers, was also abnormal in these patients.

This possibility has also been examined in patients with ALS. Lule and colleagues (2005) presented 52 emotive picture slides to 12 patients with sporadic ALS. The researchers recorded subjective reports of pleasantness and arousal, and brain responses to the affective pictures were measured with functional MRI. Patients with ALS showed lower responses in the anterior insula and extrastriate visual areas than did other participants. This suggests that arousal is reduced at the neural and behavioural levels during the course of ALS. The authors also noted a greater response in the right supramarginal area in patients with ALS than in control patients. This might represent an altered sensitivity to social and emotional cues.
Behavioural impairment is now recognised as a feature of ALS. Rating scales such as the Neuropsychiatry Inventory, Frontal Behaviour Inventory, and Frontal Systems Behaviour Scale have shown that up to 63% of patients with ALS are apathetic, irritable, inflexible, restless, and disinhibited (Lomen Hoerth 2003; Murphy 2006; Grossman 2007). Apathy and difficulties with social judgment seem to be more frequent in patients with bulbar-onset ALS than spinal-onset (Flaherty-Craig 2006; Grossman 2007). Apathy, one of the most common findings, should be differentiated from depression, fatigue, and respiratory dysfunction by careful examination of medical history and use of validated scales. For example, by contrast with apathy, depression can be linked to particular stressors, and is characteristically associated with pervasive anhedonia, sadness, tearfulness, hopelessness, suicidal ideation, and guilt.

Although there is no consensus for behavioural impairment in ALS, the clinical presentation is thought to represent abnormalities that do not meet the Neary criteria for frontotemporal dementia (Lomen Hoerth 2006) i.e. two non-overlapping supportive diagnostic features from either the Neary criteria and/or Hodges’s criteria (Strong 2009). Behavioural impairment in ALS can be also be classified on the basis of presentation of frontal-lobe-type behavioural impairment in two or more areas, as measured from a standardised caregiver interview (Murphy 2007). However, the debate of whether to classify patients with ALS who have cognitive impairment together with or separate from those who have behavioural impairment continues. Although cognitively normal patients with ALS can have profound behavioural abnormalities (Lomen Hoerth 2003), cognitive and behavioural impairments coexist in 25% or more of ALS patients (Woolley-Levine 2006). Maintenance of a division between cognitive and behavioural impairment in research studies might be useful in identification of different pathogenic mechanisms and clinical courses, but there is currently insufficient evidence to make this distinction.

2.3.6 Emotional change

2.3.6.1 Depression

Studies of depression in ALS have been inconsistent; perhaps due to sample composition and methodological considerations; the estimated prevalence of
depression amongst patients with ALS may vary significantly depending on the measure used (Wicks 2007). For example, rates of "moderate depression" or "significantly elevated rates of depression" have ranged from 22% to 75% (Moore 1998; Bocker 1990) in advanced ALS. Other studies have found lower prevalence of depression in patients with ALS (Clarke 2001; Goldstein 2002; Trail 2003).

The challenges of assessing depression in patients with ALS are manifold. In such a terminal illness, symptoms such as decreased concentration, sleep disturbance, fatigue, and anorexia are widespread, yet unadjusted depression scales that do not account for such features may over-diagnose depression. Previous studies have also highlighted the potential problems of using self-report measures in ALS such as the Beck Depression Inventory (Beck 1961) which includes questions on suicidality, given that such a "wish to die" may exist in a substantial proportion of patients with this terminal illness who may not be depressed (Albert 2005). The latter authors also demonstrate that depression and hopelessness do not correlate. Finally, subtle cognitive impairment or even frank frontotemporal dementia in ALS might confound the picture since features of the latter including lack of insight, denial, apathy, and euphoria may mask depression or hopelessness (Phukan 2007). Nonetheless, a number of researchers have explored this field and some key findings are summarised below.

A longitudinal study (Rabkin 2005) assessed 80 hospice-eligible ALS patients at monthly intervals until death or tracheostomy using the Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders (4th ed.; DSM-IV). Major depression in people with late-stage ALS was rare (<10%), though transient depressive symptoms did occur; risk of depression did not necessarily increase with the approach of death. The authors conclude that a picture of resiliency rather than despair is seen in ALS patients. This resonates somewhat with a study conducted almost 40 years ago (Brown 1970) that noted reactions to ALS included "continued attempts at active mastery and persistent suppression, denial, and isolation of depressive and anxious feelings". Later studies have failed to confirm a stereotype of stoicism in the face of adversity. Hunter (1993) found that psychological distress (as measured by the General Health Questionnaire) is widespread among patients.
at all stages of the disease whilst Peters (1978) used the Minnesota Multiphasic Personality Inventory to demonstrate no evidence of increased defensiveness in patients with ALS when compared with the general medical population. Individual patient interviews also showed no characteristic personality profile for ALS patients. Although Rabkin et al (2005) found major depression in late-stage ALS to be rare, it is worth noting that the combined rate of 19 percent for both major and minor depression seen in the Rabkin study was higher than the 2 to 9 percent prevalence rate reported for depression in the general population. The presence of depression does not appear to be associated with a desire to hasten dying in patients with end-stage ALS (Albert 2005).

36 of 100 subjects in a study by Ganzini et al (1999) endorsed the item "In the last two weeks have you felt sad, blue, depressed or lost all interest and pleasure in things you used to care about or enjoy most of the time?". However, the researchers found major depressive disorder (as diagnosed using criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) of the American Psychiatric Association (Robins 1981) in only 11%.

What may be more important is that when recognized, treating physicians in the above study appropriately prescribed SSRIs for depression, but then failed to follow up on the efficacy and attempt alternative interventions, as demonstrated by the finding that 6 of 11 treated patients were still depressed. The authors recommend that referral to a mental health professional may be appropriate when initial treatment of depression fails. This brings to mind the 1984 epidemiological study of behavioural disorders in multiple sclerosis, temporal lobe epilepsy, and amyotrophic lateral sclerosis (Schiffer 1984). The authors found that prevalence rates for psychiatric contact amongst 124 ALS patients was only 4.8% (i.e. just 6 had been referred to a psychiatrist), compared to 19.3% for multiple sclerosis and 22.9% for temporal lobe epilepsy. Another consideration in the management of depression in patients with ALS is that low mood is frequently associated with significant pain (Tedman 1997) and fatigue (Lou 2003). Conversely, as discussed below, improved quality of life and fewer symptoms of depression are linked to positive social support (Rabkin 2000; Goldstein 2002).
Another area to contemplate is the evolution of affective change over the course of ALS as severity increases. Research to date has not found a significant correlation between depression and severity of physical symptoms (Tedman 1997; Ganzini 1998; Goldstein 2002; Lou 2003, Rabkin 2000; Rabkin 2005).

Studies have also examined the link between depression and patients' views towards assisted suicide as their condition progresses. Albert et al (2005) conducted a prospective study to examine if the wish to die is associated with depression in patients with ALS. 80 patients with ALS were enrolled: 63% of eligible patients i.e. 53 died over follow-up. 10 (18.9%) of the 53 expressed the wish to die, and 3 (5.7%) hastened dying. Although patients expressing the wish to die were more likely to meet criteria for depression, differences were smaller when suicidality was excluded from the depression interview (i.e. the result was skewed by more frequent statements by patients that they "would be better off dead."). Patients who expressed the wish to die reported less optimism, less comfort in religion, and greater hopelessness. Thus presence of depression did not appear to be associated with a desire to hasten dying in patients with end-stage ALS and the authors urge caution in concluding that the desire to hasten dying in end-stage disease is simply a feature of depression. Instead, they report, the wish to die may be part of a broader syndrome of "end-of-life despair" (McClain 2003) which includes suffering, loss of interest in living, absence of pleasure, loss of interest in activity, and pessimism. Religious sensibility and spirituality are much lower in patients who demonstrate despair, again suggesting the existential roots of the wish to die in end-stage disease (Albert 2005).

Similarly Ganzini et al (1998) set out to determine attitudes of patients with ALS toward assisted suicide Patients were considered to be willing to contemplate assisted suicide if they agreed with the statement, "Under some circumstances I would consider taking a prescription for a medicine whose sole purpose was to end my life," and disagreed with the statement, "I would never request or take a prescription for a medication whose sole purpose was to end my life." 56 patients (56 percent) said they would consider assisted suicide. As compared with the patients who were opposed to assisted suicide, those who would consider it were more likely to be men, had a higher level of education,
were less likely to be religious, had higher scores for hopelessness, and rated their quality of life as lower. There was no difference in the prevalence of depression between the patients who would consider taking a lethal dose of medication and those who would not. The authors demonstrate that hopelessness and depression are not synonymous.

Another investigation set out to identify predictors of psychological distress (measured by anxiety and depression) and low self-esteem and to determine whether these change over time in 50 patients with ALS (Goldstein 2006). Interviews were held with patients and carers over the course of a year. At the first interview, negative social support and bulbar impairment were most predictive of psychological distress; pre-illness marital intimacy was the best predictor of patients' self-esteem. Over time, negative social support and pre-illness marital intimacy retained an ability to predict patients' affective state and self-esteem. The authors underlined the importance of identifying such predictors of anxiety and depression in patients with ALS given that affective state may be amenable to psychopharmacologic and psychotherapeutic interventions, and that depression may contribute to quality of life (Lou 2003).

Depression in carers may also require attention. Gauthier et al (2007) interviewed 31 ALS patient-caregiver couples over the course of nine months. They found a substantial steadiness of quality of life and depression in patients with ALS over a 9-month period, in contrast to a significant increase of burden (increase of 11%) and depression (increase from 9.7% to 19.3%) in their caregivers.

2.3.6.2 Anxiety

Anxiety had been examined less frequently in patients with ALS. Rates have varied from 11-26% (Goldstein 1998; Moore 1998; Clarke 2001; Goldstein 2002).

In examining psychosocial correlates of anxiety, one study found a relationship between anxiety assessed by the Hospital Anxiety and Depression Scale (HADS) and physical symptoms related to speech and eating, including the social impact of these impairments (Hogg 1994). They suggest that patients may become more anxious in social situations given their difficulties in communication and potential embarrassment caused by difficulties in eating.
Another study also found correlations between anxiety as assessed by the HADS and SF36, measures of emotional functioning, mental health, fatigue, and pain (Tedman 1997). They found elevated scores in females relative to males, and in married patients relative to those that were single, divorced, or widowed. The authors suggest this may be due to feelings of carer burden or loss of self esteem in relation to roles in the relationship.

2.4 Incidence and Prevalence of Cognitive Decline in ALS

The exact phenotype and natural history of impaired cognition in ALS are unclear. The confusion lies partly in the source of patients: those patients attending a behavioural clinic and later have evidence of motor system degeneration might differ from those who attend a neuromuscular clinic and later develop impaired cognition. Thus reports of the frequency, severity and type of cognitive impairment in ALS patients vary considerably. Methodologies used to assess cognitive impairment have also differed, and much of the analysis has been conducted based on a combination of non-standardized neuropsychological assessments; few studies have combined neuropsychology, neuroimaging and post-mortem verification. Some studies have not accounted for motor and speech impairment in ALS. Moreover, all studies to date have recruited patients from tertiary referral clinics, and this approach can lead to bias in definition of a common phenotype.

One of the largest studies so far (Ringholz 2005) detected cognitive impairment in 132 (47% of 279 consecutive ALS patients) who attended an ALS clinic. Most notable of these impairments was executive dysfunction alongside mild memory decline. About 15% of patients had severe impairment with features that were consistent with frontotemporal dementia.

However, there have been no large population-based clinical studies of the prevalence of cognitive decline in ALS. Current estimates, which suggest that more than half of patients with ALS have cognitive impairment, might reflect the selection bias caused by use of tertiary clinic-based referral from prevalent rather than incident populations.

There may even be heterogeneity of cognitive impairment depending on underlying genetic variants. Dementia appears to be uncommon in families with ALS who have mutations in SOD1 (Mase 2001; Strong 2003b).
study, Wicks et al (2009) found that individuals with SOD1 gene mutations (n=7) were less likely to have significant cognitive changes compared to non-SOD1 FALS patients (n=10).

Even less is known of the natural history of cognitive decline in ALS. Few longitudinal studies have characterised the progress of cognitive decline in ALS but some small, clinic-based studies suggest that cognitive impairment evolves in ALS patients over the course of their illness. A longitudinal study of 8 patients with ALS (Strong 1999) noted a progression of cognitive impairment (including processes such as working memory, problem solving/cognitive flexibility, visual perception, and recognition memory for words and faces) in bulbar-onset ALS patients over a 6-month period. Subsequent neuropathologic analysis of these patients showed neuronal loss in the anterior cingulate gyrus. In a separate study, 7 of 19 ALS patients developed cognitive deficits over a similar period of time although the between-group and within-group comparisons did not show significant differences in cognitive function over time. (Robinson 2006). These findings were not replicated by a third longitudinal study (Abrahams) that found relatively stable global cognitive functions over a 6-month period in patients who had ALS but no dementia (Abrahams 2005).

Because there have been no large scale population-based studies of cognitive function in ALS, there has been little detailed analysis of the clinical implications of cognitive impairment in disease management. There are several suggested risk factors for dementia in ALS such as older age, male sex, lower education, family history, low FVC, pseudobulbar palsy, bulbar site of onset, and increasing disease severity (Massman 1996; Abrahams 1997; Lomen-Hoerth 2003; Portet 2001) but these associations have not been consistently replicated.

2.5 The clinical continuum of cognitive impairment in ALS

Evidence that cognitive dysfunction in ALS forms a continuum, ranging from mild impairment to frontotemporal lobar dementia (Strong 2003), remains weak.

Most patients with ALS do not have overt clinical features of dementia; there is some evidence to suggest that such patients have a subtle impairment of
frontal executive functions that include verbal fluency and attention, but visuospatial abilities and psychomotor speed are usually preserved. Whether some of these neuropsychological changes are a consequence of declining motor function is unclear, but an association between increasing ALS severity and decreasing verbal fluency performance has been noted (Rippon 2006).

Ascertaining and evaluation of cognitive impairment in patients with ALS is further complicated by the existing classification system. Cognitive impairment cannot be characterised formally or uniformly with the El Escorial criteria (Appendix 1) because these criteria by definition exclude evidence of impaired cognition. Patients with ALS and cognitive impairment are currently classified within the ALS-plus category, without any further definition of the degree or extent of upper and lower motor neuron symptoms.

2.6 Optimum Methodology for examining cognitive impairment in ALS

There is currently no absolute consensus among researchers on the definition and measurement of cognitive impairment in ALS (Ringholz 2004), on the psychometric methods used to assess patients, or on the nature of cognitive decline associated with frontotemporal dementia. However, working guidelines for optimum cognitive assessment in patients with ALS have been suggested by Strong and colleagues (Strong 1996) and more conclusive consensus documents were published as a result of discussions at the Second International Frontotemporal Dementia in ALS Research Conference (London, Ontario, June 2007) (Strong 2009) which this author attended. These are discussed in section 2.6.1 below.

Identification of cognitive impairment has been improved by the use of untimed neuropsychological tests, experimental adjustments to control for slower motor speed, and examining recognition rather than free recall. However, before these modifications are used to diagnose patients with ALS, they should undergo extensive validation and be tested to ensure that they have sufficient sensitivity and statistical power to identify effects.

In patients who have features of frontotemporal dementia, neuropsychological testing may be more useful when used in combination with carer-based instruments for behaviour, such as the Neuropsychiatric Inventory or Frontal Systems Behavioural Scale (FrSBe) (Levy 1996; Strong 1996). One study
(Levy 1996) that used the Neuropsychiatric Inventory found that 77% of FTD patients and 77% of AD patients were correctly assigned to their diagnostic category. Such questionnaires allow caregivers to convey how the patient functions on a day-to-day basis with his or her premorbid status, although cognitive impairment can be underestimated (Abrahams 2005).

Depression can mimic impaired cognition as discussed above. Scales such as the Hospital Anxiety and Depression Scale (HADS; Zigmond 1983) have been used to ensure that abnormal cognitive profiles are not related to an underlying mood disorder.

2.6.1 Defining cognitive and behavioural impairment in ALS

Defining cognitive impairment in ALS has proved challenging with disparate methodologies being used in studies to date. Statistical methods used have included cluster analysis, percentile analysis and cut-off scores based on neuropsychological test data, and clinical diagnosis (Massman 1996; Lomen Hoerth 2003; Ringholz 2005; Wheaton 2007).

The issue was clarified to an extent by the introduction of consensus criteria for frontotemporal cognitive and behavioural syndromes in ALS (Strong 2009; Appendix 2 and described below). The guidelines emphasize that whilst sampling the major cognitive domains, tests should be weighted towards executive functioning. Carer-based instruments for behaviour should be used as mentioned above, as well as tests that minimize the impact of speech and motor dysfunction on performance.

Diagnostic categorisation as defined by the consensus criteria encompasses five main diagnoses which were also used in this project with some adaptations outlined in the next chapter.

1 ALS-FTD. This category applies to those who have a diagnosis of ALS (see ELS Escorial criteria; Appendix 1) as well as any one of the three subtypes of FTD: behavioural variant FTD, semantic aphasia, and non-fluent progressive aphasia (described fully in Table 1). These subtypes are defined by the Neary criteria (Neary 1998).

2 ALS-behavioural impairment (ALSbi). This categorisation refers to patients who meet partial criteria for ALS-FTD. In other words, such an individual
meets at least two non-overlapping supportive diagnostic features from either the Neary criteria (i.e. decline in personal hygiene and grooming, mental rigidity and inflexibility, distractibility and impersistence, hyperorality and dietary changes, perseverative and stereotyped behaviour, utilization behaviour) and/or Hodge's criteria (i.e. loss of insight, disinhibition, restlessness, distractibility, reduced empathy or unconcern for others, lack of foresight or planning, impulsiveness, social withdrawal, apathy or loss of spontaneity, reduced verbal output, verbal stereotypes or echolalia, verbal or motor perseveration, poor self care, gluttony, sexual hyperactivity) (Gregory 1999). The presence of two behavioural abnormalities should be supported by at least two sources from among a patient interview/observation, caregiver report, or structured questionnaire/interview. Ideally, both a clinical interview with both the patient and caregiver and a structured, well-validated questionnaire should be included (see below for recommendations). To diagnose ALSbi, the behavioural changes should not be better explained by a psychiatric condition, a psychological reaction to ALS, a premorbid personality disorder, or the presence of pseudobulbar affect also known as emotional lability.

3 ALS-cognitive impairment (ALSci). The consensus document states that to be diagnosed with ALSci, a patient with ALS must demonstrate cognitive impairment on standardised neuropsychological testing at or below the 5th percentile, compared to age- and education matched controls, on at least two tests sensitive to executive functioning. Domains other than executive functioning should also be assessed, consistent with a comprehensive neuropsychological assessment, to rule out other cognitive conditions. Other comorbidities that may account for cognitive impairment should be excluded including cerebrovascular disease, head injury, diabetes, hypothyroidism, substance abuse or psychiatric illness. In addition, a number of ALS-specific associated conditions must be considered as possible explanations for cognitive impairment, such as the presence of pseudobulbar affect, respiratory dysfunction, disrupted sleep, delirium, pain, fatigue and medication effect (especially psychotropic and narcotic analgesic medications). Patients may meet criteria for both ALSci and ALSbi but it is important to recognise that patients with prominent apathy
may have decreased motivation and may thus perform poorly on test of executive functioning.

4 ALS-comorbid dementia. This categorisation refers to those patients with ALS and a dementia that is not typical of FTD e.g. Alzheimer’s disease, vascular dementia, and mixed dementia.

5 ALS – this refers to those patients who have ALS alone without cognitive or behavioural impairments.

2.7 Does cognitive impairment matter?

The potential clinical implications of cognitive impairment in patients with ALS and their families have major importance.

2.7.1 Patients

Problems with judgement, attention, and response inhibition/generation should be taken into account when planning appropriate patient care. For example, deteriorating cognitive or executive function can compromise capacity to make decisions about health care or financial circumstances, and the ability to engage competently in end-of-life decisions. Cognitive impairment can also reduce initiation and compliance with interventions such as occupational and physical therapy: patients with ALS who also have dementia are twice as likely to be noncompliant with interventions including non-invasive ventilation (Olney 2005). Awareness of safety issues, for instance how to avoid or cope with falls or choking episodes, might additionally be compromised by cognitive impairment. The increasing use of brain–computer interfaces in patients with long-term assisted ventilation means that the evaluation of cognitive impairment and decision-making capacity by such interfaces will become highly relevant, both scientifically and ethically.

Furthermore, survival times seem to be significantly shorter for patients who have ALS and frontotemporal dementia than for patients with classic ALS (Olney 2005). In particular, patients with bulbar-onset ALS with FTLD were more than twice as likely to die at any interval after ALS onset than were patients who had bulbar-onset classic ALS, which suggests that these disease variants have different clinical trajectories (Olney 2005).
Recognising cognitive impairment in ALS is vital for our approach to clinical trials. If there is a distinction between ‘pure’ ALS, and ALS with cognitive and/or behavioural impairments, then perhaps patients should be segregated for clinical trials given that patients with fronttemporal impairment have a difference in prognosis compared to those who have ALS alone. Even if ALS and fronttemporal dementia are instead intrinsically linked, if they form a spectrum, then our approach to ALS will need to shift as we recognise the phenotype of this neuromuscular disorder has changed.

2.7.2 Carers and families
ALS requires a high level of caregiving – it takes up to 14 hours per day to care for a patient with ALS, caregivers often must give up their jobs, caregivers’ physical and psychological well-being are frequently affected (Krivickas 1997; Borasio 2001) and they must cope with their loved ones being diagnosed with a terminal illness.

The presence of cognitive impairment in patients with ALS may place additional burden on caregivers. Caregiver burden is consistently higher for patients with dementia than for patients with other disorders (Thommessen 2002), as is caregiver depression, anxiety and mortality (Schulz 1995, Schulz 1999); this might also be the case for carers when patients with ALS and dementia are compared with patients with ALS but no dementia.

2.8 What to do in clinic
Currently the frequency of impaired cognitive function in patients with “typical ALS” cannot be established definitively, and formal mechanisms to evaluate the significance of clinical findings are not in place. Notwithstanding, clinicians should be aware of the possible presence of cognitive impairment in patients with ALS. Similarly, the possible presence of anterior horn cell dysfunction in patients attending behavioural neurology clinics must be entertained. Clinicians who work with patients who have ALS should be alert to character and behavioural change, as reported by a spouse or relative, which might provide the most useful clue to a diagnosis of ALS with frontotemporal dementia.
Short batteries of tests such as the MMSE cannot be used to screen for frontotemporal dementia; these are ineffective in assessing executive function or behaviour. Such testing can however reveal behavioural abnormalities such as perseveration, inattention and disinhibition. In other simple cognitive tests, patients with frontotemporal dementia might have difficulty with proverb interpretation and cognitive estimates (e.g. the height of a well-known building). However, because many brief indices of general functioning have poor sensitivity, a negative finding does not mean that cognitive function is intact.

A screening assessment cannot make the diagnosis of ALS with frontotemporal dementia, behavioural impairment or cognitive impairment. A formal neuropsychological assessment and/or behavioural interview are required to make these diagnoses. However a screening assessment can help to determine if a formal neuropsychological evaluation is warranted (Strong 2009). It is recommended that such a screening assessment includes a verbal fluency measure that accounts for limb disability or dysarthria. A simple 2-minute word generation test is an excellent screening tool with high sensitivity for identifying patients in whom more detailed neuropsychological evaluations are needed. Patients with deficits in verbal fluency are likely to show further frontal deficits, executive deficits, or both, on more detailed testing (Lomen-Hoerth 2003). Yet these tests are often highly correlated with intellectual ability, and care should be taken to use educationally adjusted normative data rather than simple cut-off scores.

Suspicion of impaired cognition should prompt referral for formal neuropsychological examination although the Addenbrooke’s Cognitive Examination might also be helpful. This preliminary examination incorporates the MMSE with tests to evaluate the separate cognitive domains of orientation, attention, memory, verbal fluency, language, and visuospatial ability, and can be administered in a clinic in 15–20 minutes. The Addenbrooke’s Cognitive Examination might be more sensitive and specific than the MMSE in the differentiation of Alzheimer’s disease and frontotemporal dementia (Mathuranath 2000; Mioshi 2006) but it cannot be used as a substitute for formal neuropsychological testing and does not account for the limb and bulbar disability of ALS.
Consensus guidelines from the Second International Frontotemporal Dementia in ALS Research Conference (London, Ontario, June 2007) (Strong 2009) have sought to clarify the role of neuroimaging in patients with ALS and cognitive impairment. In addition to excluding other pathology, structural neuroimaging might reveal selective atrophy of frontal and anterior temporal areas, although such atrophy might not be apparent in early frontotemporal dysfunction (Gallassi 1989).

Reversible causes of impaired cognition should not be forgotten. Newson-Davis and colleagues (2001) reported that nocturnal hypoventilation and sleep disturbance can cause cognitive dysfunction in ALS, and that this dysfunction may be partially improved by non-invasive positive-pressure ventilation for 6 weeks. Scores on two of the seven cognitive tests in this study were significantly improved by non-invasive positive-pressure ventilation.

Depression and other psychosocial causes might also account for impaired cognition in patients with ALS. Thorough review of medical history and the use of scales such as the Hospital Anxiety and Depression Scale (Zigmond 1983) can help to exclude the possibility that abnormal cognition is related to these factors. Sleep disturbance and some drugs can also have a confounding effect on neuropsychological test performance. Sleep can be disturbed by immobility, pain, anxiety, or nocturnal hypoxia, and patients with subclinical or incipient respiratory failure can have non-specific symptoms that include frequent nocturnal awakening, early morning headache, and daytime sleepiness (Mustfa 2001). Respiratory function should be assessed and failure of ventilation treated before neuropsychological assessment if possible. Similarly, use of agents such as amitriptyline and dextromethorphan should be accounted for during patient assessment. These drugs are used for symptomatic relief in ALS, but can induce drowsiness that might affect the outcome of neuropsychological assessment.

Recognizing and managing caregiver burden and depression is not only vital for caregivers; it ensures optimal management of ALS (Phukan 2009). Rabkin (2005) reported that concordance between patient and caregiver distress is high, suggesting that attention to the mental health needs of caregivers may alleviate patient's distress as well. Hence the importance of offering caregiver support through respite, counselling, caregiver support groups, information on financial assistance and maintaining hope.
2.9 Future Research

Although evidence suggests that ALS and FTLD are different clinical manifestations of the same neurodegenerative disorder, the nature of cognitive impairment in ALS has yet to be understood.

Major difficulties are that the degree and progression of cognitive impairment has not been well characterized within a population-based cohort and that the clinical boundary between dementing and non-dementing ALS patients (i.e. between progressive dementia and 'subclinical cognitive impairment') remains blurred (Barson 2000). Different cognitive performance across groups of patients might be related to the severity or stage of ALS progression (Ringholz 2005), but confirmation of this suggestion would need large population-based studies that use uniform and reproducible methodologies.

Prospective longitudinal, population-based clinicopathological correlative studies are also needed to determine if ALS patients with no or mild impairment show progressive impairment over time and whether patients with mild cognitive impairment but without dementia form a separate subtype of patients with ALS, distinct from patients with normal cognition and those with dementia.

Assessment of cognition in a longitudinal population-based study poses particular difficulties because rapid disease progression causes high attrition. Ideally, such a study would use a population-based national register and include patients with ALS as categorised by the El Escorial criteria. In countries with high population densities, home visits could overcome the issue of inability to attend clinics during the later stages of the illness.

Systematic, standardised, and periodic data collection would avoid medical surveillance bias. To segregate patients with ALS into those at risk of impaired cognition and those who will remain cognitively intact, prospective longitudinal population-based studies would probably need surveillance over at least 12 months, because cognition is often impaired only late in ALS.

Revision of classification systems on the basis of known pathogenic mechanisms will improve greater diagnostic accuracy. New developments in genomics, proteomics and bioinformatics, and advances in "classical" neuropathology, might also elucidate whether pure ALS, ALS with cognitive
impairment, ALS-FTD and pure FTLDU (ubiquitin only neuropathology) truly represent a continuous spectrum of ubiquitin-associated neurodegenerative disease (Talbot 2006). Exploration of functionally related proteins (progranulin, angiogenin, TDP-43, FUS / TLS) should uncover mechanisms of neurodegeneration in ALS and related conditions.

In the meantime, a formalised validated and reproducible neuropsychological battery for ALS with frontotemporal dementia is urgently required. Consensus criteria for the definition of behavioural and cognitive impairment in ALS (Strong 2009) have helped us move closer to this aim. Standard testing can underestimate or exaggerate the presence of cognitive impairment in ALS. Future batteries will need to account for limb and bulbar dysfunction and incorporate tests that make minimal demands of speech production, fine motor control, speed of cognitive processing and peripheral motor reaction time (many of which are the most sensitive measures of cognitive dysfunction). Prospective studies would facilitate correlation of neuropsychological evaluation with dynamic imaging and pathological findings.

With new discoveries about the clinical, pathological, and molecular aspects of frontotemporal dementia in patients with ALS, new questions and challenges have arisen. Understanding this condition will lead to better care for patients with ALS and their families, and provide further valuable insights into the pathogenesis of neurodegeneration.
Chapter 3  A Population Based Longitudinal Study of Cognitive Impairment in ALS: Aims, Hypotheses and Methodology

3.1 Introduction

ALS is the most common neurodegenerative disorder of young and middle-aged adults with age-dependent onset and duration. Although predominantly a motor system degeneration, it is now well established that ALS and FTD have clinical, radiological, pathological, and genetic overlap (reviewed in Phukan 2007).

The clinical definition of cognitive impairment in ALS has proved challenging with the use of various non-standardized methodologies. There have been no large-scale population-based studies of cognition in ALS, and much of the analysis has been conducted based on a combination of non-standardized neuropsychological assessment, neuroimaging and post-mortem study of small numbers of patients attending tertiary referral clinics. Various statistical methods have also been applied, including cluster analysis, percentile analysis and cut-off scores based on neuropsychological test data, and clinical diagnosis (Massman 1996; Ringholz 2005; Lomen Hoerth 2003; Wheaton 2007).

A degree of clarification has been introduced following the publication of consensus criteria for frontotemporal cognitive and behavioural syndromes in ALS (Strong 2009). These guidelines emphasize that cognitive assessment should be weighted towards executive functioning; that the confounding effect of speech and motor dysfunction must be minimized; and that carer-based instruments for behaviour should also be used.

Although considerable progress has been made in recognizing the cognitive phenotypes associated with ALS, the population-based prevalence of cognitive impairment in ALS remains unknown. Using a detailed neuropsychological battery in a population-based cohort, this study of cognition in ALS aimed to establish for the first time the true frequency of the various cognitive phenotypes within the Irish ALS population. The recent consensus guidelines helped to formally categorize patients, and on this basis, this study has tested the utility of the guidelines as a research tool. In addition, the challenge was to identify areas of
clinical overlap in which the consensus guidelines require clarification, and also to
generate a cohort that can be further interrogated longitudinally to establish the
natural history of mild cognitive impairment in ALS.

3.2 Aims

The aims of this project were as follows:

1. To complete a population-based longitudinal study of cognition in incident
   ALS patients and to characterize the clinical phenotype of cognitive
   impairment in a population-based ALS cohort.

2. To examine the impact of impaired cognition on clinical management and
   executive decision making as well as quality of life and carer burden.

Aims 1 and 2 will also provide clinical data that will permit the pursuit of supplementary aims that are part of the larger multidisciplinary project on
the epidemiology, natural history and genetics of ALS in Ireland.

- To determine whether the presence of cognitive decline should be adopted
  as important variable for stratification within clinical trials.
- To determine whether the presence of cognitive decline in patients, coupled
  with a strong family history of neurodegeneration can be used to segregate
  patients and kindreds for sub-characterization using neuroimaging and
  genetic analysis.
- To use the dataset, combined with a similar cross-sectional data from
  Scotland, as a robust population-based preliminary dataset for a larger
  population-based European study of the genetics of cognitive decline in
  ALS.
- To collect DNA from Irish and Scottish patients for a detailed phenotype
  genotype study with particular reference to the identification of genetic
  susceptibilities for cognitive decline. A DNA bank for ALS has already been
  established, and those enrolled on the Register and engaged in research
  are routinely requested to contribute.
3.3 Specific hypotheses

3.3.1 Primary Hypothesis: The frequency and evolution of cognitive decline in ALS in a population-based cohort.

It was hypothesized that cognitive decline primarily affecting the executive domain would be present in up to 50% of the Irish ALS population, that a smaller number of patients would have overt dementia, and that a proportion of patients with cognitive or behavioural impairment would progress to develop full-blown frontotemporal dementia. The most consistently reported cognitive changes in ALS relate to dysfunction on components of the executive system (e.g. verbal fluency and attention), while abnormalities in memory and language are not as well characterised. In addition to neuropsychological evidence of cognitive change in patients with ALS (primarily in the executive domain), it was predicted that behavioural changes would also be detected.

Rationale: Although predominantly a motor system degeneration, it is now well established that ALS and FTD demonstrate clinical, genetic, radiological and pathological overlap (Wright 2005; Ringholz 2005; Phukan 2007). Evidence for this overlap is reviewed in detail in Chapter Two. However, the extent of overlap between these two neurodegenerative syndromes is not currently well defined. To date, there have been no published population based clinical studies of the incidence of cognitive decline in ALS, and neither have there been any large population-based longitudinal studies of the natural history of cognitive impairment in ALS. Much of the analysis has instead been conducted based on a combination of non-standardized neuropsychological assessment, neuroimaging and post-mortem study of small numbers of patients attending tertiary referral clinics. It may be that the current estimates suggesting that more than half of ALS patients have cognitive impairment reflect selection bias arising from the use of such clinic-based referral series. The true incidence of cognitive impairment among the ALS population might be very different. It has previously been established that in ALS, the clinical features and natural history of prevalent cohorts differ significantly from incidence-based cohorts (O'Toole 2007). Previously reported clinic-based studies are therefore likely to be biased in favour of prevalent cases and are accordingly not representative of the true pattern within the general population.
Furthermore, there have been few longitudinal studies aimed at characterizing the evolution of cognitive decline in ALS patients. This project was designed to allow definition of distinct subgroups of ALS patients with different profiles of cognitive impairment, and facilitate future correlation of these subgroups with a corresponding genetic risk.

Results of the cross-sectional study are presented in Chapter Four; results of the longitudinal study are presented in Chapter Seven.

3.3.2 Hypothesis Two: Behavioural change and patient insight in ALS

It was predicted that in addition to cognitive impairment in patients with ALS, behavioural changes would also be detected. The self and carer-rated Frontal Systems Behaviour Scale (FrSBe), were used to measure apathy, disinhibition, and dysexecutive function. Cognitive impairment was hypothesized to correlate with such behavioural manifestations. It was also hypothesised that patient and carer reports of patient behaviour would differ, indicating a deficit of insight in some patients with cognitive impairment.

Rationale: Behavioural impairment is now recognised as a feature of ALS. Although cognitively normal patients with ALS can have profound behavioural abnormalities (Lomen Hoerth 2003), cognitive and behavioural impairments can coexist in 25% or more of ALS patients (Woolley-Levine 2006). Rating scales such as the Neuropsychiatry Inventory, Frontal Behaviour Inventory, and Frontal Systems Behaviour Scale have shown that up to 63% of patients with ALS are apathetic, irritable, inflexible, restless, and disinhibited (Lomen Hoerth 2003; Murphy 2006; Grossman 2007). Apathy and difficulties with social judgment seem to be more frequent in ALS patients with bulbar-onset than non-bulbar onset (Flaherty-Craig 2006; Grossman 2007).

Results are presented in Chapter Four.

3.3.3 Hypothesis Three: The impact of cognitive / or behavioural impairment in ALS

It was hypothesised that utilisation and compliance with interventions such as non-invasive ventilation is affected in those with impaired cognition and / or behaviour. In addition, it was expected that medical decision–making capacity would be impaired in some patients with ALS.
Rationale: The most consistently reported cognitive changes in MND relate to dysfunction on components of the executive system. Given that executive functions facilitate problem solving, deteriorating cognitive or executive function could compromise capacity to make decisions about health care or financial circumstances, capacity to use and comply with interventions and the ability to engage competently in end-of-life decisions. The utilization of and compliance with interventions was assessed. Medical decision-making capacity was also evaluated.

Results are presented in Chapter Four (utilisation and compliance with interventions) and Eight (medical decision-making capacity).

3.3.4 Hypothesis Four: Quality of life (QoL) and Mood in ALS

3.3.4.1 Quality of life

It was hypothesised that physical status was not the only relevant factor in determining QoL. The aim was to ascertain QOL in those with cognitive impairment compared to those without (an exploratory hypothesis), and to explore the evolution of QOL over time.

Rationale: A number of studies have shown that appreciation of QoL mainly relies on psychological, supportive, and spiritual factors (Robbins 2001; Simmons 2001; Chio 2004) rather than physical status. Previous studies have found a substantial steadiness of quality of life in patients with MND (Goldstein 2006; Gauthier 2007) although a significant increase of burden and depression in their caregivers over time has been observed (Gauthier 2007). Patients with ALS may have lower expectations of their physical ability as their illness progresses, and instead may instead shift their focus to other domains, perhaps spiritual and psychosocial (Clarke 2001; Bromberg 2002).

3.3.4.2 Mood

In addition it was predicted that based on previous research that there would be a low prevalence of anxiety and depression in ALS patients. The Hospital Anxiety and Depression Score (HADS, Zigmond 1983), a self-report questionnaire was used to assess this hypothesis and to explore the relationship between mood and quality of life, physical impairment and cognitive and/or behavioural impairment. Longitudinal assessment of mood was also conducted. Results are presented in Chapter Five.
3.3.5 Hypothesis Five: Self-perceived burden and Carer Burden in ALS

It was predicted that carer burden would be higher in those with cognitive impairment and dementia.

As an exploratory study, the level of self-perceived burden was assessed in relation to severity of illness, quality of life, mood, carer burden and cognition.

Rationale: Caregiver burden is consistently higher for patients with dementia than for patients with other disorders (Thommessen 2002) and this might also be the case when patients with ALS and dementia are compared with patients with ALS but no dementia. Although this has not yet been examined comprehensively, Hecht (2003) reported that if problem behaviour exists, carers of ALS patients participate more often in support groups, indicating the need for assistance.

In many neurodegenerative diseases, carer burden is directly related to the need for residential or respite care. Results are presented in Chapter Six.

3.4 Significance /Relevance of this research to ALS

From a clinical perspective, the recognition that other neurodegenerative conditions can overlap with ALS has been an important step in our understanding of the pathogenesis of ALS. In particular, recent clinical and pathological data indicate that ALS and FTD may form part of a disease although this is a controversial view. Given this overlap of ALS and FTD, it is possible that these two clinically distinct conditions share a common pathogenic mechanism or pathway.

This study is designed to determine for the first time the population prevalence of cognitive impairment in ALS. The unique aspect of this study is that it will track a population-based cohort of patients with mild cognitive impairment to determine whether they progress to a more severe frontotemporal dementia phenotype. Accurate knowledge of the frequency and risk of cognitive impairment in patients with ALS is of critical importance for patients and caregivers, for disease management, and for service development. From the genetic perspective, it is anticipated that this study will ultimately provide the knowledge to identify novel gene(s) that increase
the risk of cognitive decline in ALS, and therefore provide further valuable insights into the pathogenesis of the neurodegenerative process.

3.5 Methodology

3.5.1 Participants

Patient recruitment was achieved through the Irish Register of ALS, a population-based instrument that has been in operation since 1994. Case ascertainment was undertaken as has been described previously (Traynor 1999) through this Register. In brief, multiple sources of information are utilized, including consultant neurologists, neurophysiologists, neuropathologists, and primary care physicians. Ascertainment is conducted in close collaboration with the Irish Motor Neuron Disease Association and with all practicing Consultant Neurologists in Ireland. Diagnosis of ALS is based upon the El Escorial criteria (Brooks 1994; Appendix). Once an ALS patient is enrolled in the Register, details of his/her presenting clinical features are obtained either by review of their complete medical records or, where possible, review of the patient. There is a latency of up to 3 months from first referral to the Register and complete diagnostic validation and inclusion of new incident patients. Each patient enrolled in the Register is routinely followed up over the course of their illness at intervals of not more than four months.

There are currently 204 patients with ALS alive in Ireland and enrolled on the Irish ALS Register. Between 79 and 83 new patients are enrolled each year in the Republic of Ireland.

3.5.1.1 Ethical Approval

This project had full ethical approval from Beaumont Hospital Research Ethics Committee (Appendix 3).

3.5.1.2 Patient Recruitment and Consent

All incident patients enrolled on the Register of ALS were approached initially by telephone. This was undertaken by an experienced MND research nurse, who described the study in detail. Those consenting to receive further information about the study were sent written information about the project. The information sheet and consent forms (Appendix 4, 5) provided an overview of the research project and the home-based assessment procedure.
as well as contact details for the ALS Research team who were available to answer any questions.

Participants were informed through information sheets that they could withdraw from the study at any time with no explanation required and no impact on their subsequent care. If they declined to take part, their consent form was archived in a secure filing cabinet.

Following agreement to participate in the study, the participating individual and spouse/control was contacted by the Research Fellow to arrange a suitable time to meet in the participant’s home to carry out neurological examination, cognitive testing and genetic testing.

Where possible, carers were also asked to participate by completing a number of behavioural, carer burden and family history questionnaires described below. These took about thirty minutes to complete. Carers were sent similar information leaflets and consent forms in order to make an informed decision before participating (Appendix 6). Carers were interviewed separately and out of earshot of the patient completing the neuropsychological battery of tests. Carers were guaranteed that their responses would remain confidential.

Within 7 days of this home visit, the participating individual was contacted by telephone by the Research Fellow. The purpose of this telephone conversation was to determine if the participating individual (and participating family members) had suffered psychological distress arising from completion of the questionnaires and neuropsychological testing.

Patients were informed that as part of standard practice, feedback would be provided to all patients following analysis of their neuropsychological assessments. Patients with specific deficits would be referred to the appropriate services.

3.5.1.3 **Inclusion / exclusion criteria**

The study was open to all those residing in Ireland with a diagnosis of ‘definite’, ‘probable’ or ‘possible’ ALS according to El Escorial Criteria (Brooks 1994).

Exclusion occurred if it was determined that the diagnostic inclusion criteria for ALS were not met.
Also excluded at the time of analysis were those with a history of cerebrovascular disease (detected on baseline imaging), use of psychoactive medications (except low dose psychotropic medication for emotional lability which is unlikely to affect neuropsychological test performance), uncontrolled hypertension, diabetes, exposure to heavy metals/chemicals, major head injury, a prior history of intellectual impairment or learning disability, or the use of mechanical ventilation (since the neuropsychological test battery could not be adapted for this cohort of patients).

Controls for neuropsychological assessment were selected from an age- and geographic-matched population. The same exclusion criteria applied.

3.5.1.4 Data protection
All collected data was scored and entered into Statistical Package for the Social Sciences (SPSS) version 15. Hard copies were anonymised, coded and stored in a locked cabinet at the Clinical Research Centre, Beaumont Hospital; access was restricted to Professor Hardiman, Dr Phukan and the Data Entry Research Assistant. Data was retained electronically in a secure unit at the Clinical Research Centre and on a password protected computer. All clinical information was treated in a strictly confidential manner according to the stipulations of the Irish Data Protection Acts 1988 and 2003. The data was stored on a password-protected Progeny 5.0 Enterprise (Progeny Software LLC, Indiana) database (protected by McAfee VirusScan 2005 version 9 anti-virus software) to which only Professor Hardiman, Dr Phukan and the Data Entry Research Assistant had access. Each individual entered on the database was assigned a unique numeric identifier in order to ensure anonymity. The names of the individuals were maintained in a separate password-protected encrypted database (protected by McAfee VirusScan version 9 anti-virus software) with access limited to Professor Hardiman, Dr Phukan and the Data Entry Research Assistant.

Informed consent was obtained from all patients from whom DNA samples were procured. Phlebotomy was performed during home visits where possible. 20 millilitres of blood in acid-citrate-dextrose tubes was collected for genetic analysis from each individual and stored at -70C in the Neuropathology laboratory in Beaumont Hospital and then transferred to the National Centre for Medical Genetics, Our Lady's Hospital, Crumlin. Storage was again in a
strictly confidential manner according to the stipulations of the Irish Data Protection Acts 1988 and 2003. The blood samples were coded, so that they could not be linked back to the patient without accessing two protected coded systems. To facilitate this all blood samples were bar-coded. Information concerning the results of genetic analysis was not to be made available to research participants, something that was explained in the patient information leaflet.

3.5.1.5 Healthy controls

Controls were selected from an age and geographic matched population. These participants were recruited via posters (Appendix 7), newsletters of voluntary organisations, the website of the Irish Motor Neurone Disease Association, and through patient contacts. Travel expenses were reimbursed. Controls received information leaflets as described in Appendix 8.

Each control underwent a similar battery of testing with the same fixed test order described below, and also participated in an ongoing family aggregation study. The appropriate assessment of the control population was undertaken by a graduate in neuropsychology, based at Beaumont Hospital and Trinity College Institute of Neurosciences, Trinity College, Dublin, under the supervision of Dr. Niall Pender, Director of Neuropsychology, National Centre for Neurosciences, Beaumont Hospital and Trinity College Dublin. The presence of a high intra-class correlation coefficient statistic indicated strong inter-rater reliability for our neuropsychological test battery.

3.5.2 Demographic and clinical variables

Variables recorded included:

- Date of birth
- Age
- Gender
- Years of education
- Highest qualification
- Occupation
Classifications. International Labour Office). All occupations were coded according to the most recently updated version of the International Standard Classification of Occupations (ISCO-88) adopted by the International Labor Organization (ILO), a United Nations specialized agency. The ISCO-88 is a hierarchical coding system, which classifies jobs into occupational groups according to similarity in skill level and specialization of tasks and duties performed (www.ilo.org). Ten major groups at the top level of aggregation, subdivided into 28 sub-major groups, 116 minor groups, and 390 unit groups, can be distinguished. The occupation held for the longest period of time was extracted for each case and control and considered to be the main occupation.

- **Diagnosis date and time since diagnosis**
- **Symptom onset**
- **Site of symptom onset**
  - limb vs. bulbar
- **Presence or absence of spouse**
- **Outside caregiver and hours provided**
- **Family history**
  Patients were asked about their family history of neurodegeneration, using a previously validated family history questionnaire. An unrelated family member (e.g. spouse) was asked to complete a similar questionnaire as a control.
- **Medications**
  Psychotropic medications may cause or exacerbate cognitive impairment and so use of these was documented both by the examining neurologist at the time of ascertainment, and also during the home evaluation.
- **Respiratory status**
  cognition can be impaired by incipient respiratory failure and so the respiratory status of the patient was assessed by using a transcutaneous ear sensor to measure pCO2 levels and pulse oximetry for pO2 levels.
- **The frequency and duration of use of the non-invasive ventilator was assessed where relevant** (McNally 2004; Bourke 2006).
• **Functional impairment was assessed using the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) (Appendix 9)** (Cedarbaum 1999). This validated rating instrument facilitates monitoring of the progression of disability in patients with ALS. Easy to administer, it allows comparisons to be made with the patient’s status prior to the onset of the disease. Each patient’s response (on a 5 point scale) is recorded in relation to the questions exploring the 12 functions listed in the ALSFRS-R: speech, swallowing, salivation, handwriting, cutting food and handling utensils, assisting with feeding, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnea, orthopnoea, and use of assistive ventilation. A maximum score of 48 indicates normal functioning; lower scores reflect greater disability. The ALSFRS-R has been shown to predict survival time in an ALS clinic population (Kaufmann 2005).

3.5.3 **Participant assessment**
Each patient was assessed in three stages, namely a full neurological examination, categorized according to the El Escorial Criteria (Brooks 1994) collection of detailed family history data using a previously validated questionnaire and finally, a detailed validated neuropsychological evaluation.

A battery of standardized neuropsychological instruments previously used in the study of cognitive impairment in ALS was selected (Abrahams 1995; Kazuo 1997; Neary 2000; Papps 2005) to encompass the following domains: executive function, memory, language and mood (Table 10). Adaptations to avoid potential confounding effects of motor and verbal output response times were applied as described previously (Abrahams 2000). A fixed test order was decided upon so as to vary between verbal and non-verbal tasks, thus minimising patient fatigue and discomfort and additionally to avoid interference between different tests. The tests are described below. A specific test order (Appendix 10) was required since many of the delayed recall portions required a 25-30 minute interval between part I and II e.g. Logical Memory, California Verbal Leaning Test and so as to avoid interference of certain tests with one another. Each session took approximately 1.5-2 hours each, with a break midway through testing.
<table>
<thead>
<tr>
<th>Name of test</th>
<th>Cognitive domain</th>
<th>Description</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ravens Standard Progressive Matrices</td>
<td>Intellectual</td>
<td>Increasingly difficult figures with a missing piece. Six alternative pieces offered to complete the figure, only one of which is correct. Each set involves a different principle or &quot;theme&quot; for obtaining the missing piece.</td>
<td>Measures current intellectual functioning (non-verbal intelligence). Minimizes reliance on timed performance.</td>
</tr>
<tr>
<td>Wechsler Test of Adult Reading (WTAR)</td>
<td>Intellectual</td>
<td>50-word list that minimises the current ability of the patient to apply standard pronunciation rules and also helps to assess previous learning of the word.</td>
<td>Measures premorbid intellectual ability.</td>
</tr>
<tr>
<td>Logical Memory*</td>
<td>Memory</td>
<td>Subject is asked to recount a short story immediately, and then recall it again after delay. The story incorporates 25 &quot;story elements&quot;.</td>
<td>Examines verbal learning. Measures immediate free recall after auditory presentation and delayed recall.</td>
</tr>
<tr>
<td>Paired Associate Learning Test*</td>
<td>Memory</td>
<td>Word pairs are presented for 4 trials; recall is tested immediately and after delay.</td>
<td>Tests ability to form associations between word pairs.</td>
</tr>
<tr>
<td>California Verbal Learning Tests</td>
<td>Memory</td>
<td>16-word list from 4 categories. Immediate recall and then several repeated trials examine whether or not the subject is making use of category information.</td>
<td>Examines several aspects of verbal learning, organization, and memory.</td>
</tr>
<tr>
<td>Rey Complex Figure Test.</td>
<td>Memory</td>
<td>Drawing and visual memory test that examines ability to construct a complex figure and its later recall.</td>
<td>Measures memory and visual-motor organization.</td>
</tr>
<tr>
<td>Digit span test* (forward and backward).</td>
<td>Memory</td>
<td>Series of progressively more difficult number sequences to be repeated.</td>
<td>Test of attention, alertness, and mental processing capacity.</td>
</tr>
<tr>
<td>Verbal Fluency (phonological adapted and category).</td>
<td>Executive function (+ / - language: see text)</td>
<td>Requires as many novel words as possible, excluding proper names</td>
<td>Examines frontal executive function. Abrahams' et al. (2000) fluency index analysis used to adjust for motor speech deficits.</td>
</tr>
<tr>
<td>Stroop Tests</td>
<td>Executive function</td>
<td>The respondent names the colour of the ink in which the word is printed (and must inhibit the automatic response of reading the word) instead.</td>
<td>Examines attention, mental speed, and mental control.</td>
</tr>
<tr>
<td>Brixton Test for problem solving</td>
<td>Executive function</td>
<td>Measures the ability to detect rules in sequences of stimuli; does not require a verbal response.</td>
<td>Sensitive to problems with rule detection but also to tendencies toward impulsive and bizarre behaviour.</td>
</tr>
</tbody>
</table>
### Name of test

<table>
<thead>
<tr>
<th>Name of test</th>
<th>Cognitive domain</th>
<th>Description</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Naming Test (abbreviated version).</td>
<td>Language / Naming</td>
<td>A 60-item picture-naming test.</td>
<td>Measures production aphasia and confrontation naming.</td>
</tr>
<tr>
<td>Frontal Systems Behaviour Scale</td>
<td>Behaviour</td>
<td>Both carers and patients rate the patient's behaviour before and after the onset of ALS.</td>
<td>Examines the behavioural features of fronto-striatal dysfunction.</td>
</tr>
</tbody>
</table>

*From the Wechsler Memory Scale-III*

The progression of cognitive decline in ALS was determined by the performance of up to 3 separate evaluations at home, separated by 6-month intervals. At least 2 and preferably 3 evaluations at 6 months intervals were felt to be required to fully characterize the degree of progression of impaired cognition in ALS patients, and to determine the impact of cognition on executive decision making, quality of life and survival. This approach of home visits significantly increased the completeness of follow-up particularly in the later stages of the illness when cognitive impairment is more likely to be apparent.

#### 3.5.3.1 Statistical Analysis

Patients were assigned to one of five diagnostic categorizations: ALS, ALS-cognitive impairment, ALS-behavioural impairment, ALS-frontotemporal dementia and ALS-comorbid dementia, as defined by recent consensus criteria (Strong 2009; Appendix 2).

The consensus criteria specify that ALSci is defined on the basis of two distinct tests of cognition that are sensitive to executive function. However there are several difficulties regarding such a global measure. Combination of executive measures is artificial as it fails to recognise that various executive tests reflect independent, dissociated networks (i.e. dorsolateral, cingulate and orbitofrontal). In addition in large samples such as this one, there are statistical difficulties since a measure such as the verbal fluency index has such a wide range (8-540 in our sample) and standard deviation. Finally given the recognition of more extensive temporal involvement than previously recognised in ALS (Kato 1993; Okamoto 1998; Papps 2005; Schmolck 2007) solely depending on executive tests may underestimate ALSci. Thus ALSci was defined either by two tests sensitive to executive function, or by one test
sensitive to executive function accompanied by a memory measure. The verbal fluency index was the only measure that could not be used to define as ALSci given the wide ranges and standard deviations described above.

Cognitive and behavioural results for patients groups were also compared to those of age-matched controls. Between-groups comparison of means scores of ALS patients were also compared to matched controls.

A detailed exploratory analysis was undertaken to ensure that the data met criteria for standard parametric analysis. Where transformations were unsuitable for parametric analysis, the specific non-parametric equivalents were employed. Group differences were examined using Analysis of Variance or Analysis of Co-Variance if demographic or cognitive variables contributed to task performance (Clark-Carter 1997). Patient selection minimised the need for extensive co-variation which would adversely affect the power of the statistical analysis. Cohen's (1988) guidelines were used to define correlation sizes, whereby: .00 to .29 = small correlation; .30 to .49 = medium correlation; .40 to 1.0 = large correlation.

For all specific test comparisons between patients and controls, a one-way between-groups analysis of covariance was conducted to compare the control participant means and the ALS participant means on each test. The independent variable was the grouping (group 1: ALS patients, group 2: control participants) and the dependent variable was the neuropsychological test in question. Participants' scores on the Wechsler Test of Adult Reading (WTAR) were used as the covariate in this analysis to ensure that differences in IQ between patients and controls did not act as a confounding factor.

Preliminary checks were conducted to ensure that there was no violation of the assumptions of normality linearity, homogeneity of variance, homogeneity of regression slopes, and reliable measurement of the covariate.

For analysis of the FrSBe, a Total score was formed through results on three subscales of Apathy, Executive Dysfunction and Disinhibition. Raw scores were converted to age-and education corrected T-scores; T-scores were used in data analyses. T-scores have a mean of 50 and standard deviation of 10, with higher scores on the FrSBe indicating greater pathology (Malloy 2007). New onset behavioural impairment was defined as a 2-standard deviation (SD)
change from premorbid levels on either a FrSBe subscale (Apathy, Executive Dysfunction or Disinhibition) or the Total score (Woolley-Levine 2006). It was also stipulated that current T scores that were ≥65, i.e. 1.5 standard deviations above the mean, represented clinically significant behavioural impairment (Grace 2001; Mosnik 2006)

Statistical analysis was undertaken using the Statistical Package for the Social Sciences version 15.0 (SPSS) and in collaboration with colleagues in the Neuropsychology component of Trinity Institute of Neuroscience (TCIN).

Although the test battery was adapted for those with limb and bulbar disability, some patients were not able to complete all tasks. Missing data were excluded from individual analyses but cases were included in the database.

3.5.3.2 Estimated premorbid IQ and current general intellectual ability

We measured intellectual ability using the following instruments:

1 Ravens Standard Progressive Matrices measures current intellectual functioning (Raven 1958). This well-validated and reliable measure of non-verbal intelligence minimizes reliance on timed performance. 60 items are arranged in five sets of 12 items each. Each item contains a figure with a missing piece. Below the figure are either six or eight alternative pieces to complete the figure, only one of which is correct. Each set involves a different principle or "theme" for obtaining the missing piece, and within a set the items are roughly arranged in increasing order of difficulty.

2 Wechsler Test of Adult Reading (WTAR, 2001) measures premorbid intellectual ability. This reading test is composed of a list of 50 words. It minimises the current ability of the patient to apply standard pronunciation rules and also helps to assess previous learning of the word.

3.5.4 Measures of cognitive function

Optimum methodology for examining cognitive impairment in ALS continues to evolve. Previously there was a lack of consensus among researchers on the definition and measurement of cognitive impairment in ALS (Ringholz 2005). Difficulties included the particular range of psychometric tools used to assess the patients, and the specific nature of the FTD patients participating in the
studies as it is well established that FTD is associated with a profound behavioural disorder that affects performance on all cognitive tests.

Consensus criteria were developed for frontotemporal cognitive and behavioural syndromes in ALS (Strong 2009) following discussions at the Second International Frontotemporal Dementia in ALS Research Conference (London, Ontario, June 2007; Appendix 2) which this author attended. These guidelines, which helped to direct this project, allowed us to design a validated neuropsychological test battery which would examine frontotemporal difficulties in ALS patients, while controlling for the principal confounding factors of mood, motor deficits and speed.

The following were recommendations of the consensus criteria that were incorporated into this study:

- The consensus criteria emphasise that neuropsychological assessments should include tests weighted towards executive functioning, including a verbal fluency measure. Standardized neuropsychological instruments previously used in the study of cognitive impairment in ALS (Kazuo 1997, Neary 2000, Abrahams 1995, Papps 2005) were utilised in this project. The tests employed also encompassed the following domains: memory, language, visuoperceptual function as well as mood.

- The use of carer-based instruments for behaviour is also recommended; this study used the Frontal Systems Behavior Scale (FrSBe see section 3.5.4.6) for both patients and their carers.

- In addition, the consensus document states that it is critical to use tests that minimize the impact of speech and motor dysfunction on performance, particularly in the setting of longitudinal analysis. Thus study maximised modifications to traditional neuropsychological tests including the use of untimed neuropsychological tests and adaptations (Abrahams 1996, Abrahams 2000) to avoid potential confounding effects of motor and verbal output response times.

This broad range of cognitive tests, outlined in the next section, is sufficiently robust to repeat longitudinally and to administer in one assessment visit. The tests battery takes into account the unique problems engendered by progressive dysarthria and upper extremity weakness.
3.5.4.1 Standard Test of Executive Functioning

Impaired frontal executive function has been repeatedly demonstrated in ALS patients. The rationale for our test choice is based on the evidence presented in Chapter Two.

The following tests were used to seek evidence of this:

**Verbal Fluency (phonological and category)**

Verbal fluency tests are designed to measure the speed and flexibility of verbal thought processes. Verbal fluency, a sensitive indicator of frontal or striato-frontal damage, has been found to be affected in almost all ALS/cognition studies.

Subjects are asked to produce as many novel words as possible, excluding proper nouns, plurals, or suffixes, within nine minutes beginning with a given letter ("s" words and four letter "c" words for 5 minutes and 4 minutes respectively).

Verbal fluency index analysis was used to adjust for motor speech deficits (Abrahams 1996; 2000). This adapts the task of verbal fluency to control for the speed of writing by using a copy condition. Such a modification allows meaningful assessment of patient with upper limb and consequent writing disabilities. Following the fluency tests the subject is timed as they copy the words they have written previously. This writing control condition enables the calculation of a Verbal Fluency Index (VFI), which consists of the average time(s) taken to think of each word, i.e. (total time allowed for test, 9 minutes - time to copy all words generated) / (total number of words generated).

For category fluency, subjects were asked to generate words from given categories unless bulbar involvement precluded this. Simultaneous effects on both category and letter based fluency suggests that the deficit is explained by dysfunction in components of the executive system since a disproportionate reduction in category fluency is suggestive of broader semantic impairment.

**Stroop Tests**

This brief procedure (Trenerry 1989) examines attention, mental speed, and mental control. It is one of the most widely utilised paradigms in the domain of cognitive inhibition. In the Colour-Word task, the respondent names the
colour of the ink in which the word is printed (and must inhibit the automatic response of reading the word instead).

**Brixton Test for problem solving**

This test (Burgess 1997) measures the ability to detect rules in sequences of stimuli. It does not require a verbal response. It is sensitive to problems not only with rule detection but also to tendencies toward impulsive and bizarre behaviour. The clinician thus gains qualitative and quantitative information about a subject's performance.

**3.5.4.2 Memory**

Severe memory impairment is not thought to be a common feature of the dementia associated with ALS. Immediate recall has been reported to be predominantly affected while deficits in delayed recall are highly variable suggesting difficulties in encoding rather than abnormal speed of forgetting (Bak 2001). These results are consistent with current theories that encoding is an executive component of memory and involves a neuronal circuit that arises in the left frontal lobe (Tulving 2000).

The memory tests employed in this project were as follows:

**Logical Memory (immediate and delayed recall) of the Wechsler Memory Test-III**

The Logical Memory Test examines verbal learning. It measures immediate free recall after auditory presentation and delayed recall.

Immediate and 30-minute delay trials were administered according to test manual guidelines (Wechsler, 1998). Briefly, story A is read once to the examinee - (s)he then orally provides any information recalled. The story incorporates 25 specific points or "story elements," each of which the subject must recall to obtain credit. Story B is read twice to the examinee, with any recalled information provided after each reading. The examiner records the number of free recall units and thematic units, which represent more general information, that are provided by the examinee. The examinee is instructed to try to remember the stories because he or she will be asked to tell them again later. Following 30 minutes of other testing, the examinee is asked to provide any information recalled from Story A and then Story B. A standard cue is provided if the examinee has no memory of a story. The recall and thematic
unit scores are again recorded. The immediate and delayed scores are the sum of the number of points remembered by the subject during immediate and delayed recall, respectively.

Fifteen yes/no recognition memory questions are then asked about each story and the recognition memory scores are recorded.

The percent retention scores represent the number of story units recalled on the immediate memory trial (story A plus second trial of story B) divided by the number of units recalled after the 30-minute delay (maximum = 100%).

**Paired Associate Learning Test of the Wechsler Memory Scale-III**

Word pairs presented for 4 trials (Wechsler, 1998); recall is tested immediately and after 30-minute delay. This tests the ability to form associations between word pairs which are semantically unrelated.

**California Verbal Learning Tests**

This procedure (CVLT II, 2000) examines several aspects of verbal learning, organisation, and memory. The tester reads aloud a list, called "List A". The list contains sixteen common words, each of which belongs to one of four embedded semantic categories. Thus, there are four animals, four vehicles, four vegetables and four items of furniture etc. The subject is then asked to recall as many of these items as possible. The tester records how many items the subject remembers over five trials and whether or not the subject is making use of category information. For instance, the four vegetable items might spinach, celery, onion and cabbage. The subject may only remember spinach, celery and onion. If the subject cannot remember the fourth item, but guesses that it is another vegetable, the tester concludes that the subject understood the category information in the list. If the subject guesses an unrelated word, the tester concludes that the subject was not able to understand the category information in the list. Patients with frontal lobe damage fail to effectively utilize the semantic organization present in the word lists. There is a short delay of 20 minutes, during which the subject is given other tasks to perform, and then the tester again asks the subject to recall List A.
This test thus includes the following steps:

- Learning, in five trials, of a 16 item list (List A) belonging to four embedded semantic categories
- Acquisition in one trial of an interference list of 16 items (List B) belonging to four embedded semantic categories, of which two are shared with the List A
- Short delay free recall of List A
- Short delay cued recall of List A, providing the subject with each of the four category names to facilitate recall
- 20 minute delayed free recall of List A
- Delayed cued recall of List A
- Recognition of the List A items from various foils, including interference list words that are semantically related or unrelated to target words; novel words that are prototypical of the semantic categories used in the List A; novel words phonetically similar to target words, and novel words that are semantically and phonetically unrelated to target words.

Besides the recall and recognition subtest scores, the analysis of performance includes evaluation of perseverations (multiple productions of the same item within the same trial), intrusions (production of extra list words), consistency of recall from trial to trial, semantic clustering, and serial clustering during learning of the Monday list, as well as false alarms and discriminability at recognition (a non-parametric index of accuracy of recognition, taking into account both misses and false positives: Hahn-Barma 1998).

**Rey Complex Figure Test**

This drawing and visual memory test (Rey 1995) examines ability to construct a complex figure and remember it for later recall. It measures memory as well as visual-motor organization.

**Digit span test (forward and backward)**

This is a commonly used test of attention, alertness, and mental processing capacity (Wechsler 1998). The examiner reads aloud a series of number sequences. The number sequences become progressively more difficult, the
last being nine digits read aloud. The participant must repeat these number strings forward and backwards.

3.5.4.3 Language

Significant language deficits may be seen in ALS patients with cognitive impairment, particularly in tests of naming and syntactic comprehension. Language deficits noted in studies of ALS have included reduced verbal output (Strong 1999; Bak 2004), deficits in naming of objects (Massman 1996; Abrahams 1997; Robinson 2006), perseverations, echolalia (repetition of words said by other people), stereotypic expressions (Rakowicz 1998) and semantic paraphasias (Rakowicz 1998; Strong 1999). Patients with ALS can have features of progressive non-fluent aphasia, semantic dementia that is often atypical, or both (Caseeli 1993; Doran 1995; Davies 2005).

We used two tests to examine language function.

Boston Naming Test (abbreviated version)

This 60-item picture-naming test measures production aphasia (Kaplan 1983). It examines confrontation naming and represents a measure of object naming from line drawings of both high and low frequency items.

Pyramid and Palm Trees

The Pyramid and Palm Trees test (Howard 1992) consists of 52 triplets of pictures depicting different objects. In this non-verbally based test of associative semantic knowledge the subject is presented with 52 picture triads and asked to indicate which of two possible alternatives (for example, palm or fir tree) is associated with the target (pyramid). This test has previously been used in patients with ALS (Rakowicz 1998) - in that study, patients with cognitive impairment demonstrated lower scores than controls on this test. The Pyramid and Palm Tree was used in the current project as an additional measure in those patients suspected of having semantic impairment i.e. those who had fluent, grammatical speech in the presence of confrontation naming deficits, semantic deficits for words and/or objects (as screened with the Boston Naming Test), surface dyslexia, and relatively spared syntactic comprehension.
3.5.4.4  Visuoperceptual function

Most studies report relative preservation of visuoperceptual function in ALS. A Snellen chart (Snellen 1862) was used to screen for visual impairments in participants to ensure that cognitive deficits were unrelated to such impairment.

3.5.4.5  Mood

Mood in this study was assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983). This self-report 14-item scale measures the states of anxiety and depression without contamination of scores by reports of physical symptomatology. It is valid for both hospital and community-based evaluation. It was used primarily to exclude the possibility that abnormal cognitive profiles may be related to anxiety or depression. Longitudinal assessment of mood was also conducted.

As in previous studies of ALS patients (Abrahams 1997; Abrahams 2000; Abrahams 2005), one item, “I feel slowed down”, was removed from the depression subscale as it was felt that it may be confounded by physical symptoms of ALS. The cut-off values used were thus redefined: 0-4 indicated subjects were not depressed, 5-7 indicated a borderline state and 8-18 indicated depression.

For the anxiety subscale, previously validated measures were utilised: 0 to 7 indicated an absence of anxiety; a score of 8 to 10 was suggestive of the presence of anxiety ("borderline"); and a score of 11 or higher indicated presence (‘caseness’) of anxiety i.e. abnormal.

3.5.4.6  Behaviour

Frontal Systems Behaviour Scale (FrSBe, Grace and Malloy 2001): this self and carer rated questionnaire examines the behavioural features of fronto-striatal dysfunction. Both carers and patients rate the patient's behaviour before and after the onset of the current condition. The 46-item rating scale targets three behavioural subtypes thought to be subserved by the frontal systems, including executive dysfunction, poor planning and sequencing), disinhibition (distractibility, impulsivity), and apathy (poor initiation). Each behavioural syndrome has been theoretically linked to different anatomical circuits within the frontal lobe: apathy has been associated with damage to...
mesial or anterior cingulate pathways; disinhibition and impulsive behaviour is linked with damage to orbital frontal pathways; and impairments in motor planning and executive functions is associated with damage to dorsolateral frontal pathways (Cummings 1993; Paulsen 1996). The reliability of the FrSBe has been demonstrated (Grace 2001) and has been used extensively in patients with ALS (Wooley-Levine 2006; Grossman 2007).

Each item is rated on a 5-point Likert scale. The FrSBe yields a Total score as well as scores for the three subscales. Methods of analysis are discussed in the Statistics section (3.5.3.1) above. Scores are obtained on each scale for premorbid behaviour and current behaviour, allowing measurement of change that occurs after the onset of disease. Caregivers are instructed that their premorbid ratings should reflect the patients’ behaviour as it was for several years prior to the development of ALS-related symptoms.

Previous research has demonstrated that FrSBe scores can distinguish patients with Alzheimer’s disease from those with frontotemporal dementia, Huntington’s disease and Parkinson’s-related dementia (Paulsen 1996, Malloy 2005; Malloy 2007), and can distinguish behaviour pre- and post-frontal lobe injury (Grace 1999).

Behavioural impairment was also defined as per the clinical description of the new consensus criteria (Strong 1999). This categorisation refers to patients who meet partial criteria for ALS-FTD. In other words, such an individual meets at least two non-overlapping supportive diagnostic features from either the Neary criteria (1998) (i.e. decline in personal hygiene and grooming, mental rigidity and inflexibility, distractibility and impersistence, hyperorality and dietary changes, perseverative and stereotyped behaviour, utilization behaviour) and/or Hodges’ criteria (i.e. loss of insight, disinhibition, restlessness, distractibility, reduced empathy or unconcern for others, lack of foresight or planning, impulsiveness, social withdrawal, apathy or loss of spontaneity, reduced verbal output, verbal stereotypes or echolalia, verbal or motor perseveration, poor self care, gluttony, sexual hyperactivity) (Gregory 1999). The presence of two behavioural abnormalities should be supported by at least two sources from among a patient interview/observation, caregiver report, or structured questionnaire / interview. Ideally, both a clinical interview with both the patient and caregiver and a structured, well-validated
questionnaire should be included (see below for recommendations). To diagnose ALSbi, the behavioural changes should not be better explained by a psychiatric condition, a psychological reaction to ALS, a premorbid personality disorder, or be due to the presence of pseudobulbar affect.

3.5.4.7 McGill Quality of Life Questionnaire (Cohen 1995)
This 20 item scale specifically developed to measure quality of life at the end of life.

3.5.4.8 The impact of impaired cognition and / or behaviour in ALS
The clinical impact of cognitive impairment was assessed in the following ways:

1 Competence Assessment. Medical decision-making capacity (MDC), also termed consent capacity, refers to a patient's cognitive and emotional capacity to accept a proposed treatment, to refuse treatment, or to select among treatment alternatives. This study used the Capacity to Consent to Treatment Instrument (CCTI) a conceptually based, reliable, and valid instrument for the assessment of MDC in healthy and cognitively impaired older adults (Marson 1995).

2 Utilization of and compliance with interventions for example non-invasive ventilation – discussed in Chapter Ten.

3 Carer Burden Index (Zarit 1983) – as described in Chapter Six.

3.5.4.9 Self-perceived and Carer Burden
Burden is explored in Chapter Six and the relevant tests (Self-Perceived Burden Scale and Zarit Burden Interview) are described therein.

3.5.5 Progression
The progression of ALS was determined by the performance of three separate evaluations separated by 6-month intervals (Time One and Time Two analysed in this thesis). Although the rapidly fatal nature of the disease prevented 100% follow-up of the entire cohort of patients, follow-up was optimised by home visits to assess patients and their carers. To the best of this author's knowledge, there have been no studies of ALS performed in this manner and it was felt that this approach significantly increased the completeness of follow-up particularly in the later stages of the illness when cognitive impairment was more likely to be apparent. Results for the longitudinal study, the largest of its kind to date, are presented in Chapter Seven.
Chapter 4 A population-based study of Cognitive Impairment in ALS: Results and Discussion

4.1 Participant characteristics

4.1.1 Sample Size

A total of 136 incident ALS patients who fulfilled inclusion criteria were identified to date during the study recruitment period (March 2006-August 2008), roughly reflecting the population-based incidence of ALS over an 18 month period. All patients had been included on the Irish ALS Register and accordingly had met the stringent criteria for "Possible", "Probable" or "Definite" ALS by the El Escorial World Federation of Neurology diagnostic criteria for ALS (Brooks 1994). 3 patients were subsequently excluded from the ALS Register as they were found to have features of an "overlap" syndrome with Parkinsonism (2) and Huntington's Disease (1) (Phukan 2009).

Table 11 provides a breakdown of those who met inclusion criteria for this study.

<table>
<thead>
<tr>
<th>Patients eligible for participation</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruited</td>
<td>87</td>
<td>65</td>
</tr>
<tr>
<td>Died before recruitment</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Declined to participate</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>No response</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Eligible participants</td>
<td>133</td>
<td>100</td>
</tr>
</tbody>
</table>

Of the 19 patients who refused to participate, reasons included being too unwell to undergo neuropsychological testing (n=6); and concerns that diagnosis had not been disclosed to key family members (n=4). No reason was given by 9 patients. 2 patients subsequently agreed to be assessed outside the research protocol, and scored within the normal range on neuropsychological evaluation. Overall comparison between participants and non-participants showed no differences in gender, time from onset to diagnosis, site of onset, and time from onset to time of death or marital status, although those who agreed to participate were slightly younger (63 versus 69 years; p=0.001) (Table 12).
Table 12. Characteristics of participants versus non-participants

<table>
<thead>
<tr>
<th></th>
<th>Participants</th>
<th>Non-participants</th>
<th>P</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>87</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age M (SD)</td>
<td>63 (10.2)</td>
<td>69.4 (10.0)</td>
<td>0.001</td>
<td>Independent t-test</td>
</tr>
<tr>
<td>Gender: Male</td>
<td>62.1%</td>
<td>47.8%</td>
<td>0.16</td>
<td>Chi square</td>
</tr>
<tr>
<td>Site Onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar</td>
<td>25.3%</td>
<td>32.6%</td>
<td>0.5</td>
<td>Chi square</td>
</tr>
<tr>
<td>Spinal</td>
<td>74.7%</td>
<td>67.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time: onset to dx (days)</td>
<td>368.1 (262.2)</td>
<td>357.9 (255.6)</td>
<td>0.83</td>
<td>Independent t-test</td>
</tr>
<tr>
<td>Time: onset to death</td>
<td>864 (223.4)</td>
<td>892.6 (759)</td>
<td>0.86</td>
<td>Independent t-test</td>
</tr>
<tr>
<td>Time: dx to death</td>
<td>504.9 (223.4)</td>
<td>301.7 (207.6)</td>
<td>&lt;0.001</td>
<td>Independent t-test</td>
</tr>
</tbody>
</table>

*Outliers removed
Dx = diagnosis

Eleven patients who fulfilled the El Escorial Criteria for ALS and agreed to participate were subsequently excluded from the study cohort study on the basis of previous stroke (5), psychiatric illness including schizophrenia (2), alcohol dependency (3), and permanent invasive mechanical ventilation (1).

The remaining patients (n=87; 65%) were enrolled in the study.

41 patients participated in a follow-up assessment six months after the initial visit. The results of longitudinal follow-up are discussed in Chapter Seven.

4.1.2 Demographic variables

Table 13 outlines the demographic characteristics of patients and controls.

Table 13. Demographic characteristics of patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=87)</th>
<th>Controls (n=78)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>63.5±10.2</td>
<td>61.2±9.2</td>
<td>0.238</td>
</tr>
<tr>
<td>Sex: M</td>
<td>62.1%</td>
<td>54.5%</td>
<td>0.414</td>
</tr>
<tr>
<td>Sex: F</td>
<td>37.9%</td>
<td>45.5%</td>
<td></td>
</tr>
<tr>
<td>Handedness: Right</td>
<td>93.1%</td>
<td>87%</td>
<td>0.295</td>
</tr>
<tr>
<td>Handedness: Left</td>
<td>6.9%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Site onset: Bulbar</td>
<td>25.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site onset: Spinal</td>
<td>74.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.7±3.29</td>
<td>13.4±3.45</td>
<td>0.002</td>
</tr>
<tr>
<td>Working outside home</td>
<td>18.4%</td>
<td>45.5%</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>
The population under study was typical of patients with ALS. 16 participants (18.4%) were still working outside the home. 6 patients had a family history of ALS: 4 of these had first degree relatives with ALS. All participants were Caucasian.

Controls were matched for age and gender (Table 13) and adjustments were made in the analysis where necessary to allow for differences in years of education. Although there was a significant difference in depression between these groups ($p=.01$ Kruskal-Wallis Test), neither group met criteria for moderate or severe depression. The mean score on the HADS depression scale was 4.1 (SD 4.1) for patients and 1.9 (SD 2) for controls.

The mean score on the HADS anxiety scale was 6.5 (SD 4.4) for patients and 5.9 (SD 3.8) for controls; There was no significant difference between the patients and controls on anxiety scores: $p=.2$ (Kruskal-Wallis Test).

### 4.1.3 Clinical variables

The mean score on the ALS functional rating scale (ALSFRS) was 35.31. Mean time from diagnosis to research visit was 222.1 days (7.1 months). Mean time from onset of symptoms to research visit was 677.7 days (21.8 months). All but 11 patients were on Riluzole. 26 patients were on low dose psychotropic medications, most commonly SSRIs and amitriptyline for emotional lability.

Four patients had low oxygen saturation levels (<95mmHg) and 2 of these had mild concomitant elevated carbon dioxide levels (>6kPa). However, none had clinical evidence of hypoxia or hypercapnia. Exclusion of data from these patients in the final analysis did not affect the dataset. Three patients were using non-invasive ventilation and had normal saturations at the time of study.

### 4.2 Cognitive and Behavioural Impairment

Cognitive and behavioural results for patients were compared to those of age-matched controls. Between-groups comparison of means scores of ALS patients were also compared to matched controls. Section 4.2.1 outlines the patterns of cognitive impairment identified.
Section 4.2.2 uses the recently published consensus criteria for frontotemporal cognitive and behavioural syndromes in ALS (Strong 2009; Appendix 2) to define groups as having pure ALS, cognitive impairment and/or behavioural impairment or dementia.

### 4.2.1 Patterns of cognitive impairment

For all of the comparisons between patients and controls, a one-way between-groups analysis of covariance was conducted to compare the control participant means and the ALS participant means on each test. The independent variable was the grouping (group 1: ALS patients, group 2: control participants) and the dependent variable was the neuropsychological test in question. Participants' scores on the (Wechsler Test of Adult Reading) WTAR were used as the covariate in this analysis to ensure that differences in IQ between patients and controls did not act as a confounding factor (Table 14).

Preliminary checks were conducted to ensure that there was no violation of the assumptions of normality linearity, homogeneity of variance, homogeneity of regression slopes, and reliable measurement of the covariate.

**Table 14. Mean test scores: patients versus controls**

<table>
<thead>
<tr>
<th>Test</th>
<th>ALS Participants Adjusted Mean (SD)</th>
<th>Controls Adjusted Mean (SE)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VFI Written*</td>
<td>26.7 (4.7)</td>
<td>13 (4.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>VFI spoken</td>
<td>23.1 (8.4)</td>
<td>14.4 (9.8)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Category fluency*</td>
<td>16.9 (0.66)</td>
<td>20.6 (0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroop Colour Word Standardised Percentile*</td>
<td>34.3 (3.7)</td>
<td>46.5 (3.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Brixton Spatial Anticipation Test</td>
<td>5.6 (0.23)</td>
<td>5.1 (0.23)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total Digit Span</td>
<td>11.2 (0.31)</td>
<td>11.5 (0.3)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Backwards Digit Span*</td>
<td>11.5 (0.31)</td>
<td>11.2 (0.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Logical Memory I Recall Total Score*</td>
<td>9.1 (0.37)</td>
<td>11.5 (0.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Logical Memory II Recall Total Score*</td>
<td>8.9 (0.32)</td>
<td>12.3 (0.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

98
<table>
<thead>
<tr>
<th></th>
<th>ALS Participants Adjusted Mean (SD)</th>
<th>Controls Adjusted Mean (SE)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logical Memory Percent Retention*</td>
<td>8.9 (0.33)</td>
<td>12.2 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VPA I Recall Total Score</td>
<td>9.5 (0.34)</td>
<td>10.9 (0.32)</td>
<td>0.5</td>
</tr>
<tr>
<td>VPA II Recall Total Score*</td>
<td>9.7 (0.33)</td>
<td>11.1 (0.31)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>VPA Percent Retention*</td>
<td>9.6 (0.34)</td>
<td>11.1 (0.33)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RCFT Copy Percentile</td>
<td>10.4 (0.8)</td>
<td>12.1 (0.64)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>RCFT Immediate Recall</td>
<td>44.5 (1.9)</td>
<td>47.6 (1.5)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>RCFT Delayed Recall</td>
<td>43.8 (1.9)</td>
<td>45.3 (1.5)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CVLT Free Recall Total*</td>
<td>44.5 (1.4)</td>
<td>52.9 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVLT List B Free Recall*</td>
<td>-0.72 (0.1)</td>
<td>-0.21 (0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVLT Short Delay Free Recall Total*</td>
<td>-0.68 (0.12)</td>
<td>0.02 (0.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVLT Short Delay Cued Recall Total</td>
<td>-0.9 (0.1)</td>
<td>0.03 (0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVLT Long Delay Cued Recall Total</td>
<td>-0.8 (0.2)</td>
<td>-0.1 (0.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*significant

**4.2.1.1 Executive Function**

After adjusting for WTAR scores, there was a significant difference between the ALS participants and control participants on:

- Written Verbal Fluency Index Score \([F(1, 111)=4.2, p<.05, \text{partial eta squared}= .04]\). n=70.
- Category Fluency \([F(1, 19)=14.4, p<.001, \text{partial eta squared}= .11]\).
- Stroop Colour Word Standardised Percentile, n=69; and
- Backwards Digit Span \([F(1, 135)=3.9, p<.05, \text{partial eta squared}= .03]\). n=69.

There was no significant difference between the ALS participants and control participants on Spoken Verbal Fluency Index Score \([F(1, 13)=.4, p>.05, \text{partial eta squared}= .03]\), n=9; Brixton Spatial Anticipation Test \([F(1, 134)=2.4, p>.05, \text{partial eta squared}= .02]\), n=86; and Total Digit Span Forwards and Backwards \([F(1, 135)=.43, p>.05, \text{partial eta squared}= .003]\), n=69.
4.2.1.2 Memory

After adjusting for WTAR scores, there was a significant difference between the ALS participants and control participants on:

- Logical Memory I Recall Total Score \([F(1, 136)=.22.25, p<.001, \text{partial eta squared}=.14]\), \(n=66\).
- Logical Memory II Recall Total Score \([F(1, 136)=57.4, p<.001, \text{partial eta squared}=.3]\), \(n=66\).
- Logical Memory Percent Retention \([F(1, 136)=49, p<.001, \text{partial eta squared}=.27]\), \(n=66\).
- Verbal Paired Associates I Recall Total Score \([F(1, 132)=7.8, p<.05, \text{partial eta squared}=.06]\), \(n=65\).
- Verbal Paired Associates II Recall Total Score \([F(1, 132)=6.4, p<.05, \text{partial eta squared}=.07]\), \(n=65\).
- Verbal Paired Associates Percent Retention \([F(1, 131)=8.8, p<.05, \text{partial eta squared}=.06]\), \(n=65\).
- California Verbal Learning Test Free Recall Total \([F(1, 132)=19.3, p<.001, \text{partial eta squared}=.13]\).
- California Verbal Learning Test List B Free Recall \([F(1, 132)=8.8, p<.05, \text{partial eta squared}=.06]\), \(n=63\).
- California Verbal Learning Test Short Delay Free Recall Total \([F(1, 132)=16.3, p<.001, \text{partial eta squared}=.11]\), \(n=63\).
- California Verbal Learning Test Short Delay Cued Recall Total \([F(1, 132)=23.6, p<.001, \text{partial eta squared}=.15]\), \(n=66\).
- California Verbal Learning Test Long Delay Cued Recall Total \([F(1, 132)=17.7, p<.001, \text{partial eta squared}=.12]\), \(n=66\).

After adjusting for WTAR scores, there was no significant difference between the ALS participants and control participants on Verbal Paired Associated Learning Slope \([F(1, 132)=.46, p=.5, \text{partial eta squared}=.003]\), \(n=65\); Rey Complex Figure Test Copy Percentile \([F(1, 119)=2.8, p>.05, \text{partial eta squared}=.02]\), \(n=57\); Rey Complex Figure Test Immediate Recall \([F(1, 119)=1.6, p>.05, \text{partial eta squared}=.01]\), \(n=57\); Rey Complex Figure Test Delayed Recall \([F(1, 116)=.4 p>.05, \text{partial eta squared}=.003]\), \(n=57\).
4.2.1.3 Language
As defined by the Neary criteria (1998) two patients (2.3%) had non-fluent progressive aphasia and three (3.4%) had semantic dementia. Patients mean scores (23.09, SE 0.47) on the Boston Naming Test (confrontation naming) were significantly lower than those of controls (24.7, SE 0.46), n=87.

4.2.2 Diagnoses as per consensus criteria
Using the recently published consensus criteria for frontotemporal cognitive and behavioural syndromes in ALS (Strong 2009; Appendix 2), participants were allocated to one of 5 diagnostic categorizations: ALS-FTD, ALSci, ALSbi, ALS-comorbid dementia, and ALS. Patients who met criteria for both ALSci and ALSbi were allocated to the ALS-comorbid dementia category.

4.2.2.1 ALS-FTD
The diagnosis of ALS-FTD in this study was based on patient interview, neurological examination, neuropsychological assessment, and collateral report after screening for depression. All diagnoses were formulated following a consensus meeting between the research fellow (JP), consultant neuropsychologist (NP) and consultant neurologist (OH). 16 patients (18%) met Neary criteria for frontotemporal dementia. Eleven of these had frontal variant FTD; a further 2 (2.3%) had non-fluent progressive aphasia and 3 (3.4%) had semantic dementia.

4.2.2.2 ALSci
Patients allocated to this category demonstrated cognitive impairment on standardised neuropsychological testing (to include at least one executive measure with or without a measure of memory; see section 3.5.3.1) at or below the 5th percentile, compared to age- and education matched controls. 13 patients (15%) fulfilled the criteria for ALSci. Note that this figure does not include the patients who had both ALSci and ALSbi who were allocated to the ALS-Comorbid dementia group.

4.2.2.3 ALSbi
As per the consensus criteria, patients diagnosed with ALSbi meet at least two non-overlapping supportive diagnostic features from either the Neary criteria
(1998) and/or Hodge's criteria (Gregory 1999). 7 (8%) patients in our cohort were diagnosed with ALSbi.

However, using the FrSBe scale, which was applied to a subset of 42 patient/carer pairs, 13 patients met these criteria for ALSbi, by deviating from one or more of the subscales (Apathy, Executive Dysfunction and Disinhibition) and total “Before” norms by two standard deviations.

Of the six patients who qualified as ALSbi as per consensus criteria, only three of these met the criteria for ALSbi as per FrSBe. Conversely of the thirteen patients who met criteria for ALSbi as per FrSBe, only four met criteria for ALSbi as per consensus criteria.

Apathy was the most common behaviour seen in ALS patients (as defined by both carers and patients), followed by executive dysfunction and disinhibition. Clinically significant behavioural impairment has also been defined by a T score of greater than 65; i.e. 1.5 standard deviations above the mean (Grace 2001, Mosnik 2006) (Table 15).

**Table 15.** Clinically significant behavioural impairment as measured by FrSBe score of T>65

<table>
<thead>
<tr>
<th>Premorbid</th>
<th>T&lt;65</th>
<th>T&gt;65 (clinically significant)</th>
<th>Post-ALS diagnosis</th>
<th>T&lt;65</th>
<th>T&gt;65 (clinically significant)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Self-after</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-before</td>
<td>95.2%</td>
<td>4.8%</td>
<td>Apathy</td>
<td>52.4%</td>
<td>47.6%</td>
</tr>
<tr>
<td>Apathy</td>
<td></td>
<td></td>
<td>Carer-after</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>92.9%</td>
<td>7.1%</td>
<td>Apathy</td>
<td>54.8%</td>
<td>45.2%</td>
</tr>
<tr>
<td>Carer-before</td>
<td></td>
<td></td>
<td>Self-after</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apathy</td>
<td>83.3%</td>
<td>16.7%</td>
<td>Disinhibition</td>
<td>88.1%</td>
<td>11.9%</td>
</tr>
<tr>
<td>Self-before</td>
<td>90.5%</td>
<td>9.5%</td>
<td>Carer-after</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disinhibition</td>
<td></td>
<td></td>
<td>Disinhibition</td>
<td>76.2%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Carer-before</td>
<td>90.5%</td>
<td>9.5%</td>
<td>Self-after</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive Function</td>
<td></td>
<td></td>
<td>Executive Function</td>
<td>76.2%</td>
<td>23.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carer-after</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive Function</td>
<td>88.1%</td>
<td>11.9%</td>
<td>Executive Function</td>
<td>76.2%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Self-before</td>
<td>85.7%</td>
<td>14.3%</td>
<td>Self-after</td>
<td>69%</td>
<td>31%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carer-before</td>
<td>92.9%</td>
<td>7.1%</td>
<td>Carer-after</td>
<td>69%</td>
<td>31%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Furthermore, using the FrSBe scale, a strong correlation was noted between self and carer-reported apathy change ($r=.62, n=31, p<.001$) and between self and carer-reported executive dysfunction change ($r=.25, n=31, p>.001$).
However, there was no correlation between self and carer-reported disinhibition change, \((r=.03, \, n=31, \, p>.001)\) (Spearman’s Rank Order Correlation Coefficient). This suggests that patients with ALS may have decreased awareness into the presence of disinhibition.

We found no significant difference in ALSFRS bulbar scores or ALSFRS total scores for those who were cognitively impaired (independent T test \(M=9.07, \, SD=9.22; \, t(83)=-.184, \, p=.85\); Yates’ Correction for Continuity; \(p=1\) or \(p>.05\)) or those with behavioural impairment (Chi-square Test for Independence; Yates’ Correction for Continuity; \(p=.964\) or \(p>.05\)). Cognitive and behavioural impairment was also unrelated to functional impairment as measured by ALS, or to duration of illness (Table 16). A significant difference was seen between anxiety and depression scores between those with ALSbi and those without ALSbi; however HADS scores did not meet cut-off scores for clinical depression or anxiety. There was no significant difference in impairment between the ALS patients who used non-invasive ventilation \((n=19)\) and those who did not use non-invasive ventilation \((n=68)\) (Chi-square Test for Independence; Yates’ Correction for Continuity; Asymp. Sig.=.42 or \(p>.05\)).

**Table 16. Correlates of behavioural impairment.**

<table>
<thead>
<tr>
<th>Test</th>
<th>ALSbi</th>
<th>ALSbi without behavioural impairment</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean SD</strong></td>
<td><strong>Mean SD</strong></td>
<td></td>
<td>Independent samples T test</td>
</tr>
<tr>
<td>Time since onset of ALS</td>
<td>778.4 574.8</td>
<td>621.7 452.3</td>
<td>(t(85)=1.4, , p=.166)</td>
</tr>
<tr>
<td>Time since diagnosis of ALS</td>
<td>247.22 182.8</td>
<td>209 182.2</td>
<td>Independent samples T test (t(85)=.93, , p=.356)</td>
</tr>
<tr>
<td>ALSFRS</td>
<td>35.87 7.7</td>
<td>35 8.8</td>
<td>Independent samples T test (t(85)=0.45, , p=.66)</td>
</tr>
<tr>
<td>Anxiety (HADS)</td>
<td>8.7 4.74</td>
<td>4.8 3.13</td>
<td>Independent samples T test (t(41.4)=3.6, , p=.001)</td>
</tr>
<tr>
<td>Depression (HADS)</td>
<td>6.3 4.8</td>
<td>2.3 2.2</td>
<td>Independent samples T test (t(33.6)=3.9, , p&lt;.001)</td>
</tr>
</tbody>
</table>

Regarding the relationship between ALSci and ALSbi, a significant correlation was noted between the tests of executive dysfunction (Digit Span and Stroop scores) and the Disinhibition subscale of the FrSBe. No correlation was noted between verbal fluency and any of the FrSBe subscales (not shown).
Moreover, a large number of patients with ALSbi (as defined by either change in FrSBe score or by clinical consensus criteria) also had impaired cognition. This ranged from 45% as per FrSBe to 86% for those with ALSbi as defined by the consensus criteria. (Table 17)

<table>
<thead>
<tr>
<th>Table 17.</th>
<th>Comparison of those with ALSbi (either definition – FrSBe 2SDs change or clinical consensus criteria) depending on whether cognition is intact or not.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Intact cognition (%)</td>
</tr>
<tr>
<td>ALSbi - 2 SDs Self</td>
<td>11</td>
</tr>
<tr>
<td>ALSbi - 2 SDs Carer</td>
<td>13</td>
</tr>
<tr>
<td>ALSbi-consensus</td>
<td>7</td>
</tr>
</tbody>
</table>

4.2.2.4 ALS-comorbid dementia

This categorisation refers to those patients with ALS and a dementia that is not typical of FTD e.g. Alzheimer’s disease, vascular dementia, and mixed dementia. Criteria to define other dementias included Diagnostic and Statistical Manual of Mental Disorders–IV criteria (American Psychiatric Association 1994) and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria for AD (McKhann 1984) as appropriate. Two patients had generalised dementia (severe cognitive and/or behavioural changes that did not meet Neary criteria for fvFTD), and three fulfilled criteria for Alzheimer’s dementia and/or vascular dementia. Eight patients who had both ALSbi and ALSci were also assigned to this category.

4.2.2.5 ALS

Of the total cohort of 87 patients, 32 (37%) of patients had no evidence of cognitive or behavioural impairments. These patients participated in a longitudinal study (Chapter Seven) to establish if ALSci, ALSbi or dementia developed during the course of ALS progression.

There was no difference between the subgroups (ALS, ALSci, ALSbi, ALS-FTD and ALS-comorbid dementia) with respect to age \([F(4, 82) = .61, p = .66]\), mean number of days since diagnosis \([F(4, 82) = 1.17, p = .33]\) or mean number of days since onset of symptoms \([F(4, 82) = 1.11, p = .36]\); (one-way between-groups analysis of variance).
Table 18. Incidence of cognitive impairment, behavioural impairment and dementia in a population-based cohort of patients with ALS

<table>
<thead>
<tr>
<th>ALS Group</th>
<th>n</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTD*</td>
<td>16</td>
<td>18%</td>
</tr>
<tr>
<td>ALS-comorbid dementia**</td>
<td>13</td>
<td>15%</td>
</tr>
<tr>
<td>ALSci</td>
<td>13</td>
<td>15%</td>
</tr>
<tr>
<td>ALSbi***</td>
<td>13</td>
<td>15% / 31%</td>
</tr>
<tr>
<td>No abnormality</td>
<td>32</td>
<td>37%</td>
</tr>
<tr>
<td>Total</td>
<td>87</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Includes both behavioural and language variants
**Includes 8 patients with concomitant ALSci and ALSbi, and those with dementias other than FTD
*** As defined by FrSBe. 42 carers filled out FrSBe questionnaires. 31% refers to 13 patients of a total cohort of 42; this figure would be 15% if all 87 participants were included but this was not the case due to disability or overt dementia in patients, or time limitations in patients and/or carers.

4.3 Discussion

This study presents the results of the first large-scale population-based cross-sectional study of cognition and behaviour in ALS. A battery comprising validated standardized neuropsychological assessment was used, the cohort was stratified according to recently developed consensus diagnostic criteria (Strong 2009).

4.3.1 Hypothesis One: The frequency and evolution of cognitive decline in ALS in a population based cohort.

The Primary Hypothesis of this project tested the frequency and evolution of cognitive decline in ALS in a population based cohort.

4.3.1.1 Frequency of cognitive impairment

It was hypothesized that cognitive decline primarily affecting the executive domain would be present in up to 50% of the Irish ALS population, that a smaller number of patients would have overt dementia, and that a proportion of patients with mild cognitive decline would progress to develop full-blown frontotemporal dementia. This hypothesis was explored by (a) using the consensus criteria (Strong 2009) and (b) examining patterns of cognitive impairment.
Sixteen patients (18%) of this population-based sample of ALS patients (n=87) had frontotemporal dementia, predominantly frontal variant FTD. 13 patients (15%) had cognitive impairment (ALSci) affecting executive function, memory and language; 13 patients (15%) had behavioural impairment alone (ALSbi); 8 patients (9%) had both ALSci and ALSbi concomitantly, and 37% of patients did not have cognitive or behavioural impairment.

Our findings of ALS-FTD (18%) are roughly similar to those previously reported from tertiary referral clinics. However, 24% of patients in the current analysis had cognitive impairment (with or without behavioural impairment but not meeting criteria for ALS-frontotemporal dementia) which is slightly less than the findings of one of the largest studies of 279 consecutive patients who attended an ALS clinic; the authors detected cognitive impairment in 47% of patients, with approximately 15% of meeting criteria for dementia (Ringholz 2005) i.e. 32% had cognitive impairment without dementia.

The findings of this study are more representative of ALS patients as a whole because it used validated standardized neuropsychological assessment guided by the recently developed consensus criteria (Strong 2009), accommodated for bulbar and limb disability, and was population-based; studies solely involving patients who attend multidisciplinary clinics tend to recruit patients who are younger with a longer duration illness and an increased chance of having familial ALS and are thus not representative of the population as a whole (Lee 1995; Traynor 2003; O'Toole 2007).

4.3.1.2 Patterns of cognitive impairment

Compared to age-matched controls and controlling for differences in IQ, patients had lower scores on a number of executive measures including verbal fluency (written and category), cognitive inhibition (Stroop), attention (backwards digit span) and encoding (Logical Memory I). However, verbal memory was also affected (Logical Memory II, Verbal Paired Association, California Verbal Learning Test) as was confrontation naming. There were no differences in visual memory (Rey Complex Figure Test) between patients and controls.

Executive dysfunction has been consistently noted previously in ALS (see Chapter Two). In particular the significant decrease in backwards digit span (i.e. impaired attention, alertness, mental processing capacity, working
memory) was observed in a recent study that examined endogenous event-related potential (ERPs) in 20 non-demented ALS patients and 20 controls (Pinkhardt 2008). ALS patients showed a distinct decrease of the fronto-precentral negative difference wave (Nd), i.e., the main ERP indicator of selective attention.

The memory deficits in ALS are usually expected to be related to executive dysfunction i.e. similar to encoding deficits seen in FTD. However, this study reports a range of memory deficits that also involved retrieval and retention which may signal more extensive temporal lobe involvement in ALS. Neuropathological studies (Kato 1993; Okamoto 1998) and serial MRIs (Kato 1993) have provided some evidence for primary pathology in the temporal lobes and limbic system of non-demented ALS patients. However, the role of temporal pathology in ALS remains controversial, since the reported alterations are non-specific, limited to subgroups and difficult to distinguish from age-related changes (Schreiber 2005).

In addition, severe amnesia at presentation in FTD is commoner than previously thought. A retrospective case review of a large multicentre neuropathological series of 71 patients with FTD identified eight (11%) in whom memory loss was either the sole or leading complaint, supported by neuropsychological evidence of genuine memory deficits in each case (Graham 2005). The authors suggest that memory impairment in FTD relates not only to frontal and temporal atrophy but also, in some cases, to additional bilateral hippocampal involvement as additionally seen on neuroimaging (de Pol 2005).

Whether this pertains to ALS is uncertain, but the emerging possibility of temporal lobe / amygdala involvement (Papps 2005; Schmolck 2007) suggests that solely depending on executive tests may underestimate ALSci.

The observation of semantic dementia and non-fluent progressive aphasia in our cohort is unsurprising given that language networks are involved in clinical and neuroimaging studies of ALS patients (Caseeli 1993; Doran 1995; Abrahams 2000; Davies 2005). Language dysfunction may also have partially contributed to the decreased verbal fluency seen in this analysis. This possibility is supported by an fMRI investigation that demonstrated abnormal activation of inferior frontal gyrus and Broca’s area during verbal fluency and naming tasks in sporadic ALS patients without aphasia or dementia (Abrahams 2004).
A trend towards impaired confrontation naming was observed in patients compared to controls. Confrontation naming differs from fluency procedures in that the responses (words to be retrieved) are more fully determined by external stimuli (pictures of objects) and thus less dependent on executive function (Abrahams 2004). The present findings of a trend towards impairment in confrontation naming are consistent with a functional imaging study of 21 ALS patients which involved a confrontation naming fMRI task (Abrahams 2004). The authors discovered impaired activation in less extensive prefrontal regions, including the inferior frontal gyrus and regions of the temporal, parietal and occipital lobes. Other studies have also reported naming impairments (Massman 1996; 1998; Strong 1999; Robinson 2006).

We identified more subtle language deficits (not formally described within the consensus criteria) consistent with findings from other studies that have reported reduced verbal output (Strong 1999; Bak 2004), perseverations, echolalia, stereotypic expressions (Ferrer 1991; Rakowicz 1998) and semantic paraphasias e.g., sock for glove, or rabbit for squirrel (Rakowicz 1998; Strong 1999). Additionally, two patients themselves reported distress at no longer being able to write Christmas cards due to inability to spell (despite having previously been "good spellers"); such deficits were independent of physical disability, educational status, and were corroborated by family members. Whether these language deficits, particularly reduced verbal output, form a continuum with aphasia remains to be explored.

ALSci was not found to be more common in bulbar-onset patients than spinal-onset patients as has previously been reported (David 1986; Neary 2000; Schreiber 2005; Ringholz 2005). This conflicting result might be explained by the fact that this was a population-based study that included a broad range of patients with bulbar involvement; also bulbar scores in this analysis (calculated from the three speech and swallowing questions of the ALSFRS) rather than site of onset alone.

We also postulated that mild cognitive decline would progress to develop full-blown frontotemporal dementia in some patients. This hypothesis is explored in Chapter Seven.
4.3.2 Hypothesis Two: Behavioural change and patient insight in ALS

It was predicted that in addition to cognitive impairment in patients with ALS, behavioural changes would also be detected. Given the overlap between ALS and frontotemporal dementia (see Chapter Two), one would expect the changes in ALS to be consistent with those described by the Neary criteria (1998).

4.3.2.1 Incidence of behavioural impairment

One of the key observations from our study relates to the classification of ALSbi. The prevalence of ALSbi in our cohort, as measured by the FrSBe, was found to be 31% (13 of 42 patient / carer pairs). However, using the consensus criteria, only 7 patients (8%) patients fulfilled the diagnostic criteria for ALSbi. Furthermore, there was limited overlap between the two sets of defining criteria. Of the 6 patients who qualified as ALSbi according to the consensus criteria, only 3 met the criteria for ALSbi according to the FrSBe. Conversely of the 13 patients who had ALSbi according to the FrSBe criteria, only 4 met the ALSbi consensus criteria.

This discrepancy could be explained by a number of factors. Firstly the FrSBe paradigms do not take into account the physical disability or the terminal nature of ALS, and accordingly may be over-sensitive to pathological behavioural change (Grossman 2007; Strong 2009). For example, question number 1 ('Speaks only when spoken to') and number 46 ('Starts conversations spontaneously') may be biased for those who suffer from ALS-related dysarthria. However we tried to counter this difficulty by having a research assistant administer all carer-rated FrSBes and we measured new onset change by defining the latter as a two standard deviation in T score. Also there was no significant difference between ALSFRS for patients with pure ALS and for patients with behavioural and / or cognitive impairment.

In addition, the Neary supportive criteria may have potentially underestimated the incidence of ALSbi; strict application of the Neary criteria may underrate the prevalence of behavioural variant (frontal) FTD (Piguet 2009) and the same underestimation may apply to ALSbi.
Finally the disparity of ALSbi prevalence between the two methods used might have been due to the fact that the number of valid FrSBe questionnaires returned was 42 due to disability or overt dementia in patients, or time limitations in patients and carers. It is possible that carers who had observed behavioural changes in their relative may have been more likely to fill in the FrSBe.

Behavioural impairment, as defined by both criteria, was unrelated to duration of illness and site of ALS onset; although depression and anxiety scores as measured by the HADS were significantly different in the presence or absence of ALSbi, these scores did not meet criteria for moderate or severe mood disturbance. This confirms that behavioural changes do not simply represent an adjustment process or reaction to the diagnosis of ALS.

This is supported by longitudinal analysis demonstrating that these behavioural changes became more prominent over time in a subset of patients even with improvement / stability of mood (Chapter Five; Chapter Seven).

65.5% (n=57) were completely behaviourally intact according to the criteria of 2SD below the control norm and a score of greater than 65 on the FrSBe subscales as well as absence of FTD.

How do our estimates of behavioural impairment compare to other studies? Comparison is challenging since varying methodologies have been used, often in clinic-based cohorts. This study even found widely different rates of behavioural impairment when different definitions were used. Murphy and colleagues (2007), found 5% of their sample of ALS patients presented with FTLD whilst 22% demonstrated behaviour impairment as defined by a score of 3 on two or more domains of the caregiver rated Neuropsychiatric Inventory (Cummings 1994). One study (Woolley-Levine 2006) also defined behavioural impairment as two standard deviations change from premorbid levels on a caregiver rated FrSBe subscale or total scale. 58% of patients in this study without cognitive impairment had behavioural impairment; the most prevalent area of behaviour change again was also apathy. Cognitive impairment and behavioural impairment was found to co-occur in 25% of participants.
4.3.2.2 Patterns of behavioural impairment

Caregivers reported that 45.2% patients had clinically significant apathy. Disinhibition (23.8%) and executive function (23.8%) were also prominent. A previous study of 72 caregivers of patients with various dementia subtypes reported that apathy was less burdensome to caregivers than disinhibition, possibly since more passive behaviours are associated with apathy (Davis 2007). Others have noted that apathy scores are predictive of performance on activities of daily living (Norton 2001) and that higher FrSBe Disinhibition and Executive scores are more likely to be associated with caregiver burden (Rymer 2002; Davis 2007).

Our observation of a high prevalence of apathy in ALS contrasts with patterns of behavioural impairment in patients with pure frontotemporal dementia, who tend to show dramatic changes in disinhibition (Malloy 2007). However, it must be noted that the FrSBe disinhibition scale includes behaviours that might be missed because of bulbar involvement and limb disability (e.g. swearing, or childlike behaviours), and that on this basis disinhibition may be under-reported. Spinella et al (1994; 2005) have demonstrated that disinhibition and executive dysfunction are associated with polysubstance abuse, binge eating, and difficulty delaying gratification in simulated gambling tasks. Again, the disability of ALS may preclude some of these behaviours but we have observed binge eating and gambling in several of our study patients. These behavioural changes were independent of mood and physical disease parameters, suggesting that they are due to an underlying organic neurodegeneration (Grossman 2007).

4.3.2.3 Patient insight

It was hypothesised that patient and carer reports of patient behaviour would differ, indicating a deficit of awareness in some patients with cognitive impairment.

The absence of correlation between self and carer-reported disinhibition is suggestive of patients' diminished awareness of the presence of disinhibition (or perhaps carers' overestimation of it). However comparing patient's self-rating with a proxy response bears crucial psychometric limitations such as treating ordinal data as if continuous data and simply adding all items to a
total score and disparate views and interpretations between patients and
carers on individual questions (Chan 2008). Comprehensive models of
awareness are reviewed in O’Keeffe (2007). Nonetheless if such loss of insight
is present in some patients with ALS it could contribute to increased stress and
caregiver burden, poor patient–caregiver interaction, poor compliance with
medication, and performance of dangerous or difficult activities (McGlynn
1989; Hutchinson 1997; Seltzer 1997; Cotrell 1999).

4.3.2.4 Correlation of cognitive impairment with behavioural impairment
Cognitive impairment has been hypothesized to correlate with behavioural
impairment (Grossman 2007; Murphy 2007). The relationship between FrSBe
subscales and the verbal fluency index was accordingly examined. No
correlation was found even though it had been expected that the executive
subscales of the FrSBe would correlate with verbal fluency – the latter being
classically described as an executive measure. The lack of correlation may
relate to the FrSBe executive measure and VFI being independent and
dissociated; i.e. one is not a surrogate measure of the other. The absence of
correlation could also be attributable to the large standard deviation seen in
VFI scores as well as loss of power. Finally, the disparity might reflect
concomitant underlying language impairment in those with progressive verbal
fluency deficits.

Conversely, a correlation was noted between tests of executive function (e.g.
digit span, Stroop scores) and FrSBe-Carer Executive and Disinhibition
subscales. This correlation of impaired performance on executive
neuropsychological measures and behavioural impairment lends further
support to the association between behavioural and cognitive impairment. It
also suggests that the reported impaired executive function on
neuropsychological testing may be indicative of how carers are affected in
their daily routine.

A substantial number of patients with ALSbi (as defined by either change in
FrSBe score or by clinical consensus criteria) also had impaired cognition -
45% as per FrSBe to 86% for those with ALSbi as defined by the consensus
criteria.
Premorbid levels of apathy, disinhibition and executive dysfunction were evaluated through the self-rated and caregiver ratings on the FrSBe. These can be subject to a "halo effect," whereby current behavioural disturbances influence retrospective ratings of premorbid behaviour (Malloy 2007). As measured by a T score of >65, carers rated elevated clinically significant premorbid behavioural impairment in 7.1% to 11.9% of patients. These elevated premorbid ratings may have occurred since behavioural changes can precede the diagnosis of ALS or because a characteristic personality profile prevails in ALS patients (Brown 1970; Grossman 2006). Hence, we used a change score of 2 standard deviations (compared to premorbid levels) to be certain that we were measuring new onset behavioural impairment.

But not all patients had behaviour change (37%). Gibbons et al (2008) have suggested that a spectrum of behavioural change exists - extremes where some are free of behavioural changes, others have prominent impairment, and the remainder has more subtle changes. This theory has yet to be confirmed and would require neuroimaging and post-mortem studies in our patients to evaluate it further.

4.4 Limitations

65.4% of 133 eligible patients were enrolled. Participants and non-participants demonstrated no differences in gender, time from onset to diagnosis, site of onset, and time from onset to time of death. Participants did have a higher mean age than non-participants. We cannot definitively ascertain that those who refused to participate may have had early insight into their cognitive / behavioural changes and opted out on that basis. All studies of ALS and cognition to date have faced problems of presenting patients with lengthy test batteries and ensuing patient fatigue. We tried to circumvent this by using as a concise test battery and taking breaks during testing as required.

The recently published consensus criteria are subject to limitations. ALSbi and ALSci are not mutually exclusive as demonstrated by the overlap in this study. The consensus guidelines state that it is important to recognize that patients suffering from apathy will have poor motivation and hence perform poorly, particularly on demanding tests of executive functions. This raises the risk of
misdiagnosis of concurrent ALSci and ALSbi. Patients may also change diagnostic categories as the disease progresses (Strong 2009).

A number of patients who met criteria for ALSci also had ALS-FTD. The difficulties of using two executive tests to define ALSci, the limitations of behavioural questionnaires such as the FrSBe, and the possibility of the Neary criteria underestimating FTD are discussed above. In addition, some evidence now points to hippocampal involvement in ALS (Kato 1993, Okamoto 1998; Papps 2005, Schmolck 2007), the findings of memory changes in this study merit further investigation. Solely depending on executive tests may underestimate cognitive impairment in ALS.

4.5 Implications and Future Research

Evaluation of cognitive and behavioural impairment in ALS has proved challenging because of the lack of standardised test batteries, varying modes of statistical analysis, and selection bias. The population-based study was conducted at an opportune time following the publication of consensus criteria, allowing us to construct a validated neuropsychological and behavioural test battery, stratify patients accordingly, and identify areas of the guidelines that require clarification.

63% of patients had cognitive and / or behavioural impairment ranging from mild deficits in executive, memory and language domains to overt dementia.

We compared the consensus criteria’s definition of ALS behavioural impairment to the self-rated measure of the FrSBe. These methods provided disparate results with little overlap; it is possible that the self-report measures may be over-sensitive to behavioural change whilst the consensus criteria underestimate it. There was also significant overlap between cognitive and behavioural impairment (seen in up to 86% of patients) which emphasises that classification of patients into cognitive or behavioural impairment subgroups, whilst useful in the research setting can be difficult to apply to clinical practice.

Memory deficits were more prevalent than previously expected and hence this study supports the concept that encoding is associated with frontal-subcortical circuits and that temporal pathology in ALS patients is more common that perceived heretofore. Omitting measures of memory may thus underestimate ALSci.
The importance of cognitive impairment in ALS is clear. Executive functions facilitate problem solving; thus deteriorating cognitive or executive function could compromise capacity to make decisions about health care or financial circumstances, capacity to use and comply with interventions and the ability to engage competently in end-of-life decisions (Phukan 2007). The impact of cognitive impairment on psychological well-being, burden, and capacity is discussed in future chapters. Accurate knowledge of the frequency and risk of cognitive impairment in patients with ALS is of critical importance for patients and caregivers, for disease management, and for service development.

Behavioural impairment has equally wide-reaching ramifications for patient care, decision-making and capacity. These changes are consistent with the stories we hear from caregivers every day. They report that their loved ones are less motivated and likely to initiate activities (independent of mood and disability) and more likely to be frustrated. Although these are to be expected in ALS, an illness which robs patients of their independence and freedom, it seems that behavioural change represents an intrinsic part of the disease process. Carers carry a high degree of burden because of patients’ behavioural impairment (not surprising given that there may be an increase in patients’ self-centredness and reduced concern for the feelings and needs of others (Gibbons 2008). We have found that letting carers know that these changes occur as part of the disease can bring a sense of relief since they finally understand that a patient is not “just being difficult”.

An extension of this population-based study is currently underway. This will facilitate ongoing evaluation of the utility of consensus criteria. Analysis is also ongoing in our research group in order to address some limitations of current neuropsychological test batteries in ALS; for example the FrSBe merits modification to allow for the physical disability of ALS and more focused test batteries will decrease the chance of fatigue contributing to attentional and concentration difficulties.
Categorisation in this study has identified subgroups, albeit with some overlap, that can be followed over time to explore if cognitive and behavioural impairment progress to frontotemporal dementia. Future studies of imaging and pathological correlates of frontotemporal dysfunction as measured clinically will provide greater insight into ALS and neurodegeneration alike. Finally, population-based studies with such correlates will enable identification of genes that increased the risk of cognitive decline in ALS.
Chapter 5  Psychological Well Being in ALS: Quality of Life and Mood

5.1  Introduction

Amyotrophic Lateral Sclerosis is a terminal neurodegenerative disease which carries an inexorable decline in physical function. Psychological well-being becomes crucial as the illness progresses (Clarke 2001; Bromberg 2002; Lou 2003). Even after controlling for confounding factors (length of illness, disease severity, age), patients with psychological distress have a greater risk of mortality and a greater likelihood of dying in any given time period than those with psychological well-being (McDonald 1994; Johnston 1999).

This chapter examines quality of life in patients with ALS, and mood and burden in patients and their caregivers.

5.1.1  Quality of Life in ALS

The concept of health-related quality of life is a relatively new-found one; in 1947, the World Health Organization began to define health as not only the absence of disease and infirmity but also as a state of physical, mental, and social well-being and autonomy. The importance of health-related quality of life has steadily grown to achieve the status of a major outcome, although the definition of quality of life (QOL) varies according to the investigator, the perspective from which it is defined (patient/relative/physician/society), and the instruments used (McSweeny 1995).

The World Health Organisation Quality of Life Group defines quality of life as:

... an individuals' perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards and concerns. It is a broad ranging concept, incorporating in a complex way individuals' physical health, psychological state, level of independence, social relationships, personal beliefs, and their relationships to salient features of their environment. (World Health Organisation Quality of Life Group 1995).

Evaluating and addressing quality of life is fundamental in ALS given that palliative care is central in disease management (Oliver 2000) and that
improving quality of life is the core concept of palliative care (World Health Organization 2002). Quality of life in ALS is also of essential since it is a decisive consideration in patients’ decisions to refuse treatment and, in some cases, in physicians’ decisions to withhold or withdraw life-sustaining medical treatment (Jonsen 1992). Anticipated or perceived poor quality of life is one reason that is reported to lead to the request of physician-assisted suicide (Ganzini 1998; Bascom 2002; Kübler 2005).

Most studies have found that quality of life in patients in ALS is not solely determined by physical status or duration of ALS as perhaps might be expected (Simmons 2000; Clarke 2001; Robbins 2001; Goldstein 2002; Lou 2003; Chio 2004). There is no empirical support for the assumption that measuring the impact of physical function on various predetermined areas of life validly reflects that person’s QoL (Hardiman 2004).

Instead poor quality of life is correlated with suffering, poor social support, sense of burden, fatigue and increasing hopelessness (Ganzini 1999; Lou 2003; Chio 2004). Hence, consideration of spiritual, religious and psychological factors is necessary in QOL assessment rather than consideration of physical function alone (Lou 2003).

5.1.2 Mood in ALS

5.1.2.1 Patients - mood
Depression is not an inevitable consequence of ALS (Rabkin 2000; Kübler 2005). However mood is a crucial determinant in quality of life (Badger 2001; Chio 2004), the importance of which has been discussed above.

Nonetheless studies of the prevalence of mood disorders in ALS have been inconsistent, partly because some studies have used self-report measures whilst others have used standardised ones (Rabkin 2005; Wicks 2007) and partly due to disparities in sample composition. Studies using self-report measures including Beck’s Depression Inventory, the ALS-Depression Inventory, the Hospital Anxiety and Depression Scale and the Centre for Epidemiologic Study—Depression have reported depression rates of 23% - 44% (Moore 1998; Lou 2003; Kübler 2005).
At least two studies have however used standardised measures in ALS. Ganzini et al (1999) employed the Diagnostic Interview Schedule; 11% of patients (n=100) had current major depression. Rabkin (2000) evaluated 56 ALS patients using the Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders (4th ed.; DSM-IV) and reported that 88% of patients had no diagnosis, 2% had major depression, and 10% had minor depression. Depressive symptoms did not increase after an interval of 5.5 months in 20 of those patients, despite a progressive decline in physical function.

A study of 80 patients with late stage ALS reported that major depression in people is rare - 81% had no depressive disorder (Rabkin 2005). The authors concluded that although transient depressive symptoms may occur, depression does not generally increase as death approaches. However the combined rate of 19% for both major and minor depression seen in this study was higher than the 2 to 9% prevalence rate reported for depression in the general population.

A picture of resiliency was outlined in an analysis that noted reactions to ALS included “continued attempts at active mastery and persistent suppression, denial, and isolation of depressive and anxious feelings” (Brown 1970). Where lower rates of depression than expected have been found, this has been attributed to denial as a psychological defence (Moore 1998). It may also occur as a response shift away from focusing on physical domains and instead on psychosocial and existential ones. Another possibility is the emergence of compensatory cognitive or neuroplastic changes whereby emotional responses are altered towards positive valence and towards a more balanced arousal state (Lulé 2005). Schmolck et al (2007) noted that 30 ALS patients (n=60) demonstrated an inability to correctly recognize threat in a given social context

But it is clear that results of studies on mood in ALS are conflicting and many studies do not support a picture of persistent stoicism in the face of adversity.

As with quality of life, poor social support has been found to be predictive of depression (Goldstein 2006). Some authors found a correlation between depression and physical impairment (Hogg 1994, Hunter 1993), whereas others did not (Tedman 1997; Rabkin 2000; Rabkin 2005).
Rates of anxiety as measured primarily by self-report questionnaires have varied from 11-26% (Goldstein 1998; Moore 1998; Clarke 2001; Goldstein 2002) although this may be equivalent to that of general medical patients (Rabkin 2000). State anxiety may be significantly higher during the diagnostic phase (Vignola 2002). Potential correlates of anxiety include hopelessness, pain, fatigue (Rabkin 2000), physical symptoms related to speech and eating, plus the social impact of these impairments such as embarrassment (Hogg 1994). Another proposed contributory factor to anxiety levels is marital status: elevated scores have been seen in married patients relative to those that were single, divorced, or widowed, perhaps due to feelings of carer burden or loss of self esteem in relation to roles in the relationship (Tedman 1997).

5.1.2.2 Caregivers - mood
Cross-sectional studies have reported that 10% to 19% of caregivers are depressed (Goldstein 2006; Rabkin 2008). Correlates of caregiver depression include reliance on avoidance, perceived burden, fatigue, and feeling that the patient was critical and unappreciative (Rabkin 2008). Two studies found no decline in mood over time despite a progressive decline in patients’ physical function (Rabkin 2000; Goldstein 2006).

Prevalence of anxiety amongst caregivers has ranged from 38% to 79% (Goldstein 2006; Vignola 2008). The level of anxiety may change with ALS progression; a cross-sectional study of 75 carers (Vignola 2008) discovered that 79% had a medium to high level of state anxiety during the diagnostic phase, with a slight decrease to 71% during the follow-up phase (as measured by the State-Trait Anxiety Inventory). Goldstein (1998) reported that caregivers’ anxious mood increased with shorter duration of symptoms, reflecting caregivers’ uncertainty over future disease progression.

5.2 Instruments for evaluation of psychological well-being in ALS
5.2.1 QOL
Evaluation of QOL in particular has traditionally proved challenging in ALS given the level of physical disability, communication impairment, and sometimes cognitive impairment that are part of the disease. Questionnaires have often been generic or disease-specific and include the Short Form-36
(Tedman 1997) and the Sickness Impact Profile (Bergner 1981; Hogg 1994; Damiano 1999).

The McGill Quality of Life questionnaire (MQOL; Cohen 1995) has been used in patients with ALS and their carers (Chio 2004; Chio 2005; Simmons 2000; Lou 2003; Gauthier 2007). It examines five domains: physical well-being, physical symptoms, existential well-being, psychological symptoms and support.

It is also feasible to assess individual QOL in ALS for example using the Schedule for the evaluation of Individual Quality of Life i.e. SEIQoL (O’Boyle 1992). This instrument is derived from a decision analysis technique known as judgment analysis, allows respondents to nominate the areas of life which are most important, rate their level of functioning or satisfaction with each, and indicate the relative importance of each to their overall quality of life (Hickey 1996).

Assessing QOL in cognitively impaired older adults poses unique challenges:

1 Varying deficits of memory, attention, judgment, insight, and communication influence the ability of individuals with cognitive impairment to comprehend questions or communicate their own subjective states

2 Behavioural or non-cognitive symptoms, including depression, agitation, or psychosis, may impact QOL ratings.

3 Judgments about what is important to QOL may change as dementia progresses or as the individual’s living situation changes (Logsdon 2002).

5.2.1.1 Mood

Evaluation of mood in ALS requires consideration of factors such as decreased concentration sleep disturbance, fatigue and anorexia. The Beck Depression Inventory (Beck 1961) includes questions on suicidality but although some ALS patients may “wish to die”, they may not be depressed; depression and hopelessness do not correlate (Albert 2005). In addition, subtle cognitive impairment or even frank frontotemporal dementia in ALS might confound the picture since features of the latter including lack of insight, denial, apathy, and euphoria may mask depression or hopelessness.
5.3 Hypotheses: Psychological Well-Being in ALS

5.3.1 Hypothesis One: Physical Status and QOL
It was expected that physical status would not be the sole determinant of quality of life (QOL) in patients with ALS as reported by other studies (Simmons 2000; Robbins 2001; Goldstein 2002; Chio 2004). Health-related QoL is only a subset of overall QoL and other factors, such as existential features, that are not directly relevant to health, may be of importance to patients' wellbeing, and may compensate for increasing disability that would otherwise intuitively predict a poor quality of life (Hardiman 2004).

5.3.2 Hypothesis Two: Cognitive Impairment and QOL
It was hypothesised that QOL would differ in those with cognitive impairment compared to those without. This was an exploratory hypothesis.

5.3.3 Hypothesis Three: Evolution of QOL over time in ALS
It was predicted that QOL would not deteriorate over time (six months). Previous studies have found a substantial steadiness of quality of life in patients with ALS (Goldstein 2006; Gauthier 2007) despite a significant increase of caregiver burden and depression (Gauthier 2007). Patients with ALS may have lower expectations of their physical ability as their illness progresses, and instead may instead shift their focus to other domains, perhaps spiritual and psychosocial (Clarke 2001; Bromberg 2002).

5.3.4 Hypothesis Four: Prevalence of mood disorders in patients and carers and the relationship of mood to quality of life, physical impairment and cognitive impairment.
It was hypothesised that based on previous research that there would be a low prevalence of anxiety and depression in ALS patients.

It was predicted that mood would be a crucial determinant in quality of life in accordance with other studies (Badger 2001; Chio 2004).

This study also explored the relationship between mood and severity of physical and cognitive / behavioural symptoms. Some authors have a correlation between depression and physical impairment (Hogg 1994, Hunter 1993) whilst others have not (Tedman 1997; Ganzini 1998; Goldstein 2002; Lou 2003; Rabkin 2000; Rabkin 2005). In addition it was postulated that
behavioural and cognitive impairment in patients would confer a higher degree of anxiety and depression upon their carers, as seen in dementia not associated with ALS (Schulz 1995; González-Salvador).

5.3.5 Hypothesis Five: Evolution of mood over time
This exploratory analysis examined the evolution of mood in patients with ALS over a 6 month period.

5.4 Methodology
5.4.1 Participants
Consecutive patients with ALS, part of a large-scale study of cognition and behaviour, were invited to participate in this study at two six-month intervals. Recruitment, inclusion and exclusion criteria, and ethical approval are described in Chapter Three. All had met criteria for probable or definite ALS (Brooks 1994).

Consecutive carers, part of a large scale study of carer burden in ALS, were invited to participate in this population-based study on a one-off basis; only primary informal caregivers were included in this study; paid caregivers were not.

5.4.2 Participant Assessment
Two interviewers attended each home visit so that the patient and family caregiver could be interviewed simultaneously, separately and out of earshot of one another by the same neurologist and psychologist (also affiliated with Trinity College Dublin and Beaumont Hospital) on each occasion.

Full neuropsychological assessment was conducted (Chapter Three). All subjects filled out the HADS and MQOL themselves but assistance was provided as required. All participants were guaranteed that their responses would remain confidential.

Patients with communication impairments were facilitated in participation through use of Augmentative and Alternative Communication devices (AAC).
5.4.2.1 Predictor variables recorded

1 Demographic variables: age, sex, occupation, years of education, disease duration. In the case of patients, time since onset and since diagnosis were also recorded.

2 Clinical status: functional impairment - ALSFRS-R, site of ALS onset (bulbar or spinal), use of non-invasive ventilation and gastrostomy feeding tube.

3 Cognitive status (as per consensus criteria; see Chapter Three).

4 Mood as measured by the Hospital Anxiety and Depression Scale (Zigmond 1983).

5 Social support: presence of family or outside caregiver(s) and care hours provided.

5.4.2.2 QOL Instrument

Patients and carers completed The McGill Quality of Life questionnaire (MQOL; Cohen 1995). This is a 16 item measure with each item rated on an 11-point scale ranging from 0 to 10, with higher scores indicating greater well-being. The five domains include: physical well-being, physical symptoms, existential well-being, psychological symptoms and support. Self perceived QOL in the past two days is recorded in a single item scale (MQOL-SIS), rated from 0 (very bad) to 10 (excellent). A total rate (Tot-MQOL) is obtained as the mean value of the score of the five domains. Internal consistency of the subscale of the MQOL has been verified (Cohen 1996). The MQOL subscales were found to have high internal consistency in a sample of participants with HIV, Cronbach’s alpha reported were: .83 for the total scale; .84 for the Physical domain; .77 for Psychological domain; .86 for the Existential well-being domain; and .83 for the Support domain. Although the MQOL was initially designed to measure quality of life in people with life threatening illnesses, it has also been used in patients with ALS and their carers (Chio 2004; Chio 2005; Simmons 2000; Lou 2003; Gauthier 2007).

In cognitively impaired patients, we ensured comprehension of questions and selection of appropriate responses through the use of explicit instructions, face-to-face administration by a trained interviewer (this author), the use of visual cues to remind the respondent of the response options, and finally assessment of the respondent’s comprehension by asking follow-up questions when the response was unclear or inconsistent (Logsdon 2002).
5.4.2.3 Mood Evaluation

This was assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983). This self-report 14-item scale measures the states of anxiety and depression without contamination of scores by reports of physical symptomatology. It is valid for both hospital and community-based evaluation. It was used primarily to exclude the possibility that abnormal cognitive profiles may be related to anxiety or depression.

As in previous studies of ALS patients (Abrahams 1997; Abrahams 2000; Abrahams 2005), one item, "I feel slowed down", was removed from the depression subscale as it was felt that it may be confounded by physical symptoms of ALS. The cut-off values used were thus redefined for this subscale: 0-4 indicated subjects were not depressed, 5-7 was suggestive of depression ("borderline state") and 8-18 indicated depression. For the anxiety subscale, previously validated measures were utilised: 0 to 7 indicated an absence of anxiety; a score of 8 to 10 was suggestive of the presence of anxiety ("borderline"); and a score of 11 or higher indicated presence ('caseness') of anxiety i.e. abnormal.

5.4.3 Statistical Methods

T-tests were performed to investigate QOL and mood in those with ALS (Group 1) versus their carers (Group 2).

Relationships between the MQOL sub-scores / total were explored between different variables including functional impairment, time since diagnosis, mood, and cognition using Spearman’s Rank Order Correlation Coefficient ($r_s$). Where transformations were unsuitable for parametric analysis, Spearman’s Rank Order Correlation Coefficient ($r_s$) was used. Group differences were examined using Analysis of Variance or Analysis of Co-Variance if demographic or cognitive variables contributed to task performance (Clark-Carter 1997). Patient selection minimised the need for extensive co-variation which would adversely affect the power of the statistical analysis. Cohen’s (1988) guidelines were used to define correlation sizes, whereby: .00 to .29 = small correlation; .30 to .49 = medium correlation; .40 to 1.0 = large correlation (Cohen 1988). Preliminary checks were conducted to ensure that there was no
violation of the assumptions of normality linearity, homogeneity of variance, homogeneity of regression slopes, and reliable measurement of the covariate.

All collected data was scored and entered into Statistical Package for the Social Sciences (SPSS) version 15.

5.5 Results

5.5.1 Participants

45 patients with ALS were recruited (Table 19).

Table 19. Demographics of patients participating in QOL study

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64.14</td>
<td>11.16</td>
</tr>
<tr>
<td>Time since diagnosis</td>
<td>207.9</td>
<td>206.45</td>
</tr>
<tr>
<td>Time since onset</td>
<td>583.26</td>
<td>427.95</td>
</tr>
<tr>
<td>Mean ALSFRS</td>
<td>38</td>
<td>8</td>
</tr>
</tbody>
</table>

15 patients participated in a second visit; the average time between baseline and second visit was 195.9 days, SD=35.05.

23 carers were also enrolled with mean age 60.45 (SD 9.43). All but three were spouses; the others were grown-up children of patients or in one case a family friend who had become an (unpaid) carer for up to ten hours a day.

Not all participants participated in the second assessment. 8 patients had died; 7 patients were too unwell or physically disabled to complete the questionnaires; 8 patients had developed severe dementia that precluded participation; 3 patients opted out of the six-month assessment; 4 patients returned incomplete questionnaires.

5.5.2 Measures

5.5.2.1 QOL

QOL in patients versus carers.

The only statistically significant difference (using a Bonferroni adjustment because of the number of comparisons carried out; alpha level = .008) between ALS sufferers and caregivers was on the physical subscale of the McGill QOL Questionnaire (p<.008; Table 20).
Table 20. Caregiver and patient mean (SD) MQOL

<table>
<thead>
<tr>
<th>Scale</th>
<th>Caregivers Mean (SD)</th>
<th>Patients Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MQOL-Total</td>
<td>122.4 (24.2)</td>
<td>114.1 (18.1)</td>
</tr>
<tr>
<td>MQOL-Single Item Scale</td>
<td>6.6 (2.2)</td>
<td>6.4 (1.7)</td>
</tr>
<tr>
<td>MQOL-Physical</td>
<td>34.8 (7.1)</td>
<td>23.1 (7)</td>
</tr>
<tr>
<td>MQOL-Existential</td>
<td>44.7 (10.9)</td>
<td>42.2 (7.7)</td>
</tr>
<tr>
<td>MQOL-Psychological</td>
<td>26.2 (9.4)</td>
<td>30.5 (7.5)</td>
</tr>
<tr>
<td>MQOL-Support</td>
<td>15.7 (3.4)</td>
<td>17.5 (2.7)</td>
</tr>
</tbody>
</table>

MQOL=McGill Quality of Life; Tot=Total; PW=physical well-being; Ph=physical symptoms; EW=existential well-being; Ps= psychological symptoms; Su= support.

Correlates of Quality of Life in patients with ALS

Possible correlates of QOL were explored including: functional impairment, hours of outside care, use of non-invasive ventilation (NIV) and use of radiologically inserted gastrostomy (RIG).

In summary there were significant correlations between total QOL subscale and depression (medium negative correlation); single item scale QOL subscale and depression (medium negative correlation); physical QOL subscale and ALSFRS (medium positive correlation) (Table 21).

In the non-invasive ventilation (NIV) group (n=8), statistical power of correlations was low; thus the different means and standard deviation were assessed qualitatively; there was a trend towards higher QOL in NIV users but there were few participants in the analysis (Table 22).

Conversely, and with the same important caveats, those with RIG had lower QOL scores difference than those without RIG on all MQOL subscales except the psychological subscale (Table 23).
Table 21. Correlates of Quality of Life in patients with ALS

<table>
<thead>
<tr>
<th>QOL Subscale</th>
<th>ALSFRS</th>
<th>Hours of outside care</th>
<th>ALS Duration</th>
<th>Depression</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>$r_s = .38$, $n=32$, $p&lt;.05$ *</td>
<td>$r_s = -.26$, $n=28$, $p = .2$</td>
<td>$r_s = -.38$, $n=42$, $p = .05$</td>
<td>$r_s = -.39$, $n=45$, $p = .39$</td>
<td>$r_s = .15$, $n=45$, $p = .33$</td>
</tr>
<tr>
<td>Physical</td>
<td>$r_s = .32$, $n=32$, $p = .2$</td>
<td>$r_s = -.26$, $n=28$, $p = .2$</td>
<td>$r_s = -.26$, $n=45$, $p = .11$</td>
<td>$r_s = -.06$, $n=42$, $p = .70$</td>
<td>$r_s = .13$, $n=45$, $p = .39$</td>
</tr>
<tr>
<td>Existential</td>
<td>$r_s = .32$, $n=32$, $p = .08$</td>
<td>$r_s = -.26$, $n=28$, $p = .17$</td>
<td>$r_s = -.13$, $n=45$, $p = .39$</td>
<td>$r_s = -.37$, $n=42$, $p = .70$</td>
<td>$r_s = .2$, $n=45$, $p = .19$</td>
</tr>
<tr>
<td>Single item scale</td>
<td>$r_s = .21$, $n=32$, $p = .08$</td>
<td>$r_s = -.3$, $n=41$, $p = .50$</td>
<td>$r_s = -.12$, $n=45$, $p = .44$</td>
<td>$r_s = -.37$, $n=42$, $p = .02$</td>
<td>$r_s = .13$, $n=45$, $p = .34$</td>
</tr>
<tr>
<td>Psychological</td>
<td>$r_s = -.00$, $n=32$, $p = .1$</td>
<td>$r_s = -.11$, $n=28$, $p = .58$</td>
<td>$r_s = .03$, $n=45$, $p = .86$</td>
<td>$r_s = .24$, $n=42$, $p = .05$</td>
<td>$r_s = -.06$, $n=45$, $p = .72$</td>
</tr>
<tr>
<td>Support</td>
<td>$r_s = .2$, $n=32$, $p = .31$</td>
<td>$r_s = .2$, $n=28$, $p = .50$</td>
<td>$r_s = -.10$, $n=45$, $p = .50$</td>
<td>$r_s = -.34$, $n=42$, $p = .50$</td>
<td>$r_s = .09$, $n=45$, $p = .57$</td>
</tr>
</tbody>
</table>

*Statistically significant correlation.

.00 to .29 = small correlation; .30 to .49 = medium correlation; .40 to 1.0 = large correlation (Cohen 1988).

Table 22. Quality of life in patients with and without non-invasive ventilation.

<table>
<thead>
<tr>
<th>NIV</th>
<th>No NIV</th>
<th>alpha value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>M (SD)</td>
<td>N</td>
</tr>
<tr>
<td>-----</td>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>Single Item Scale</td>
<td>8</td>
<td>7.3 (1.4)</td>
</tr>
<tr>
<td>Physical Scale</td>
<td>8</td>
<td>21.6 (6.7)</td>
</tr>
<tr>
<td>Psychological Scale</td>
<td>8</td>
<td>31.4 (7.6)</td>
</tr>
<tr>
<td>Existential Scale</td>
<td>8</td>
<td>45.0 (6.4)</td>
</tr>
<tr>
<td>Support Scale</td>
<td>8</td>
<td>18.4 (2.1)</td>
</tr>
<tr>
<td>Total Scale</td>
<td>8</td>
<td>119.4 (20.2)</td>
</tr>
</tbody>
</table>
Table 23. Quality of Life in patients with and without radiologically-inserted gastrostomy.

<table>
<thead>
<tr>
<th></th>
<th>RIG</th>
<th>No RIG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>M (SD)</td>
</tr>
<tr>
<td>Single Item Scale</td>
<td>4</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>Physical Scale</td>
<td>4</td>
<td>22 (8.2)</td>
</tr>
<tr>
<td>Psychological Scale</td>
<td>4</td>
<td>34.8 (6.2)</td>
</tr>
<tr>
<td>Existential Scale</td>
<td>4</td>
<td>38.8 (6.6)</td>
</tr>
<tr>
<td>Support Scale</td>
<td>4</td>
<td>16.8 (3.3)</td>
</tr>
<tr>
<td>Total Scale</td>
<td>4</td>
<td>112.3 (18.8)</td>
</tr>
</tbody>
</table>

QOL and cognitive and/or behavioural impairment

QOL in patients with pure ALS (n=18) was compared to QOL in patients with behavioural, cognitive impairment and dementia (i.e. ALS-impaired; n=27). Of note there was no difference between ALSFRS in both groups. There were significant differences (p<0.05) between the groups in total quality of life as well as the psychological and existential subscales (Table 24).

Table 24. Quality of life in patients with ALS versus patients with ALS with cognitive and/or behavioural impairment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOL_SIS</td>
<td>Pure ALS</td>
<td>6,8889</td>
<td>2,16629</td>
</tr>
<tr>
<td></td>
<td>ALS with Impairment</td>
<td>6,0741</td>
<td>2,16486</td>
</tr>
<tr>
<td>QOL_PHY</td>
<td>Pure ALS</td>
<td>22,5000</td>
<td>6,85351</td>
</tr>
<tr>
<td></td>
<td>ALS with Impairment</td>
<td>22,3333</td>
<td>7,31174</td>
</tr>
<tr>
<td>QOL_PSYCH</td>
<td>Pure ALS</td>
<td>31,8333</td>
<td>9,72716</td>
</tr>
<tr>
<td></td>
<td>ALS with Impairment</td>
<td>25,7407</td>
<td>9,48518</td>
</tr>
<tr>
<td>QOL_EXIS</td>
<td>Pure ALS</td>
<td>46,3333</td>
<td>10,18650</td>
</tr>
<tr>
<td></td>
<td>ALS with Impairment</td>
<td>38,7778</td>
<td>9,68080</td>
</tr>
<tr>
<td>QOL_SUPP</td>
<td>Pure ALS</td>
<td>18,0000</td>
<td>2,86972</td>
</tr>
<tr>
<td></td>
<td>ALS with Impairment</td>
<td>16,6667</td>
<td>3,67946</td>
</tr>
<tr>
<td>QOL_TOT</td>
<td>Pure ALS</td>
<td>120,0000</td>
<td>25,84797</td>
</tr>
<tr>
<td></td>
<td>ALS with Impairment</td>
<td>103,5185</td>
<td>21,53239</td>
</tr>
</tbody>
</table>

MQOL=McGill Quality of Life; SIS-single item scale; PHY=physical well-being; PSYCH=psychological symptoms; EXIS=existential well-being; SUPP= support; TOT=total.

*=significant difference on subscales between Groups
**QOL over time**

A one-way repeated measures ANOVA was conducted to compare scores on the McGill’s Quality of Life Total Scale at Time 1 and Time 2 (Table 25). There was no significant effect for time [Wilk’s Lambda=.99, \( F=(1, 14)=.14, p=.72 \), multivariate partial eta squared =.01]. The same is true for all other MQOL subscales (not shown).

**Table 25.** Quality of Life (Total Scale) at baseline and six months later

<table>
<thead>
<tr>
<th>Time period</th>
<th>N</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time 1</td>
<td>15</td>
<td>111.53</td>
<td>24.79</td>
</tr>
<tr>
<td>Time 2</td>
<td>15</td>
<td>109</td>
<td>23.74</td>
</tr>
</tbody>
</table>

ALSFRS scores over this six month period deteriorated: Time 1: \( M=39.15, SD=5.84 \); Time 2: \( M=31.3, SD=9.77, t(26)=6.88, p<.001 \).

**5.5.2.2 Mood**

**Patient Mood**

The mean HADS scores for patient depression and anxiety were 4.1(4.1) and 6.5 (4.4) respectively. 10.3 % \((n=6)\) met the cut-off score for moderate-severe depression. 15.3% \((n=9)\) met the cut-off for moderate-severe anxiety.

There was a significant difference in depression between the patients, spouse controls and recruited controls \((p=.01)\). Mean ranks for the groups suggested that the patients had the highest depression scores \((n=59; \text{mean rank}=53.9, M=4.1, SD=4.1)\), followed by the spouse controls \((n=13; \text{mean rank}=46.4, M=2.8, SD=2.7)\) and then recruited controls \((n=24; \text{mean rank}=34.4, M=1.5, SD=1.4)\). However all HADS mean scores were within normal range and not indicative of moderate-severe mood disorder.

There was no significant difference in anxiety between patients with ALS \((n=58)\) and all controls \((n=37)\) (Kruskal-Wallis Test; \( p=.2 \)).

ALSFRS was a significant correlate of depression \((r_s=-.31, n=58, p=.02; \text{medium negative})\) but not of anxiety.

Of note, 15 patients were on low dose psychotropic medications, most commonly SSRIs and amitriptyline, initiated after diagnosis for emotional lability. 2 patients reported depression at some point in their lives for which they received antidepressant treatment. 3 patients received antidepressant
treatment indicated specifically for depression after diagnosis; one of these had moderate depression on HADS evaluation and received counselling after that assessment.

**Table 26.** Mood and clinical variables in patients

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar</td>
<td>15</td>
<td>4.8</td>
<td>4.2</td>
<td>0.43</td>
</tr>
<tr>
<td>Spinal</td>
<td>43</td>
<td>3.8</td>
<td>4.05</td>
<td></td>
</tr>
<tr>
<td>NIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIV</td>
<td>12</td>
<td>3.17</td>
<td>2.48</td>
<td>0.39</td>
</tr>
<tr>
<td>No NIV</td>
<td>46</td>
<td>4.3</td>
<td>4.39</td>
<td></td>
</tr>
<tr>
<td>RIG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIG</td>
<td>52</td>
<td>5</td>
<td>2.76</td>
<td>0.02</td>
</tr>
<tr>
<td>No RIG</td>
<td>6</td>
<td>3.96</td>
<td>4.21</td>
<td></td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar</td>
<td>15</td>
<td>6.93</td>
<td>3.49</td>
<td>0.67</td>
</tr>
<tr>
<td>Spinal</td>
<td>43</td>
<td>6.37</td>
<td>4.69</td>
<td></td>
</tr>
<tr>
<td>NIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIV</td>
<td>12</td>
<td>7.58</td>
<td>4.7</td>
<td>0.35</td>
</tr>
<tr>
<td>No NIV</td>
<td>46</td>
<td>6.24</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>RIG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIG</td>
<td>52</td>
<td>9.83</td>
<td>4.6</td>
<td>0.03*</td>
</tr>
<tr>
<td>No RIG</td>
<td>6</td>
<td>6.13</td>
<td>4.24</td>
<td></td>
</tr>
</tbody>
</table>

NIV = non-invasive ventilation. RIG = radiologically-inserted gastrostomy. Independent samples t-test in all except RIG (Mann-Whitney U Test). *significant

**Caregiver mood**

22.6% (n=7) met the cut-off score for moderate-severe anxiety; none met the cut-off for moderate-severe depression. There was no significant correlation between ALSFRS and carer mood.

The mean depression and anxiety scores of caregivers of patients with impairment (ALS FTD, ALS co-morbid dementia, ALS-ci, ALS-bi; n=38) were significantly higher than compared to caregivers of those patients with no impairment (pure ALS; n=20); (Table 27). However all mean scores were still within normal range.

**Table 27.** Caregiver mood: Pure ALS versus ALS-impaired

<table>
<thead>
<tr>
<th></th>
<th>Caregiver depression</th>
<th>Caregiver anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure ALS (n=20)</td>
<td>M=2.05, SD=1.79;</td>
<td>M=6.64, SD=4.59;</td>
</tr>
<tr>
<td>ALS-impaired (n=38)</td>
<td>M=5.13, SD=4.54;</td>
<td>M=7.75, SD=3.75;</td>
</tr>
<tr>
<td></td>
<td>t(56)=3.68, p=.001</td>
<td>t(29)=.471, p=.47</td>
</tr>
</tbody>
</table>

There was a significant correlation was between patient anxiety and carer anxiety (rs=.43, n=24, p=.04). There was a small positive non-significant correlation between patient depression and carer depression (rs=.29, n=23,
a medium positive non-significant correlation between patient anxiety and carer depression ($r_s=.35$, $n=24$, $p=.1$); and a medium positive non-significant correlations between patient depression and carer anxiety ($r_s=.4$, $n=23$, $p=.06$).

5.5.2.3 Evolution of mood over time

**Table 28.** Means and range of scores (Hospital Anxiety and Depression Scale) in patients with ALS at Time Two

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Two Anxiety</td>
<td>34</td>
<td>0</td>
<td>18</td>
<td>6.79</td>
<td>4.64</td>
</tr>
<tr>
<td>Time Two Depression</td>
<td>34</td>
<td>0</td>
<td>11</td>
<td>3.29</td>
<td>3.35</td>
</tr>
</tbody>
</table>

8.8% (3 patients) met the criteria of moderate to severe depression at Time Two (compared to 10.3% i.e. 6 patients at Time One). There was no significant difference between depression scores at Time One ($M=4.16$, $SD=4.21$) and Time Two ($M=3.88$, $SD=3.55$, $n=34$, Asymp. Sig. >.05; Wilcoxon Signed rank Test).

23.5% i.e. 8 patients met the criteria of moderate to severe anxiety at Time Two (compared to 15.3% i.e. 9 patients at Time One). There was a significant difference between anxiety scores at Time One ($M=8.3$, $SD=5.11$) and Time Two ($M=7.2$, $SD=4.9$, $n=26$, Asymp. Sig. <.05].

However mean depression and anxiety scores at Time Two did not meet criteria for moderate to severe anxiety. There was no significant correlation between Time Two mood and ALSFRS or time since diagnosis.

5.6 Discussion

5.6.1 Hypothesis One: Physical Status and QOL

It was expected that physical status would not be the sole determinant of QOL in patients with ALS as seen in other studies (Goldstein 2002; Simmons 2000; Robbins 2001; Lou 2003; Chio 2004).

Results showed a statistically significant correlation between ALSFRS and the physical scale with non-significant but positive correlations for the total scale, the existential scale, the single item scale and the support scale. However there was no correlation between ALSFRS and the QOL psychological scale.
suggesting that some aspects of quality of life in ALS are not influenced by physical impairment.

Another determinant of QOL was mood as seen previously (Lou 2003; Chio 2004; Gauthier 2007). Lower rates of depression were significantly correlated with several QOL subscales. In addition, patients who had a greater amount of self-perceived burden had substantially lower quality of life (total and psychological subscales). Because patients and caregivers may overestimate the psychosocial impact of the disease on the other (Adelman 2004), this suggests that addressing patients’ (mis)perception of being a burden might impact positively on their corresponding quality of life.

In addition, this study suggests that QOL was also influenced by the use of non-invasive ventilation. There was a trend towards higher QOL in patients who used non-invasive ventilation but results could only be analysed via comparisons of means. The positive impact of NIV on QOL without increasing the caregiver burden or stress has been noted previously (Bourke 2006; Mustfa 2006). Numbers were particularly small for the present analysis however. Bearing this important caveat in mind, mean total QOL and mood scores were lower for those who had a RIG than those who did not. The disparity between QOL being higher with NIV and conversely lower in RIG-users might be due to increased functional impairment in those with RIG, disturbed sleep with RIG, and increase in caregiver stress associated with RIG compared to NIV.

There was no significant difference between ALS sufferers and their carers on any of the subscales of the McGill Quality of Life Questionnaire except for the physical subscale. There are no validated cut-off scores for the QOL so it is impossible to define what MQOL score represents a “good” quality of life.

5.6.2 Hypothesis Two: Cognitive Impairment and QOL

QOL in patients with pure ALS was higher than QOL in those with cognitive and / or behavioural impairment and dementia independent of functional impairment. These results were significant for the total, psychological and existential subscales.

The concept of QOL incorporates physical health but also psychological state, level of independence, social relationships, and personal beliefs (World Health
Organisation QOL Group, 1995). The current analysis implies that some of these facets are compromised to a greater level in those with both ALS and cognitive / behavioural impairment compared to those with ALS alone. Intuitively, it would be expected that patients with features of behavioural changes such as apathy and disinhibition would experience a marked change in their social relationships, level of independence, psychological state and autonomy, perhaps leading to a lower self-rated quality of life.

Lower quality of life is associated with patients' decisions to refuse treatment (Jonsen 1992). These decisions are yet more challenging in patients with frontotemporal dysfunction which compromises problem solving, capacity to make decisions about health care or financial circumstances, capacity to use and comply with interventions, and the ability to engage competently in end-of-life decisions.

The MQOL has not been validated in patients with cognitive impairment but those with mild-moderate dementia are able to reliably and validly rate their own QOL (Logsdon 2002; Brod 1994; Lawton 1997) although not all authors agree with this (Albert 1998). Unequivocal, simple language, an untimed interview format, and explicit instructions helped to facilitate self-report of QOL in the present study. Two patients with fvFTD were unable to comprehend instructions for completing the MQOL and were thus excluded from participation.

Although QOL scales have been modified for use in dementia, these are most commonly applicable to those with Alzheimer's disease. Specific modifications are required for ALS-dementia to acknowledge the particular challenges of this condition (impairment of attention, language and judgement; loss of insight; suboptimal agreement between self-reports and proxy-reports) and the importance of relevant domains.

### 5.6.3 Hypothesis Three: Evolution of QOL over time in ALS

It was hypothesised that QOL would not deteriorate over time (Bremer 2004; Goldstein 2006; Nygren 2006; Gauthier 2007). Although a limited number of responses were available at the time of second testing it seems that patients with ALS have a stable of QOL over time in the face of increasing functional impairment.
This stability has been postulated to be due to patients with ALS having lower expectations of their physical ability as their illness progresses, associated with a shift of focus to other domains, perhaps spiritual and psychosocial, with acceptance of and adjustment to the presence of ALS (Ganzini 1999; Waldron 1999; Dal Bello-Haas 2000; Simmons 2000; Clarke 2001; Bromberg 2002; Goldstein 2002; Foley 2007). This may represent recalibrations of the terms or internal standards of reference used by a subject to judge QoL (Wilson 1999). Gauthier et al (2007) suggested that steadiness of QoL over time in ALS may also be associated with the use of denial as well as optimism, flexibility, and humour as psychological defences, or a reduction of insight, related to patients' subtle cognitive impairment.

Bromberg et al (2002) reported that caregivers appeared to demonstrate reciprocal response shifts, as they were forced to change expectations in opposite directions. This is supported by significant increases of burden and depression in caregivers over time (Gauthier 2007; Vignola 2008).

5.6.4 Hypothesis Four: Prevalence of mood disorders in patients and carers and the relationship of mood to quality of life and physical impairment and cognitive impairment.

5.6.4.1 Prevalence of mood disorders in patients at baseline

Mean HADS scores for patient depression and anxiety were well below cut-offs for moderate-severe mood disorder as predicted.

The HADS scale was primary used to confirm that cognitive and behavioural impairment could not be attributed to a mood disorder alone. It is a self-report measure and thus it is difficult to contextualise these rates with regard to existing literature given that studies have used a variety of standardised and self-report measures.

However our finding that mean scores in patients were below cut-offs for moderate-severe depression and the absence of depression in almost 90% of patients is broadly consistent with other studies that have shown that depression is not an inevitable consequence of the disease (Rabkin 2000; Kübler 2005). Reasons for this may include, as seen in regard to QOL above, the use of denial as a psychological defence (Moore 1998), a response shift away from focusing on physical domains, and altered emotional responses.
towards positive valence possibly indicating compensatory cognitive or neuroplastic changes (Lulé 2005). The difficulty in some ALS patients in judging the approachability of unfamiliar faces has been suggested to represent an inability to correctly recognize threat in a given social context (Schmolck 2007). Although these findings may occur due to the external stigma of disability of ALS (Gotkine 2008), the authors postulate that amygdala dysfunction and decreased perception of threat might explain why patients with ALS have a relatively low rate of depression compared with other similarly debilitating diseases, even in late stages.

Mean HADS scores for anxiety were also well below cut-offs for moderate-severe disorder and did not differ between patients and controls. 15.3% (n=9) met the cut-off for moderate-severe anxiety. This is consistent with rates of 11-26% as measured primarily by self-report questionnaires (Moore 1998; Goldstein 1998; Clarke 2001; Goldstein 2002).

The rates of moderate-severe depression and anxiety in 10-15% of patients may be similar those seen in the general population (Murphy 1988) but there are additional concerns in ALS since mood is a crucial determinant in quality of life (Badger 2001; Chio 2004) and is associated with significant pain and fatigue (Tedman 1997; Lou 2003). In addition, patients with psychological distress have a greater risk of mortality than those with psychological well-being (McDonald 1994; Johnston 1999).

There is a need to focus on managing depression when it is present. Treating physicians often appropriately prescribe SSRIs in ALS patients, but then fail to follow up on the efficacy or attempt alternative interventions (Ganzini et al 1999).

The current analysis did not compare rates of mood disorders to other neurodegenerative disorders. Unexpectedly, neurodegenerative conditions with better outcomes than ALS seem to have a higher prevalence of depression (Wicks 2007), although this may relate to the pathology of the underlying condition and the longer duration of illness. Depression has been reported in up to 50% of patients with Alzheimer’s disease, multiple sclerosis, and Parkinson’s disease (McDonald 2003; Patten 2003; Gottberg 2006; Raskind 2008).
5.6.4.2 Mood and QOL, physical symptoms, and cognitive/behavioural impairment

There was a significant correlation in this study between quality of life (MQOL single item scale, total scale, psychological scale) and depression as seen previously (Badger 2001; Chio 2004).

Some authors have noted a correlation between depression and physical impairment (Hunter 1993; Hogg 1994) whilst others have not (Tedman 1997; Ganzini 1998; Goldstein 2002; Lou 2003; Rabkin 2000; Rabkin 2005). Although there was no correlation between patient anxiety and ALSFRS in this study, there was a significant correlation between patient depression and ALSFRS suggesting that the inexorable physical decline of ALS may contribute to lower mood in patients. However, mean depression scores were not indicative of moderate-severe depression and a number of factors other than functional impairment contribute to psychological well-being in ALS. The present analysis found no significant correlation between ALSFRS (functional disability) and carer mood suggesting that functional disability is not a contributory factor.

Although patient numbers very much limit the significance of these findings, this analysis sows the seeds for future investigation.

5.6.4.3 Longitudinal evolution of mood in patients

There was no difference in mean depression scores over a period of six months and anxiety levels decreased significantly over the same period. This in agreement with prior work that suggests that state anxiety may be significantly higher during the diagnostic phase (Vignola 2002).

This stability of mood in ALS has also been reported previously (Rabkin 2000; Goldstein 2006) and is perhaps due to patients’ use of coping strategies enabling them to live with the disease (Kübler 2005) reported a negative correlation between the severity of depressive symptoms and time since diagnosis and postulated that this may be due to patients’ use of coping strategies enabling them to live with the disease for such a long time.

5.6.4.4 Caregiver Mood

Absence of moderate to severe depression was observed in carers but higher levels of anxiety were noted. More carers (22.6%; n=7) than patients (15.3%;
n=9) met cut-off scores for anxiety. The caveats for interpretation of this are the limited responses and the similar rates of mood disorders seen in the general population (Murphy 1988).

Comparison with other studies must also be made with caution given the use of a self-report measure in this study that was primarily engaged to out-rule psychological distress contributing to cognitive impairment. In a study of 71 patient-caregiver pairs (Rabkin 2008), 13% of caregivers had major depression (DSM-IV) and 10% had minor depression. The same study noted found correlates of caregiver depression included reliance on avoidance, perceived burden, fatigue, and feeling that the patient was critical and unappreciative. In a cross-sectional study of 75 carers (Vignola 2008), 79% had a medium to high level of state anxiety during the diagnostic phase, with a slight decrease to 71% during the follow-up phase (as measured by the State-Trait Anxiety Inventory). These values are higher than those found by Goldstein et al (1993); the latter study used the HADS and reported that 42% of caregivers were anxious.

The non-significant positive correlation between patient and caregiver depression and anxiety might represent a trend seen elsewhere (Rabkin 2000; Chio 2005; Jenkinson 2005; Gauthier 2007) yet not in others (Le Coco 2005; Rabkin 2005; Goldstein 2006) This concordance between psychological distress in patients and in carers has been reported in couples coping with other neurological disorders (Thommessen 2002). It seems intuitive that caregiver well-being impacts on patients, suggesting that attention to the mental health needs of caregivers may alleviate the patient's distress as well (Rabkin 2000).

There were significant differences in carer anxiety and depression scores for patients with impairment (ALS-FTD, ALS co-morbid dementia, ALSci and ALSbi) versus those with no impairment but all means scores were within normal range and were not indicative of moderate-severe anxiety or depression. Yet cognitive and behavioural impairment appear to confer a higher degree of depression and anxiety upon caregivers in other neurodegenerative, dementing conditions. Up to 50% of dementia caregivers experience depression, anxiety, and feelings of burden, strain, and stress particularly when behavioural disturbances are present (Schulz 1995;
González-Salvador 1999) which can compromise patient care and diminish the ability to objectively assess patient affect (Teri 1997). Why were higher levels of depression and anxiety not found in caregivers of ALS patients with behavioural and cognitive impairment? It might be that such impairment in ALS is marked by apathy (Chapter Four) rather than, aggression, swearing, impulsivity, wandering and paranoia that are seen in later Alzheimer’s disease and classic FTD. The prominent physical disability of ALS precludes some of these behaviours which would be thought to cause a higher degree of carer burden and stress.

Psychological distress in carers does not end when a loved one dies. The death of a patient with ALS has a lasting effect on their family (Radunović 2007). In a study of 32 families, ALS caused lasting emotional and financial hardship in families, 82% of carers reported self-defined burn-out, and 37% of respondents felt they were coping poorly, sometimes years after the patient’s death (Martin 2001). The authors also reported that in most cases however, the disease led to a strengthening of family ties.

5.7 Limitations

32 patients and 23 carers participated in this analysis of quality of life and mood. This is a great deal fewer than the 87 patients and matched controls who participated in the primary study of cognition in ALS. Some patients / carers reported time limitations that meant they could not fill in the QOL and mood questionnaires. Two patients were unable to complete these questionnaires because of fronttemporal dementia despite the use of unequivocal language and an untimed interview format to facilitate self-report of QOL. Selection bias could have resulted since patients and carers with lower mood and QOL were less willing to participate. The same could apply to those patients with cognitive and / or behavioural impairment. Conversely participants may have been more likely to engage in this study because of a desire to discuss concerns surrounding mood and QOL. Notwithstanding the limited recruitment at Time Two and the resulting limitations of statistical power, it is anticipated that these findings will aid in opening new avenue of research in the future.
The MQOL requires modification and validation in this population. It has been noted by Hickey et al (1996) to impose an external value system, with fixed and standardised weighting of component parts and general derivation from grouped data. The authors suggest that the measure may thus not be relevant to an individual's present life situation. The MQOL should not be underestimated however, as three of the five domains examined are non-health related (i.e. existential well being, psychological symptoms and support domains) which avoid over-emphasis on the physical impairment of ALS. In addition, other health-related questionnaires such as SIP and SF-36 have been equally criticised because they can cause distress and may have limited validity in the ALS population (Neudert 2001; Goldstein 2002). The SIP for example places a relatively heavy emphasis on physical dysfunction (mobility, ambulation), and patients with dementia and serious communication difficulties may be unable to complete it (McSweeny 1995). An alternative is to examine individual QOL rather than generic or disease-specific measures by using the SEIQoL whereby patients indicate the relative importance of various domains to their overall quality of life. However instruments such as the SEIQoL might be less useful in large samples (Felgoise 2003).

The use of a self-report measure (HADS) to assess mood in ALS also has its limitations. Cross-sectional studies using self-report symptom measures have demonstrated substantially higher rates of depressive symptoms in ALS than studies using standardized methods to generate psychiatric diagnoses (Rabkin 2005); however we adapted the HADS questionnaire by removing a question that related to the disease rather than mood state (“I feel slowed down”) and adapted the scoring method accordingly. This approach has been used in other studies in ALS (Abrahams 1997; Abrahams 2000; Abrahams 2005; Wicks 2007). Some patients in the present study were taking anxiolytics/antidepressant medications (most commonly low dose SSRI’s), often for emotional lability rather than a primary mood disorder. A significant effect of antidepressant medication usage has been previously noted for measures of mood, with higher levels of anxiety and depression identified amongst patients on any kind of antidepressant (Wicks 2007). However patients in the latter study may have being prescribed medication with depression/anxiety as the primary indication. The estimated prevalence rates might be artificially low in
this analysis because a proportion of patients were taking medications with an 
anxiolytics or anti-depressant effect.

Nonetheless the attributes of this study include population-based patient 
recruitment, (increasing ability to extrapolate our findings and avoiding biases 
from tertiary clinics), the use of assessment tools from previous studies of 
ALS, incorporation of statistical methods to increase the power of analysis, and 
integration of the recent consensus criteria to define frontemporal dysfunction 
in ALS (Strong 2009).

5.8 Implications, Clinical Applications, and Future Research

This chapter has outlined the importance of evaluating quality of life and mood 
in ALS. Maintaining psychological well-being is crucial in optimising palliative 
care (World Health Organization 2002) and in influencing patients’ most vital 

85-90% of patients with ALS did not have clinical depression or anxiety in this 
study but it is worth acknowledging that those patients with a mood disorder 
are more likely to have diminished quality of life, significant pain and fatigue 
an elevated risk of mortality (McDonald 1994; Tedman 1997; Badger 2001; 
Lou 2003; Chio 2004; Johnston 1999).

Just over 22% of carers had moderate-severe anxiety. Given that caregiver 
well-being impacts on patients, attention to the mental health needs of 
caregivers may alleviate the patient’s distress as well (Rabkin 2000).

The first step in addressing quality of life and mood simply involves asking 
patients and caregivers about their concerns in clinic. This analysis 
demonstrates that quality of life in ALS is not solely influenced by physical 
impairment but that other determinants include mood, self-perceived burden 
(Chapter Six), the presence of social support, and the presence of cognitive 
and behavioural impairment.

Thus ameliorating psychological well-being requires a multidisciplinary 
approach that addresses:

1. Physical disability – physiotherapy and occupational therapy play a key role 
in this.
Social and financial support e.g. home help, national ALS associations and meetings for patients and carers, community support groups, counselling, access to social workers and specialist ALS nurses, care packages etc.

The presence of frontotemporal dysfunction. Cognitive and behavioural impairment have been identified in other neurodegenerative disorders to confer a higher degree of depression and anxiety upon caregivers. Although we showed that behavioural and cognitive impairment was associated with higher scores on the HADS scale, these scores were still within the normal range. Nonetheless, informing caregivers about the presence of frontotemporal dysfunction can help them understand that patients’ behaviours are not simply him or her “being difficult”. Daily structure, creating routines, assisting with sequencing and problem-solving, and behavioural strategies can assist both patients and their loved ones.

A screening battery that incorporates both neuropsychological measures appropriate for patients with ALS (see Strong et al 2009) and mood and QOL questionnaires could highlight patients and carers who would benefit from assistance.

Larger population-studies to replicate, add statistical power, and expand upon our findings are crucial. Future research should focus on creating reliable, standardised screening tools modified for those with ALS, taking into account communication difficulties, impaired mobility, and potential fatigue.

Finally, maintaining hope is vital in the care of patients and their caregivers. Although we cannot promise that a cure for ALS will be found in the lifetimes of those who participated in this study, we live in hope nonetheless. We have discovered that even giving patients the opportunity to partake in research studies has provoked remarks such as “I feel like I’ve done something worthwhile” and “Even if I’m not around for a cure I feel like I might be helping scientists to find one”. Until that cure is found, facilitating patients and their carers in having the best quality of life and well-being they can possibly have is one of the most important things that we can do.
Chapter 6  Self-Perceived and Carer Burden in ALS

6.1  Introduction

The importance of psychological distress in patients and their carers was discussed in the previous chapter. The presence of burden, diminished quality of life and mood disorders confers a greater risk of mortality and a greater likelihood of dying in any given time period compared to those with psychological well-being (McDonald 1994; Johnston 1999).

6.2  Burden in MND – patients and carers

6.2.1  Patients

There is now a small but growing body of evidence to suggest that worry about creating burden to others is a common and troubling concern for people who are nearing the end of their lives (McPherson 2007b).

The construct of self-perceived burden to others has been defined as "empathic concern engendered from the impact on others of one's illness and care needs, resulting in guilt, distress, feelings of responsibility, and diminished sense of self" (McPherson 2007a). Cousineau et al (2003) similarly define a patient's self-perceived burden as a multifaceted concept that encapsulates:

1. The frustration, worry, and guilt that arise from a care recipient's feelings of dependence on the caregiver and

2. The associated concerns over the degree to which the care provided negatively affect their caregiver's physical health, emotional/mental health, and financial well-being.

Self-perceived burden is reported as a significant problem by up to 65% of terminally ill patients and is correlated with loss of dignity, suffering, a 'bad death', lower quality of life, poorer physical, emotional, and functional well-being; more depressive symptoms; and greater financial distress (Cohen 2002; Vig 2003; Simmons 2007; McPherson 2007b). It is also implicated in clinical decisions, such as those pertaining to life-sustaining treatment among older adults (Zweibel 1989; Cohen-Mansfield 1992; McPherson 2007b),
advance directives (Singer 1998; McPherson 2007b) and whether to accept hospice over home care (Murray 2003; Thomas 2004). In addition, self-perceived burden has been identified as a relevant factor in death-hastening acts among patients with life-threatening illness (McPherson 2007b).

Despite this clinical significance, self-perceived burden may go unnoticed by caregivers and by clinical staff (Heaven 1997; Steinhauser 2000; McPherson 2007a). This may reflect that family members are less attuned to patients' psychological issues than they are to more overt physical problems (McPherson 2007a). Alternatively, misunderstanding may occur when patients with a high level of self-perceived burden conceal their psychological distress in an effort to protect an already burdened caregiver. This is consistent with evidence that participants with higher levels of burden are less likely to seek help from others (Cousineau 2003).

Self-perceived burden has been examined more commonly in patients with cancer than in patients with ALS. However, Ganzini et al (2007) found that 91% (total n=100) of patients with ALS felt that their medical condition was a cause of stress for family members, 65% felt they were a burden to their families, and 48% thought that their medical condition resulted in financial hardship.

As mentioned above, self-perceived burden has been identified in other terminal illnesses as a relevant in clinical decisions. Given that patients with ALS often have to make crucial decisions surrounding feeding tubes, non-invasive ventilation, and advance directives, the importance of recognising and managing burden in ALS patients becomes clear. This is particularly true when patients may overestimate the psychosocial impact of the disease on caregivers in late stage ALS (Adelman 2004).

6.2.2 Carers

Caregiver burden has been described as the extent to which caregivers feel that their emotional or physical health, social life, and financial status have suffered as a result of caring for their relatives (Zarit 1980).

Pearlin's Stress Process Model of Caregiving (Pearlin 1990) recognises both the objective and subjective stressors of burden. Objective stressors include disease characteristics and symptoms e.g. behavioural problems and physical
disability. Subjective stressors are the extent to which specific problems are perceived as stressful for the caregiver i.e. their perception of strain and the emotional reactions of worry, anxiety, depression, frustration and fatigue (Pinquart 2003). Subjective burden may be determined by the quality of the caregiver’s relationship with the patient, their coping strategies, availability of social support, characteristics of the person receiving care, and the duration and amount of caregiving, spirituality and religiousness (Zarit 1986; Pinquart 2003; Colgrove 2007; Steadman 2007). Thus carer burden may reflect a dynamic interaction between external or objective stressors and subjective perceptions or emotional reactions to these (Rymer 2002).

Notwithstanding, some caregivers cope quite well with their role. They experience few symptoms of distress and report positive gain from the experience (Kramer 1997; Schulz 1997).

There is no doubt as to the high demands of caregiving in ALS in particular – it takes up to 14 hours per day to care for a patient with ALS, a condition with progressive physical disability. Caregivers often must give up their jobs and curtail their social lives and have compromised physical and psychological well-being (Krivickas 1997; Borasio 2001). In addition, caregivers must cope with their loved ones being diagnosed with a terminal illness that lacks a curative therapy. A correlation with functional impairment worsening over time has been observed in ALS studies (Hecht 2003; Chio 2005; Gauthier 2007) but functional disability may be less important than psychosocial factors (Goldstein 2006). This association between carer burden and patients’ functional impairment has not been reported in other neurological conditions (Evans 1987; Evans 1992; Kalb 1995).

Previous studies suggest that caregivers’ overall psychological well-being (burden and depression) deteriorates as ALS progresses whereas patients’ psychological well-being remains relatively stable (Gauthier 2007).

Surprisingly the mean total burden of care for ALS in one study (Hecht 2003) was found to be low compared with dementia, mixed neuropsychiatric and internal diseases although this finding has not been replicated in population-based cohorts.
ALS research to date has rarely examined the impact of cognitive and behavioural impairment on ALS caregivers. Studies of caregiver outcomes have excluded patients with dementia (Goldstein 2006). Yet, caregiver burden is consistently higher for patients with dementia and problem behaviour than for patients with other disorders (Grasel 1997; Coen 1999; Mafullul 2000; Thommessen 2002; Hecht 2003; Pinquart 2003); dementia caregivers are more likely to experience depression, anxiety, (Schulz 1995), use psychotropic medication (Draper 1992; Kiecolt-Glaser 1991; Baumgarten 1992) and have a significantly higher mortality risk than non-caregiving controls (Schulz 1999). A small unpublished study (presented at an ALS symposium in 2005) suggested that caregiver burden may be significantly higher in caregivers of ALS patients with cognitive change although cognition was not formally assessed and other variables such as physical disability and mood were not controlled for (Pioro 2005).

6.3 Hypotheses: Burden in ALS

6.3.1 Self-perceived burden
Hypothesis One (exploratory): Possible correlates of self-perceived burden such as severity of illness, quality of life, mood, carer burden and cognition were examined.

6.3.2 Carer Burden

6.3.2.1 Level of Carer Burden
Hypothesis Two: It was hypothesised that carer burden would be high in this analysis given the progressive physical disability of ALS, the grim prognosis and the lack of a curative therapy (Hecht 2003).

6.3.2.2 Impact of carer burden
Hypothesis Three: It was predicted that carer burden would influence caregivers’ QOL and mood (Hecht 2003; Chio 2005). Importantly, caregiver well-being impacts on patients (Rabkin 2000; Borasio 2001; Hebert 2001; Chio 2005).
6.3.2.3 Carer Burden and Cognitive and/or Behavioural Impairment

Hypothesis Four: It was expected that carer burden would be higher in those with cognitive impairment and dementia. As many as 50% of dementia caregivers experience depression, anxiety, and feelings of burden, strain, and stress (Schulz 1995); higher levels of caregiver burden exist for patients with dementia and problem behaviour than for patients with other disorders (Grasel 1997; Mafullul 2000; Thommessen 2002; Hecht 2003). Factors that likely lead to elevated caregiver burden in dementia include patients' behavioural problems, increased need for supervision, and limited ability of care receivers to express gratitude (Pinquart 2003). The patient's awareness of his/her cognitive impairment is predictive of emotional distress in caregivers (Rymer 2002); given the loss of insight that can occur in frontotemporal dementia, caregivers of patients with ALS and dementia were expected to experience a higher level of burden than caregivers of patients with ALS without dementia (Phukan 2007).

6.4 Methodology

Consecutive patients with ALS were invited to participate in this study. They were part of the large scale longitudinal study of cognition and were thus recruited from a population-based cohort through the Irish register of ALS (see Chapter Three). Consecutive carers were also asked to participate as a one-off basis. Only primary informal caregivers were included during these home visits; paid caregivers were not. Inclusion and exclusion criteria, ethical approval and participant recruitment were as described in the previous chapter. Because the Self-Perceived Burden Scale has not been validated in patients with dementia, this subgroup were also excluded from participation.

Two interviewers attended each home visit so that the patient and family caregiver could be interviewed simultaneously but separately (out of earshot). All subjects filled out the burden questionnaires themselves but assistance was provided as required. Predictor variables were recorded as described in the previous chapter i.e. demographics, clinical status as per ALSFRS, cognitive status, and burden.
6.4.1 Burden Instruments

Self-perceived burden scale (SPBS; Cousineau 2003).

This self-report measure analyses the degree of self-perceived burden experienced. Participants are instructed to think about the person (or people) who helps with day-to-day activities such as shopping for groceries, getting medications, preparing meals; questions are answered with regard to that person (those people) who are unpaid e.g. family member, friend or child. Items on the SPBS evaluate the frequency with which the respondent experiences a range of concerns associated with self-perceived burden (e.g., "I think that I make things hard on my caregiver"). Aspects of burden examined include the experience of guilt, indebtedness, loss of control, dependence, interference in caregiver’s lives, physical strain adversely affecting the caregiver’s health, anger, resentment, frustration and helplessness. The SPBS utilises a 5-point Likert scale and summative score to indicate the degree of burden. Respondents can choose from "none of the time"=1 to "all of the time"=5 so that total scores from 25 to 125. Two questions are reverse coded. Higher scores indicate that the patients perceive themselves to cause a higher burden to their caregivers. Cronbach alpha is reported at .85. The instrument takes approximately 10 minutes to complete. This scale has been used in ALS and has been validated in other disorders (Chio 2005; Gauthier 2007). It has the advantage of having multiple items to assess the SPB construct, which tends to improve reliability (McPherson 2007a).

Zarit Burden Interview (change) (ZBI; Zarit 1983)

There are 22 items in this self-administered questionnaire for caregivers. Questions refer to the caregiver/patient relationship and evaluate the caregiver’s health condition, psychological well-being, finances, and social life. Items are scored on a scale from 0 to 4, with higher scores indicative of greater distress. One item is a measure of overall burden and a summative score from all 22 items was used in this study. A statistically derived cut-off has been described previously as 24-26 points to identify family caregivers at risk for depression and in need of further assessment and intervention (Schreiner 2006). However a cut-off score of 27 was chosen due to the addition of item 22 in the creation of the summative scale. The ZBI has
emerged as the most widely utilised burden measure with high internal consistency and good test-retest reliability (O’Rourke 2003). It also has been used previously in caregiver of patients with ALS (Adelman 2004; Goldstein 2006).

6.4.2 Statistical Methods
T-tests were performed to investigate burden in those with ALS (Group 1) versus their carers (Group 2).

Relationships between the burden scores were explored between different variables, including functional impairment, time since diagnosis, mood, and cognition. All collected data was scored and entered into Statistical Package for the Social Sciences (SPSS) version 15.

Where transformations were unsuitable for parametric analysis, Spearman’s Rank Order Correlation Coefficient ($r_s$) was used. Group differences were examined using Analysis of Variance or Analysis of Co-Variance if demographic or cognitive variables contributed to task performance (Clark-Carter 1997). Patient selection minimised the need for extensive co-variation which would adversely affect the power of the statistical analysis. Cohen’s (1988) guidelines were used to define correlation sizes, whereby: .00 to .29 = small correlation; .30 to .49 = medium correlation; .40 to 1.0 = large correlation (Cohen 1988). Preliminary checks were conducted to ensure that there was no violation of the assumptions of normality linearity, homogeneity of variance, homogeneity of regression slopes, and reliable measurement of the covariate.

6.5 Results

6.5.1 Participants
A total of 24 patients with ALS were recruited. Mean age was 61.47 (SD 9.54). Mean time since diagnosis was 221.17 days (SD 127.22) and mean time since onset was 843.67 (SD 639.52). Mean ALSFRS was 37.46 (SD 6.9).

32 carers were also enrolled. Mean age was 58.25 years (14.07). 65.6% of carers were female. All but three were spouses; the others were grown-up children of patients or in one case a family friend who had become an (unpaid) carer for up to ten hours a day.
6.5.2 **Self-Perceived Burden**

Mean SPBS score in the current analysis was 52 (16.58) with a range of 28-86.

Correlations of self-perceived burden correlations were explored using Spearman's Rank Order Correlation Coefficient ($r_s$) unless otherwise stated.

6.5.2.1 **Correlates of self-perceived burden**

Significant negative correlations were noted between self-perceived burden and age, and between self-perceived burden and total QOL (as measured by the McGill QOL instrument) (Table 29).

Significant positive correlations were found between self-perceived burden and anxiety (Table 30).

There was no correlation between self-perceived burden and the number of hours of home help ($r_s=.08, n=22, p=.72$) or between self-perceived burden and years of education: ($r_s=.02, n=24, p=.94$).

Independent samples t-test showed no differences in self-perceived burden scores in those whose carers were partners ($32.3\%; M=50.2, SD=16.7$) versus those carers were their children ($4.6\%; M=46, SD=15.6; t(19)=.34, p=.74$). There was also no significant difference in SPBS scores for males ($M=53.1, SD=19.2$) versus females [$M=50.4, SD=13; t(22)=.32, p=.7$].

**Table 29.** **Negative correlates of self-perceived burden**

<table>
<thead>
<tr>
<th>Measure</th>
<th>R</th>
<th>N</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALSFRS</td>
<td>$r_s=-.16$</td>
<td>24</td>
<td>.47</td>
</tr>
<tr>
<td>Age</td>
<td>$r_s=-.43$</td>
<td>24</td>
<td>$p&lt;.05^*$</td>
</tr>
<tr>
<td>MQOL total scale</td>
<td>$r_s=-.62$</td>
<td>13</td>
<td>.02*</td>
</tr>
<tr>
<td>MQOL single item scale</td>
<td>$r_s=-.41$</td>
<td>13</td>
<td>.17</td>
</tr>
<tr>
<td>MQOL existential scale</td>
<td>$r_s=-.35$</td>
<td>13</td>
<td>.27</td>
</tr>
<tr>
<td>MQOL support scale</td>
<td>$r_s=-.33$</td>
<td>13</td>
<td>.27</td>
</tr>
<tr>
<td>MQOL psychological scale</td>
<td>$r_s=-.34$</td>
<td>13</td>
<td>.27</td>
</tr>
<tr>
<td>MQOL physical scale</td>
<td>$r_s=-.13$</td>
<td>13</td>
<td>.68</td>
</tr>
</tbody>
</table>

*MQOL: McGill Quality of Life Questionnaire
*significant
Table 30. Positive correlates of self-perceived burden

<table>
<thead>
<tr>
<th>Measure</th>
<th>R</th>
<th>n</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>rs=.21</td>
<td>24</td>
<td>.04*</td>
</tr>
<tr>
<td>Depression</td>
<td>rs=.15</td>
<td>21</td>
<td>.51</td>
</tr>
<tr>
<td>Carer Burden</td>
<td>rs=.3</td>
<td>21</td>
<td>.2</td>
</tr>
<tr>
<td>Time since symptom onset</td>
<td>rs=.16</td>
<td>21</td>
<td>.2</td>
</tr>
<tr>
<td>Time since diagnosis</td>
<td>rs=.16</td>
<td>21</td>
<td>.08</td>
</tr>
</tbody>
</table>

*significant

6.5.3 Caregiver burden

6.5.3.1 Level of Carer Burden

Caregiver burden scores ranged from minimal (2 points) to substantial burden (54 points) (n=32). The mean score was 21.63 (SD=14.01). Ten people scored above 27 points, the statistically-derived cut-off for high burden.

There was a small but non-significant negative correlation between carer burden and ALS Functional Rating Scale: rs=-.18, n=32, p=.33 (i.e. trend towards higher carer burden for patients with greater disability) and a medium positive, statistically significant correlation between carer burden and number of hours per day spent caring: rs=.43, n=32, p<.05. (Spearman’s Rank Order Correlation Coefficient (rs)).

6.5.3.2 Impact of carer burden

There were significant negative correlations between carer burden and carer QOL (total and existential scales); see Table 31. These results indicate lower QOL in those carers who report higher levels of burden (or vice-versa).

Table 31. Negative correlations of carer burden

<table>
<thead>
<tr>
<th>Carer Measures</th>
<th>r</th>
<th>N</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MQOL Total scale</td>
<td>rs=-.47</td>
<td>23</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>MQOL single item scale</td>
<td>rs=-.23</td>
<td>23</td>
<td>.28</td>
</tr>
<tr>
<td>MQOL existential scale</td>
<td>rs=-.51</td>
<td>23</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>MQOL support scale</td>
<td>rs=-.35</td>
<td>23</td>
<td>.11</td>
</tr>
<tr>
<td>MQOL psychological scale</td>
<td>rs=-.3</td>
<td>23</td>
<td>.17</td>
</tr>
<tr>
<td>MQOL physical scale</td>
<td>rs=-.29</td>
<td>23</td>
<td>.17</td>
</tr>
</tbody>
</table>

MQOL: McGill Quality of Life Questionnaire
*significant
Large positive, statistically significant correlation were found between:

- Carer burden and carer mood (carer anxiety, $r_s = .61, n = 31, p < .01$; and carer depression, $r_s = .57, n = 31, p < .01$).
- Carer burden and patient anxiety $r_s = .16, n = 25, p < .05$ (however no such correlation was seen with patient depression $r_s = .08, n = 24, p = .7$).
- Carer burden time elapsed from diagnosis date: $r_s = .43, n = 32, p < .05$.

Levels of carer burden were compared between those who had outside care provided (Group 1) and those who did not (Group 2). Of note there was no statistically significant difference in ALSFRS scores between Group 1 ($M = 36.3, SD = 5.6$) and Group 2 ($M = 36.8, SD = 9$; $t(29) = -.15, p = .88$). Those with outside care had a statistically significant increase in carer burden (Group 1: $M = 30.6, SD = 14.4$) versus those who did not (Group 2: $M = 17.1, SD = 12.1$; $t(29) = 2.7, p = .0$; independent samples t-test).

There was no difference in carer burden in males ($M = 20.4, SD = 11.8$) versus females ($M = 22.3, SD = 15.3$ $t(30) = -.36, p = .72$; independent samples t-test).

### 6.5.3.3 Carer Burden and Cognitive and / Or Behavioural Impairment

Carer burden (independent variable) in carers of patients with pure ALS ($n = 11$) was compared to carer burden in carers of patients with behavioural, cognitive impairment and dementia ($n = 21$). Of note there was no difference between ALSFRS in both patient groups ($t$ test; $p = 0.257$). Independent t-tests demonstrated no significant differences ($p = 0.332$) between the groups in carer burden i.e. the presence of cognitive and / or behavioural impairment in patients did not confer a higher burden upon caregivers.

### 6.6 Discussion

#### 6.6.1 Self-perceived

**6.6.1.1 Hypothesis One**

As an exploratory study, possible correlates of self-perceived burden such as severity of illness, quality of life, mood, carer burden and cognition were examined.

Self perceived burden has been linked to functional disability in patients with ALS (Chio 2005) and in patients with cancer (Simmons 2007). This finding is
echoed by the present study which found a trend, albeit non-significant, towards increased self-perceived burden with increased functional impairment. This may be attributable to patients' concerns about their increasing disability and physical needs, to their concerns for the psychosocial well-being of their loved ones, or alternatively may occur because some patients overestimate the psychosocial impact of the disease on their carers (Adelmann 2004).

Self-perceived burden was also found to correlate significantly with quality of life (MQOL total scale) in this project as well as non-significant correlations with the MQOL subscales i.e. higher self-perceived burden associated with lower QOL, or vice-versa. This replicates similar conclusions reported elsewhere (Cohen 2002; Vig 2003; Simmons 2007). Wilson (2007) found that in patients with advanced cancer, self-perceived burden was correlated with existential issues (loss of control, loss of dignity, hopelessness) and mood to an ever greater extent than physical status. The impact of self-perceived burden on QOL in what is already a devastating disease underpins why the former should be addressed to lessen patients' suffering.

Higher self-perceived burden was also associated with higher levels of depression, anxiety (statistically significant), carer burden and duration of illness as seen previously in patients with ALS (Chio 2005; Gauthier 2007) and in terminally ill patients also (Akechi 2004; Wilson 2007). The question remains however: do depression and anxiety occur as a result of this self-perceived burden or do they precede it?

The positive albeit non-significant correlation, between the self-perceived burden scale and carer burden in this study suggests that patients may have awareness of the impact of their condition on their carers; such patient insight is predictive of emotional distress in caregivers (Rymer 2002) and has been reported elsewhere (Chio 2005; Hecht 2003; Gauthier 2007). Numbers were too small to analyse whether this correlation between self-perceived and caregiver burden was present for those patients with ALS-FTD specifically; given the loss of insight that is inherent to this condition, such a correlation would not be expected thus leading to higher levels of carer burden (Phukan 2007).

But although patients may understand burden placed on caregivers, this understanding may be incomplete since self-perceived burden scores do not modify over time and with increasing disability (Gauthier 2007). A number of
carers in the present investigation felt that patients did not appear to understand that they could not cope with the intense physical and emotional demands exerted upon them; for example several patients refused to avail of respite even though carers had explicitly expressed their preference for same. This may have occurred because patients were unaware of the extent caregiver burden or because patients had a lack of insight related to frontotemporal dysfunction.

Self-perceived burden in this study was moderately but not significantly correlated with time since onset / diagnosis and significantly correlated with age. There was no significant correlation between self-perceived burden and number of hours of home help, the presence of a carer who was either a spouse or a child, patient gender or years of education – the latter finding was also reported by originators of the SPBS (Cousineau 2003).

6.6.2 Caregiver Burden

6.6.2.1 Hypothesis Two

It was predicted that carer burden would be high given the progressive physical disability of ALS, the grim prognosis and the lack of a curative therapy (Hecht 2003).

Although the degree of carer burden varied widely in this study, almost a third of carers (31.25%; n=32) described a high level of burden. In turn, higher levels of burden were associated with increased patient disability, increased number of hours spent caring, and longer duration of ALS. This is consistent with previous reports of increased carer burden with the worsening of patients’ disability, disease duration and increased numbers of hours of care (Hecht 2003; Chio 2005; Gauthier 2007). The implications of carer burden are discussed in the next section.

6.6.2.2 Hypothesis Three

It was predicted that carer burden would influence caregivers’ QOL and mood. Borasio et al (2001) observed that caring for a patient with ALS can take up to 14 hours each day; that 60% of tracheostomy caregivers lose their job as a result of caregiving; and that caregivers awaken up to 15 times per night. Caregivers’ physical and psychological well-being is unsurprisingly compromised (Krivickas 1997; Borasio 2001).
The present analysis demonstrated that higher levels of caregiver burden were linked to decreased quality of life in carers as seen previously (Chio 2005; Gauthier 2007). Negative correlations were observed between carer burden and all MQOL subscales with the largest and statistically significant correlations relating to the total and existential subscales. Similarly carer burden displayed a large positive correlation with carer mood (anxiety and depression).

This is of distinct concern since this study observed high levels of burden in almost a third of caregivers who were thus subject to diminished quality of life, depression and anxiety. In addition, caregiver well-being impacts on patients (Borasio 2001; Hebert 2001; Rabkin 2000; Chio 2005); this highlights the need to address the psychological state of caregivers.

Consistent with previous studies (Hecht 2003; Chio 2005), the presence of additional outside carers did not lower the burden on family carers. Higher burden in carers who had outside care was unrelated to the degree of patients' functional well-being (ALSFRS) and thus did not simple represent a higher need for care as reported elsewhere (Hecht 2003). It may be that those carers with higher burden in the first instance are more likely to avail of outside care or alternatively that outside carers are not sought until late into the illness when carer burden is already high.

This study also identified that carer burden had a small positive correlation with patient anxiety but no such correlation with patient depression, indicating that mood in patients with ALS can be affected by carer mood and vice versa. Studies of non-ALS patients have shown that depression in patients confers increased burden upon carers, perhaps even more so than physical impairment (Coyne 1987; Scholte 1998).

6.6.2.3 Hypothesis Four

It was predicted that carer burden would be higher in those caring for ALS patients with cognitive impairment, behavioural impairment and dementia. This hypothesis was made on the basis of elevated burden in carers of those with dementia compared to other disorders (Grasel 1997; Coen 1999; Mafullul 2000; Thommessen 2002; Hecht 2003; Pinquart 2003) and contributory
features of ALS-FTD including loss of insight, behavioural change and increased need for supervision.

However this study found that the presence of cognitive and/or behavioural impairment in patients did not confer a higher burden upon caregivers.

This unexpected result could have occurred because the hypothesis presumed that previous caregiver burden studies in dementia (mainly Alzheimer’s) could be extrapolated to ALS with frontotemporal dysfunction. However behavioural and cognitive changes that occur in many ALS patients are entirely different to those with Alzheimer’s dementia; for example studies (including this one) have consistently noted that apathy is the most common early behavioural change seen in those with ALS. One might postulate that apathy would be less burdensome to carers than some of the behaviours seen in later Alzheimer’s such as perseveration, paranoia, aggression and wandering since more passive behaviours are associated with apathy (Davis 2007). Although disinhibition does occur in frontotemporal dementia (Malloy 2007), the rapid physical decline of ALS precludes some of its characteristic behavioural manifestations including aggression, swearing, compulsions and impulsivity.

Finally premorbid personality in ALS patients specifically might be responsible for the findings of equivalent carer burden for patients with ALS plus dementia compared to patients with ALS alone. ALS sufferers are often described as “pleasant and warm”, “especially nice”, and may exert a great deal of emotional control (Wilbourn 1998; Borasio 2001; Grossman 2006). However, not all authors support the concept of a characteristic personality profile in ALS (Peters 1978). A large-scale study of carer burden in ALS-dementia would increase statistical power of this study’s findings.

6.7 Limitations

24 patients and 32 carers participated in this analysis of self-perceived and carer burden. This limited statistical power of some of our findings. Not all carers were willing to participate which could have led to selection bias i.e. either missing carers who were over-burdened or conversely those who had low levels of burden and felt the study did not apply to them. Similarly not all patients returned the SPBS; perhaps this sample was thus not representative all patients with ALS.
However, some degree of extrapolation is possible given the study's population-based nature (thus avoiding bias from tertiary centres), the use of standardised but adapted questionnaires previously used in ALS, incorporation of statistical methods to increase the power of analysis, and the integration of the recent consensus criteria (Strong 2009). Most importantly this is one of the first studies to examine burden in caregivers of ALS patients with cognitive impairment, behavioural impairment and dementia thus sowing the seed for future research in this area.

6.8 Implications, Clinical Applications and Future Research

This study found that self-perceived burden impacts markedly on patients’ quality of life and mood. This finding echoes other studies that have demonstrated that increased self-perceived burden is associated with loss of dignity, suffering, and a 'bad death' (McPherson 2007b), lower quality of life; poorer physical, emotional, and functional well-being; more depressive symptoms and greater financial distress (Simmons 2007). ALS patients must make decisions regarding advanced directives, choice of hospice care over home care and various interventions (e.g., feeding tubes, non-invasive ventilation); yet elevated self-perceived burden is implicated in such clinical decisions. A study of 97 hospitalised elderly patients found that respondents ranked "not wanting to be a burden" (73%) as the single most important factor when making decisions on medical care (Cohen-Mansfield 1997). This finding was echoed in other studies examining decisions around life-extending medical treatment and cardiopulmonary resuscitation (Zweibel 1989, Mead 1995).

The first step in addressing is self-perceived burden is having open discussions with patients and their families in an attempt to detect psychological distress, facilitate communication and awareness, and address misunderstandings, especially since patients with ALS can overestimate the psychosocial impact of the disease on their carers (Adelmann 2004). Cognitive and behavioural assessment of patients with ALS is also fundamental since disturbances in either can contribute to carer burden as discussed below.

This study identified carer burden in almost a third of carers which impacted upon carers' quality of life and mood. Addressing carer burden would thus
positively influence patients and families alike. The level of emotional support for caregivers is not consistent in all centres (Hebert 2005) but can be addressed by ALS multidisciplinary teams being available to talk, understanding correlates of burden, anticipating fears and problems, and providing appropriate referrals for counselling and support groups (Gallagher 2000; Radunović 2007). Interventions such as social problem solving (e.g. problem orientation, definition and formulation, problem solving skills, decision making, solution implementation) and stress appraisal could also represent a mechanism for lessening caregiver burden and distress (Hooker 2002; Elliott 2003; Murphy 2008).

Although clinicians can do little to alter the course of progressive dementia in ALS, informing carers about the evolution of FTD may mean that carers do not have to deal with events that are entirely unexpected. Behavioural interventions for patients aimed at increasing daily structure, creating routines, assisting with sequencing and problem-solving, and behavioural strategies to reinforce unwanted, inappropriate behaviours may be particularly useful in dementia caregiver interventions (Davis 2007).

Investigation of larger population-based cohorts would increase the statistical power of our findings. Standardised burden measures in ALS would be welcome, particularly since self-perceived burden has infrequently been evaluated in ALS. In addition, investigation is needed regarding the effects of elevated self-perceived burden on crucial decision-making. Similarly, there has been sparse research into burden in caregivers of patients with specific behavioural patterns e.g. predominant apathy versus predominant disinhibition. Further research may also clarify which strategies are best for addressing burden in ALS patients and their caregivers to alleviate psychological distress in a disease which already robs them of so much.
Chapter 7  A Population Based Longitudinal Study of Cognitive Impairment in ALS

7.1  Introduction

There have been no large population-based longitudinal studies of the natural history of cognitive impairment in ALS. Some small, clinic-based studies suggest that cognitive impairment evolves in ALS patients over the course of their illness. Strong et al (1999) noted a progression of cognitive impairment (including processes such as working memory, problem solving/cognitive flexibility, visual perception, and recognition memory for words and faces) in bulbar-onset ALS patients (n=8) over a 6-month period. Neuropathological analysis of these patients demonstrated neuronal loss in the anterior cingulate gyrus. Robinson et al (2006) reported that seven of nineteen patients with ALS developed cognitive deficits over a similar period of time although the between-group and within-group comparisons did not show significant differences in cognitive function over this period. (Robinson 2006). A third longitudinal study found relatively stable global cognitive functions over a 6-month period in patients who had ALS but no dementia (Abrahams 2005). Kilani (2004) also reported in a study of 18 patients and 19 matched controls that mild executive cognitive deficits, unlike neuromuscular function and depression, did not deteriorate over 12 months.

7.2  Aim

To complete a population-based longitudinal study of cognition in incident ALS patients with diagnosis classification guided by the recent consensus guidelines (Strong 2009).

7.3  Diagnosis classification and the role of the consensus guidelines

The consensus criteria for frontotemporal cognitive and behavioural syndromes in ALS were published as a result of discussions at the Second International Frontotemporal Dementia in ALS Research Conference (London, Ontario, June 2007) which this author attended.
Diagnostic categorisation as defined by the consensus criteria encompasses five main diagnoses which are outlined in full in Appendix 2 i.e. ALS-FTD (both behavioural and language variant); ALS-behavioural impairment (ALSbi); ALS-cognitive impairment (ALSci); ALS-comorbid dementia and ALS – the latter refers to those patients who have ALS alone without cognitive or behavioural impairments.

The utility of the consensus criteria were explored in the current longitudinal study, results of which are outlined below. Firstly it is worth mentioning that although guidelines facilitated categorisation of subgroups to track the evolution of cognitive and behavioural impairment over time, several difficulties were encountered.

Misclassification occurred in at least 9 patients (22%) with use of the consensus criteria highlighting the potential weakness of these parameters. This included 6 patients originally meeting criteria for behavioural impairment (i.e. ALSbi or ALS-comorbid dementia) and then being found to have no behavioural impairment six months later. Similarly 2 patients had ALSci at baseline met criteria only for ALSbi or pure ALS at Time Two.

Practice effects on tests in conjunction with relatively stable cognition over time may explain this shift from ALSci to pure ALS. Patients often expressed that they found T2 testing less stressful because they “knew what to expect” and also that the trauma of their initial diagnosis was further behind them. A finding of cognitive at impairment at T1 might thus be due to such confounding factors and not due to a neurodegenerative process.

The shift from ALSbi to ALS might occur because criteria required to meet ALSbi at T2 are difficult to identify with increasing physical disability. Patients with greater levels of functional impairment are less likely to demonstrate impulsiveness, hyperorality restlessness, distractibility, motor perseveration and sexual hyperactivity. Correspondingly a decline in personal hygiene may not be observed since patients become dependent on others for self-care. Finally, the syndromes of ALSbi and ALSci are not mutually exclusive and whilst creation of subgroups is useful in the research setting, this can be difficult to apply to clinical practice.
The discrepancy between supportive Neary criteria versus self-rated and carer-rated measure of the FrSBe (the latter is recommended as a supportive measure) was discussed in Chapter Four. Both measures yielded disparate outcomes at both baseline assessment and at follow-up with limited overlap between the two sets of defining criteria. This might be due to FrSBe paradigms not accounting for the physical disability or the terminal nature of ALS, and accordingly being over-sensitive to pathological behavioural change (Grossman 2007; Strong 2009). In addition, strict application of the Neary criteria may underrate the prevalence of behavioural variant (frontal) FTD (Piguet 2009) and the same underestimation may apply to ALSbi.

These various problems in defining behavioural impairment currently mean that definition of ALS-cognitive impairment (a quantitative assessment of cognition compared to matched controls) is more reliable than that of ALSbi despite the former’s shortcomings.

Nonetheless the results below discuss impairment in both cognitive and behavioural terms; the Future Directions section explores how the issues above might be addressed.

7.4 Specific Hypotheses

7.4.1 Primary hypothesis: Evolution of cognitive and behavioural impairment over time.

It was hypothesized that cognitive decline (affecting executive domains in particular) and behavioural impairment in a proportion of patients would worsen over time with some progressing to develop full-blown frontotemporal dementia.

Rationale: Given that ALS and frontotemporal dementia (FTD) show clinical genetic, pathologic and radiological overlap (Phukan 2007), and given that FTD is a neurodegenerative disease, one might expect progressive cognitive and/or behavioural change in ALS. Some studies have corroborated this prediction (Neary 1990; Strong 1999; Neary 2000; Robinson 2006). Similarly up to 15% of patients with FTD develop ALS (Lomen-Hoerth 2002; Vercelletto 2003). However other studies have reported relatively stable cognition or slow progression over time (Kilani 2004; Abrahams 2005).
It is not yet known with certainty whether frontotemporal syndromes in ALS are part of a biological spectrum or continuum with inevitable progression to dementia (Strong 2008). Abrahams et al (2005) noted that extra-motor structural abnormalities may be present in ALS patients with no evidence of cognitive change. The authors conclude that these findings support the hypothesis of a continuum of extra-motor cerebral and cognitive change in this disorder. However studies to date have used pooled data, have not been population-based, and have not assessed cognitively well-characterised patients with pathological and imaging correlates.

A finding that not all patients develop impaired cognition would argue against such a continuum being expressed in individual patients over time, at least in a subset. Instead it would support the possibility that pure ALS, ALS with impairment, and ALS with dementia exist as clinically discrete entities presenting in individual patients without progression from one “category” to another. However, as it is known that “pure” ALS and ALS-dementia can occur in different members of the same family, a “continuum” clearly exists with regard to pathogenic mechanisms. The factors that determine whether individual patients are likely to “travel” across such a continuum remain to be determined.

Prospective longitudinal, population-based clinical studies are therefore needed to determine the presence and extent of progression of cognitive and behavioural impairment in ALS.

7.4.2 Hypothesis Two: Factors predicting the development of cognitive and behavioural impairment over time.

It was hypothesised that certain factors would predict the development of cognitive and behavioural impairment in ALS over time in a subset of patients. This exploratory work was based on our clinical experience that patients with no impairments at baseline testing seem to be less likely to develop deficits over time.

This study sought to determine whether factors such as baseline categorical diagnosis (pure ALS versus ALS-impairment) or deficits on specific executive tests would predict the presence of dementia at follow-up. Although pathological and imaging correlates would be required to strengthen this
conclusion, the present aim was to identify clinical predictors at baseline evaluation that would foresee which patients would later develop such impairment.

7.4.3 Hypothesis Three: Survival in patients with cognitive and behavioural impairment

It was also postulated that patients with cognitive and behavioural impairment would have a more rapid progression of ALS. Shortened survival times have been observed in patients with ALS-dementia compared to those with ALS alone, possibly due to non-compliance with interventions such as non-invasive ventilation (Olney 2005).

7.5 Methodology

7.5.1 Participants

Case ascertainment, patient and control recruitment, inclusion and exclusion criteria, ethical approval and data protection have been described in detail in Chapter Three (Section 3.5). Patients with a diagnosis of ALS-FTD at T1 were not assessed at T2.

7.5.2 Participant assessment

Repeat neuropsychological and behavioural assessment was conducted after six months with the same fixed test order although the WTAR measuring premorbid intellectual ability was omitted as the first assessment was valid for all subsequent evaluations. Demographic details were confirmed, note was made of changes in medication, occupational status, home help, respiratory function and level of physical disability (ALSFRS-R).

This chapter presents results collected over a six month period; the twelve month project is ongoing.

7.5.3 Statistical Analysis

This analysis was conducted as described in Chapter Three. Patients were assigned to categorical groups including ALS, ALS-cognitive impairment, ALS-behavioural impairment, ALS-frontotemporal dementia and ALS-comorbid dementia as defined by consensus guidelines (Appendix 2).
Paired sample t-tests were used to compare the means of patients’ scores at Time One and Time Two to determine whether significant change had occurred between Time One and Time Two (null hypothesis: there was no significant difference between the means of the two variables).

Survival of subgroups was compared with graphical illustration of the as examined by plotting Kaplan-Meier curves. Survival was defined as the time from the onset of diagnosis to time of death, or the current date if the patients were still alive. Only diagnosis at Time One was examined in the analysis. As not all patients died, it was necessary to use ‘survival’ analysis methods to distinguish survival times from those who subsequently died from those who did not die. A formal statistical analysis of survival in the various groups was examined using the logrank test.

Initially comparisons were made between all five subgroups (ALS, ALSci, ALSbi, ALS-comorbid dementia and ALS-FTD. For subsequent analysis the diagnoses were combined together to compare all ALS-impaired diagnoses against “pure” ALS diagnosis.

Statistical analysis was undertaken using the Statistical Package for the Social Sciences version 15.0 (SPSS) and in collaboration with colleagues in the Neuropsychology component of Trinity Institute of Neuroscience (TCIN).

7.6 Results

7.6.1 Participant characteristics

7.6.1.1 Sample size

87 patients on the Irish register participated at Time One (T1). These patients were identified during the study recruitment period (March 2006-August 2008).

41 patients participated at Time Two (T2) assessment some six months later (195.9 days, SD=35.05). 46 patients did not participate (Table 32) of whom 19 had a preceding diagnosis of dementia.

Of those who died between T1 and T2 (n=11), one patient had evidence of cognitive impairment at baseline, another patient had behavioural impairment, one had both cognitive and behavioural impairment, and eight patients had “pure” ALS on first assessment.
Of those who were too unwell for follow up at T2 (n=5), two patients had evidence of cognitive impairment at baseline, two patients had behavioural impairment, and one patient had "pure" ALS.

Of those who declined to participate (n=5), two patients had cognitive impairment at baseline, one patient had behavioural impairment, and two patients had "pure" ALS.

<table>
<thead>
<tr>
<th>Table 32.</th>
<th>Reasons for non-participation at Time Two</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Excluded on the basis of FTD / AD / VaD*</td>
<td>19</td>
</tr>
<tr>
<td>Died</td>
<td>11</td>
</tr>
<tr>
<td>Declined</td>
<td>5</td>
</tr>
<tr>
<td>Unwell</td>
<td>5</td>
</tr>
<tr>
<td>Emigrated</td>
<td>1</td>
</tr>
<tr>
<td>No response</td>
<td>3</td>
</tr>
<tr>
<td>Pending at time of analysis</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
</tr>
</tbody>
</table>

*FTD = fronttemporal dementia; AD = Alzheimer's disease; VaD = vascular dementia.

There were no significant differences in age or mood between those who participated in one assessment versus those who participated in two (independent samples t-test); however there was a significant difference in ALSFRS (Table 33).

<table>
<thead>
<tr>
<th>Table 33.</th>
<th>Characteristics of patients who participated in one interview versus those who participated in two interviews.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participation in one interview only</td>
<td>Participation in two interviews</td>
</tr>
<tr>
<td>Mean Age</td>
<td>65.14 (10.8)</td>
</tr>
<tr>
<td>ALSFRS*</td>
<td>37.55 (6.81)</td>
</tr>
<tr>
<td>Depression</td>
<td>4.4 (4.21)</td>
</tr>
</tbody>
</table>

*This significance was maintained when the data were transformed using a reflect and logarithm procedure to normalise the distribution of the ALSFRS scores.

7.6.1.2 Demographic variables

17.1% (n=7) of patients had bulbar onset disease, and 82.9% (n=34) had limb onset ALS. 7% of patients were working outside the home at Time Two compared to 18.4% at Time One.
7.6.1.3 Clinical variables

At Time Two, mean ALSFRS was 32.78 (8.35). Mean time since diagnosis was 424.10 days (SD 147.36). All but 4 patients were on Riluzole. 21 patients were on low dose psychotropic medications, most commonly SSRIs and amitriptyline for emotional lability.

4.7% (n=2) had oxygen saturations below 95mmHg. One of these patients was using NIV for 5 hours each day, the other patient was not.

17% (n=7) had elevated carbon dioxide levels above 6kPa – however 5 of these patients only had marginal elevations (i.e. 6.1 – 6.2mmHg). One other patient with a CO2 level of 6.9mmHg was using NIV for 10 hours each day.

The following results section is divided into three key parts:

1 T1 versus T2 performance on cognitive testing (7.5.2)
2 T1 versus T2 performance on behavioural testing (7.5.3)
3 Evolution of ALS with / without impairment over time. (7.5.4)

7.6.2 Time One versus Time Two performance on cognitive testing

Comparisons between patients and controls were first made through evaluation of paired differences and then as guided by consensus criteria.

7.6.2.1 Paired differences

Paired differences of the cohort (Table 34) demonstrated scores on each test over a six month interval. There was a statistically significant increase (i.e. improvement) in:

- Logical Memory 2 Recall Total Score Scaled from Time One (M=8.71, SD =3.13) to Time Two (M=10.58, SD=3.36; t(30)=-4.28, p 0.00).
- Verbal Paired Associates 1 Recall Total Score Scaled from Time One (M=9.39, SD =3.05) to Time Two (M=10.16, SD=3.31; t(30)=-2.30, p 0.029).
- Verbal Paired Associates 2 Recall Total Score Scaled from Time One (M=9.39, SD =3.04) to Time Two (M=10.42, SD =3.12; t(30)=-3.41, p 0.002).
- Rey Complex Figure Test 2 Immediate Percentile from Time One (M=42.52, SD =37.31) to Time Two (M=51.41, SD=40.08; t(28)=-2.31, p 0.00).
7.6.2.2 Consensus criteria

By Time Two 7% (n=3) of the entire T2 patient cohort (n=41) had ALSci i.e. impairment on standardised neuropsychological testing at or below the 5th percentile, compared to age- and education matched controls at T1 (Table 35). This includes patients with ALSci at Time One and patients with a new diagnosis of ALSci at T2.

Table 34. Paired Differences on Neuropsychological Testing at Time One and Time Two

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
<th>SD</th>
<th>SEM</th>
<th>Sig. (2-tailed) SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 Raven's (36) - T2 Raven's (36)</td>
<td>0.46</td>
<td>3.82</td>
<td>0.63</td>
<td>0.470</td>
</tr>
<tr>
<td>T1 BNT (30) - T2 BNT (30)</td>
<td>-0.12</td>
<td>2.93</td>
<td>0.46</td>
<td>0.790</td>
</tr>
<tr>
<td>T1 LM1 RTS Scaled - T2 LM1 RTS Scaled</td>
<td>-0.68</td>
<td>2.45</td>
<td>0.44</td>
<td>0.130</td>
</tr>
<tr>
<td>**T1 LM2 RTS Scaled - T2 LM2 RTS Scaled</td>
<td>-1.87</td>
<td>2.43</td>
<td>0.44</td>
<td>0.000</td>
</tr>
<tr>
<td>*T1 VPA1 RTS Scaled - T2 VPA1 RTS Scaled</td>
<td>-0.77</td>
<td>1.87</td>
<td>0.34</td>
<td>0.030</td>
</tr>
<tr>
<td>*T1 VPA2 RTS Scaled - T2 VPA2 RTS Scaled</td>
<td>-1.03</td>
<td>1.68</td>
<td>0.3</td>
<td>0.000</td>
</tr>
<tr>
<td>T1 Digit Span Scaled - T2 Digit Span Scaled</td>
<td>0.41</td>
<td>1.88</td>
<td>0.33</td>
<td>0.230</td>
</tr>
<tr>
<td>T1 Digit Span Scaled - T2 Digit Span Scaled (Backwards)</td>
<td>0.72</td>
<td>2.92</td>
<td>0.52</td>
<td>0.170</td>
</tr>
<tr>
<td>T1 Stroop Standardized percentile - T2 Stroop Standardized percentile</td>
<td>1.69</td>
<td>14.95</td>
<td>2.64</td>
<td>0.530</td>
</tr>
<tr>
<td>T1 Brixton Percentile equivalent - T2 Brixton Percentile equivalent</td>
<td>-6.66</td>
<td>30.39</td>
<td>4.75</td>
<td>0.170</td>
</tr>
<tr>
<td>T1 Written VFI Score - T2 Written VFI Score</td>
<td>-11.9</td>
<td>88.24</td>
<td>16.39</td>
<td>0.470</td>
</tr>
<tr>
<td>T1 VFI Score - T2 Spoken VFI Score</td>
<td>-0.54</td>
<td>5.28</td>
<td>3.73</td>
<td>0.910</td>
</tr>
<tr>
<td>T1 Category Fluency - T2 Category Fluency</td>
<td>0.72</td>
<td>4.75</td>
<td>0.95</td>
<td>0.460</td>
</tr>
<tr>
<td>T1 Rey Copy Percentile - T2 Rey Copy Percentile</td>
<td>2.14</td>
<td>7.68</td>
<td>1.43</td>
<td>0.140</td>
</tr>
<tr>
<td>**T1 Rey Immediate Percentile - T2 Rey Immediate Percentile</td>
<td>-8.9</td>
<td>20.73</td>
<td>3.85</td>
<td>0.030</td>
</tr>
<tr>
<td>T1 Rey Delayed Percentile - T2 Rey Delayed Percentile</td>
<td>-6.97</td>
<td>20.07</td>
<td>3.73</td>
<td>0.070</td>
</tr>
<tr>
<td>T1 Stan CVLT free recall 5 - T2 Stan CVLT free recall 5</td>
<td>-0.28</td>
<td>0.94</td>
<td>0.19</td>
<td>0.150</td>
</tr>
<tr>
<td>T1 Stan CVLT short delay free recall - T2 Stan CVLT short delay free recall</td>
<td>-0.22</td>
<td>0.72</td>
<td>0.14</td>
<td>0.140</td>
</tr>
<tr>
<td>T1 Stan CVLT short delay cued recall - T2 Stan CVLT short delay cued recall</td>
<td>-0.2</td>
<td>1.09</td>
<td>0.22</td>
<td>0.370</td>
</tr>
<tr>
<td>T1 Stan CVLT long delay free recall - T2 Stan CVLT long delay free recall</td>
<td>-0.2</td>
<td>0.96</td>
<td>0.19</td>
<td>0.310</td>
</tr>
<tr>
<td>T1 Stan CVLT long delay cued recall - T2 Stan CVLT long delay cued recall</td>
<td>-0.14</td>
<td>0.91</td>
<td>0.19</td>
<td>0.460</td>
</tr>
</tbody>
</table>

T1 = Time 1. T2 = Time 2. BNT = Boston Naming Test; LM RTS = Logical Memory Recall Total Score; VPA = Verbal Paired Associates; VFI = Verbal Fluency Index; CVLT = California Verbal Learning Test.

**Significant at 0.001
* Significant at 0.05
7.6.2.3 Consensus criteria

Table 35. ALS subgroups at Time Two

<table>
<thead>
<tr>
<th>ALS Group</th>
<th>Time Two n</th>
<th>Time Two %</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTD*</td>
<td>4</td>
<td>9.80</td>
</tr>
<tr>
<td>ALS-comorbid dementia</td>
<td>8</td>
<td>19.5</td>
</tr>
<tr>
<td>ALSci</td>
<td>3</td>
<td>7.3</td>
</tr>
<tr>
<td>ALSbi**</td>
<td>8</td>
<td>19.5</td>
</tr>
<tr>
<td>No abnormality</td>
<td>8</td>
<td>19.5</td>
</tr>
<tr>
<td>Unknown caseness</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>100</td>
</tr>
</tbody>
</table>

*Includes fvFTD, NFPA and SD
** As defined by FrSBe

7.6.3 Time One versus Time Two performance on behavioural testing

7.6.3.1 Neary Criteria

Of the patients who had participated at both T1 and T2, behavioural impairment as defined by supportive Neary criteria (Appendix 2) at T2 was seen in an additional 4 patients. 2 had had ALSbi at T1, 2 others had not.

7.6.3.2 FrSBe

20% (n=8) of all patients at T2 had behavioural impairment as defined by deviating from one or more of the subscales (Apathy, Executive Dysfunction and Disinhibition) and total "Before" norms by two standard deviations or by a T score of greater than 65 (Grace 2001; Mosnik 2006). This includes all patients with ALSbi (as per FrSBe) at T1 in addition to those newly diagnosed with ALSbi at T2.

7.6.3.3 Dementia

10% had FTD (n=4) at T2. Three had frontal (behavioural)-variant FTD, one other had NFPA. As discussed in the next section, all had evidence of cognitive or behavioural impairment on baseline testing.

8 others (20%) had ALS-comorbid dementia at T2 - they had all had had ALSbi or ALSci at baseline indicating a significant clinical progression of their impairment.

Defining caseness in nine patients was difficult as they appeared to have shifted between consensus categories over time - for example from ALS-
comorbid dementia to ALSci (n=4), ALSci to “pure” ALS (n=2), ALSbi to “pure” ALS (n=2) and ALSci to ALSbi (n=1). Potential reasons for this are discussed below.

**Table 36.** ALS subgroups percentages at T1 and T2

<table>
<thead>
<tr>
<th>ALS Group</th>
<th>Time One (%) n=87</th>
<th>Time Two (%) n=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTD*</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>ALS-comorbid dementia</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>ALSci</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>ALSbi**</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>No abnormality</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td>Unknown caseness</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

*Includes fvFTD, NFPA and SD
** As defined by FrSBe

7.6.4 **Evolution of cognitive and behavioural impairment**

The progression of cognition and behaviour is described in Table 37.

**Table 37.** Evolution of ALS, ALSci and ALSbi

<table>
<thead>
<tr>
<th>Time Two</th>
<th>ALS***</th>
<th>ALSbi**</th>
<th>ALSci</th>
<th>ALSi-CD</th>
<th>ALSFTD***</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS n=8</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ALSci n=4</td>
<td>0</td>
<td>n/a*</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ALSbi FrSBe n=8**</td>
<td>0</td>
<td>3</td>
<td>n/a*</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>ALS-CD n=4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

* Non-applicable since concomitant ALSbi and ALSci are defined as ALS-comorbid dementia.
** ALSbi is defined as per FrSBe in this graph. However 2 patients with pure ALS developed ALSbi at T2 (as per Neary supportive criteria) in contrast to 8 new cases of ALSbi based upon FrSBe criteria.
***“Pure” ALS

7.6.5 **Survival in patients with cognitive and behavioural impairment**

Survival was measured from the date of onset of symptoms.

Initially the survival in the five diagnosis groups was examined separately (Figure 1).
A logrank test gave a p-value of 0.15 i.e. no evidence of a difference in survival between the five groups.

A comparison of survival in patients with ALSci only compared to the pure ALS group was also made. The logrank test gave a p-value of 0.93, again no evidence of a difference between groups.

Subsequently the four impaired ALS groups (ALSci, ALSbi, ALS-comorbid dementia and ALS-FTD) were combined together and compared to the pure ALS group (Figure 2). The logrank test yielded a p-value of 0.75 i.e. no evidence of a difference in survival between groups.
Figure 2. Survival in ALS versus ALS-impaired

7.7 Discussion

This was the largest ever longitudinal study of cognition and behaviour in ALS. It was unique in that it tracked a population-based cohort of ALS patients. Home visits facilitated follow-up of 2-3 times the number of patients in other longitudinal studies to date.

7.7.1 Hypothesis One: Evolution of cognitive and behavioural impairment over time.

It was hypothesized that cognitive decline (affecting executive domains in particular) and behavioural impairment in a proportion of patients would worsen over time with some progressing to develop full-blown frontotemporal dementia.

1 The progression of cognitive impairment over time was examined through paired differences at Time One and Time Two. There was a statistically significant increase in some measures of memory; however there was no change over time with regard to other cognitive domains even with increasing functional impairment. This is in agreement with prior research that has shown relatively stable cognition or slow progression over time.
(Abrahams 2005; Kilani 2004) and even improvement in measures of memory (Röttig 2005; Lakerveld 2007). As per consensus criteria, 2 of 4 patients still carried diagnosis of ALSci at T2 testing; another had developed accompanying behavioural impairment, and a final patient was diagnosed with ALS-FTD.

Improvements in memory tests may be due to practice effect due to more than one exposure to the same test as seen with a number of memory tests (Bornstein 1994; Claus 1991; Crawford; McCaffrey 1992). It might also be due to fewer cognitively impaired patients participating in the 6-month assessment due to increased disability or elevated risk of mortality (Olney 2005).

Lakerveld et al (2007) reported that learning and memory significantly improved in patients in the later stages of the disease even after controlling for depression, ventilation dependency and duration of disease. Interestingly, the authors postulate that these improvements in advanced disease occur since preserved skills such as learning and memory are more utilised and trained ("trained what remained") in order to (a) adapt to the social environment and (b) remember conversations because clarification of same is compromised by communication difficulties. This idea of memory "training" is also supported by Papps et al (2005).

Yet this concept of longitudinal improvement in memory conflicts with the suggestion of greater temporal lobe involvement in ALS than previously recognised (Kato 1993; Okamoto 1998; Schmolck 2007).

This attrition rate of this study makes interpretation particularly difficult yet reflects the reality of ALS progression seen at clinics where 80% of patients have a life expectancy of 3-5 years from the time of diagnosis.

2 Behaviour in ALS was explored longitudinally. Of 8 patients with evidence of behavioural impairment at baseline, 3 still were classified as having ALSbi, 2 developed accompanying ALSci, and 3 others developed FTD (Table 37); i.e. patients with ALSbi were prone to progress but did not inevitably develop dementia over a six month interval.

It is impossible to be certain how cognitive and behavioural impairment evolved within the original cohort since not all participated at T2. Yet it
seems that ALSci and ALSbi do not inexorably progress to dementia as correctly suggested by the original hypothesis; only a subset of patients in this study showed such evolution over a six month period. To definitely determine whether discrete categorical entities can be defined within the ALS spectrum of disease, a longer length of follow-up with pathological correlates will be required.

7.7.2 Factors that predict development of cognitive and behavioural impairment in ALS over time

The diagnosis at baseline (ALS, ALSbi, ALSci, ALS-FTD) gives some indication of prognosis (Table 37). Although larger numbers are required to carry out meaningful statistical comparisons, preliminary analysis of this dataset suggests that that the majority of patients with pure ALS at the time of first testing do not develop cognitive and / or behavioural impairment over a six month period. 75% of patients with a diagnosis of "pure" ALS at baseline remained that way after six months. In fact no patient with "pure" ALS developed dementia.

Conversely, 50% of patients with ALSci progressed to dementia and 63% of those with ALSbi had progressed to dementia.

These preliminary findings corroborate our clinical suspicion that patients with no impairments are less likely to develop deficits over time. A population-based longitudinal analysis over 18 months is now underway to further explore these conclusions.

7.7.3 Survival in patients with cognitive and behavioural impairment

This analysis found that patients with cognitive and behavioural impairment did not have lower survival rates than did those with ALS alone. Of note these groups did not differ with respect to age, site of onset or ALSFRS. There was also no correlation between cognitive / behavioural impairment and time since first symptom (Chapter Four).

This finding contradicts previous findings. Olney et al (2005) reported that patients with ALS who also have dementia were twice as likely to be noncompliant with interventions including non-invasive ventilation and that survival times were significantly shorter than for patients with classic ALS.
These diminished survival rates were thought to reflect patients' lack of insight and incapacity to use and comply with interventions that could prolong their lives e.g. non-invasive ventilation use, nutritional advice from dieticians, safety awareness recommendations from occupational therapists, and methods to avoid choking as discussed with speech and language therapists.

Another possibility for decreased survival in ALS patients with cognitive impairment is the presence of a distinct genetic and pathological signature operating in this subset of patients contributing to a different phenotype. For instance, the progranulin gene (*PGRN*) acts as a modifier of the course of disease in ALS patients, through earlier onset and shorter survival (Sleegers 2008).

The hypothesis of decreased survival in cognitive and behaviourally impaired patients was however refuted. The suggestion of longer survival times in ALS and ALSbi (see Figure 1) is not borne out statistically but might be evident with longer follow-up and refinement of the consensus criteria to better distinguish ALS subgroups.

### 7.8 Limitations

#### 7.8.1 Participants

Attrition rates are high in studies of ALS due to the progressive and devastating nature of the illness (Strong 1999; Abrahams 2005). Almost 60% of eligible patients were assessed at both T1 and T2. However data was available for 80% as 20% already had a diagnosis of dementia. Kilani et al (2004) reported that 13 of 20 ALS patients (65%) were interviewed 12-months after the initial assessment. Schreiber (2005) reported a 37% participation rate after 12 months. The patients who died, declined to participate, or were unwell may have had a different cognitive profile and evolution thereof to this study's participants. Nonetheless the current analysis is the largest longitudinal population-based study to date and has demonstrated that home visits can optimise follow-up, particularly in the later stages when disability prevents travel to clinic.

This analysis only examined patients after a six month interval but average time after diagnosis was 424.10 days (SD 147.36) which suggests that cognitive and or behavioural impairment would be detectable at that stage.
In many cases progressive bulbar and limb disability precluded certain tests at Time Two; accommodation was made so that tests were adapted if possible. Nonetheless this analysis could be liable to under- or over-estimation of cognitive and behavioural impairment.

The possibility of practice effects contributing to improvement might be expected to be defined with further control recruitment. But Schreiber et al (2005) noted that comparison with normal controls would not solve the problem since repetition effects are known to express themselves differentially in healthy subjects and cognitively deficient persons with the former seemingly exhibiting higher learning effects (des Rosiers 1987; Darby 2002).

Perhaps one of the greatest limitations to this work was the difficulty posed by the inability of the consensus criteria to classify 22% of patients at T2. These patients met criteria for cognitive and/or behavioural impairment at T1, yet were classified as having no impairment six months later. Confounding factors, practice effects, and insensitivity of the criteria to recognise impairments with increasing disability are contributory factors (Section 7.3). A parsimonious approach would classify this cohort as “pure ALS” with confounders operating at T1; however, the phenomenon indicates the urgent requirement to perform an appropriate validation study of the consensus criteria, and appropriate adjustment prior to their application to clinical practice.

The difficulties posed by the existing criteria made the identification of early prognostic indicators (such as impaired verbal fluency) difficult. Such predictors may be possible to establish in the ongoing larger cohort - our preliminary data suggested that in those with “pure” ALS at T1 who progressed to “ALSci”, evidence of mild verbal fluency deficits was an early marker of evolving cognitive difficulties.

### 7.9 Clinical applications

The unique aspect of this study is that it tracked a population-based cohort of patients with mild cognitive impairment to determine whether they progress to a more severe frontotemporal dementia phenotype.
Perhaps one of the most important outcomes of this study is the observation that the recent consensus criteria require a more rigorous validation process prior to their use in clinical practice.

With replication in larger cohorts, and using modified criteria, this and future studies may help guide clinicians in advising patients and their families about the risk of cognitive and behavioural impairment. Patients with pure ALS at presentation are less likely to develop dementia 15 months after symptom onset; although some patients with cognitive and behavioural impairment progress to FTD over the same interval this is not inevitable. With refinement of the consensus criteria it might be possible to predict which patients will develop dementia on the basis of selected neuropsychological tests.

The evolution of cognitive and behavioural impairment in a subset of patients underscores the importance of regular evaluation in ALS given the potential of compromised capacity, decline in psychological well-being in patients and their caregivers, and decreased survival.

7.10 Future Research

Future prospective studies should incorporate pathological and imaging correlates with neuropsychological evaluation since radiological and autopsy evidence of frontotemporal dysfunction may not be evident on routine neuropsychological testing. This research should confirm whether ALS patients fall into true subgroups (no/mild/severe impairment) with differential rates of progression.

Ideally patients should be followed up for the longest periods possible with acceptance that attrition rates may limit this approach. However Lakerveld et al (2008) examined cognitive function in patients late stage ALS (average 56.8 (43.8) months since diagnosis; mean ALS-FRS 11.9 months (8.2)) and demonstrated that evaluation at this late-stage is possible albeit with a less comprehensive test battery and challenges in accommodating for limb and bulbar disability. As evidenced by missing data at Time Two assessment in the present study, the formulation of a test battery that provides optimal broad evaluation of late-stage patients with ALS is very much needed.
Finally, this study was an initial "stress test" of the new consensus criteria. The development of the El Escorial criteria for ALS diagnosis (Brooks 1994) likewise led to validation studies which refined and revised these criteria (1998). With further population-based longitudinal studies the new consensus criteria will similarly be improved to define frontotemporal cognitive and behavioural syndromes in ALS.
Chapter 8  Medical Decision-Making Capacity in patients with ALS

8.1 Introduction

Medical Decision-Making Capacity (MDC) refers to an individual's cognitive and emotional capacity to accept a medical treatment, refuse treatment, or select among treatment alternatives (Grisso 2003). Also known as consent capacity, it plays a pivotal role in determining whether a person can exercise autonomy (Raymont 2002). Compromise of MDC has important clinical, legal, and ethical consequences for patients, their families, and clinicians.

The legal history of capacity in case law has been well-described elsewhere (Raymont 2002). Criteria for incapacity were developed in the case of a patient with schizophrenia who refused amputation of his gangrenous leg and applied for an injunction stipulating that amputation could not be performed without his written consent. This resulted in the development of the 'Eastman' test of capacity [Re C [1994] 1 All E.R. 819]. This asks the following questions:

1. Can the patient comprehend and retain the information given to them about the proposed treatment?

2. Does the patient believe the information given to them?

3. Can the patient weigh the information in the balance and arrive at a choice?

The UK Mental Capacity Act (2005) incorporates the concepts in defining inability to make decisions but omits whether the patient believes the information given to them and adds the stipulation that (s)he should be able to communicate his / her decision (whether by talking, using sign language or any other means).

The Irish Mental Capacity Bill 2008 defines capacity as the ability to understand the nature and consequences of a decision in the context of available choices at the time the decision is made; it seeks to emphasise capacity, dignity and autonomy rather than a lack thereof and allows for defining either temporary or permanent capacity. It follows the principles of the UK Mental Capacity Act (2005) noted above. The new Irish Bill also aims
to reform the current cumbersome system of Wards of Court whereby the incapacitated individual is deemed unable to make any decisions; legislation is instead incorporated regarding enduring powers of attorney / personal guardians who can make decisions on behalf of a person who has agreed to pass on decision-making powers in the event of incapacity. Also proposed is an Office of Public Guardian to supervise this personal guardianship. However certain judgments regarding non-therapeutic sterilisation, withdrawal of artificial life-sustaining treatment or organ donation are only to be made in the High Court. However, the Bill has yet to be implemented despite its acknowledgement that the 1871 Lunacy Regulations Ireland Act is outdated, inappropriate and in need of urgent reform. Current legislation may also contravene the Hague Convention on the International Protection of Adults and the UN Convention on the Rights of Persons with Disabilities.

In one UK study of 302 consecutive acute medical in-patients up to 40% were found to lack mental capacity (Raymont 2004); those with neurological conditions and infectious diseases were most commonly found to lack decision-making capacity.

Obtaining valid informed consent from patients is premised on the disclosure of appropriate information to a competent patient who is permitted to make a voluntary choice (Appelbaum 2007). Healthcare providers should be able to identify the presence of capacity (facilitating autonomy) or incapacity (protecting patients and obtaining substitute decisions).

However, healthcare providers often fail to identify the presence of capacity or incapacity (Fitten 1990a; Fitten 1990b; Cohen 1993; Etchells 1997); are sometimes unaware of the recommended criteria for defining capacity or lack thereof; and may see particular clinical diagnoses or mental status examination as surrogate measures for incapacity (McKinnon 1989).

8.2 Decision-Making Capacity in patients with ALS

Capacity compromise is an inevitable consequence of Alzheimer’s disease (Marson 1994; Kim 2002). It is also found in varying rates in schizophrenia (Jeste 2006; Candilis 2007), stroke (Rosenbaum 2005; White-Bateman 2007; Akinsanya 2009) and depression (Applebaum 1999; Lapid 2003).
But of course most medical and surgical conditions are heterogeneous; thus a lack of decision-making capacity cannot be made on the basis of disease diagnosis alone.

Capacity in ALS has not been systematically examined to date. With the realisation that frontotemporal and executive dysfunction is common in ALS (Phukan 2007) and that diminished insight is a predictor of impaired capacity (Cairns 205), it might be expected that a substantial number of patients with ALS would have reduced medical-decision making capacity.

Executive functions are traditionally thought of as higher-level mental processes that enable the control and organisation of other cognitive processes (Shallice 1988). They are a heterogeneous set of skills that facilitate problem solving and responses to novelty. The frontal-striatal systems are also implicated in non-executive behavioural regulation, response initiation, motivation and elements of memory functioning (Cummings 2007). The compromise of executive function as seen in ALS affects abstraction, hypothesis generation, formulating and carrying out plans, response inhibition/generation, making voluntary decisions, and goal-directed attention, may thus affect patients' ability to make treatment decisions (Workman 2000).

Loss of insight represents denial or unawareness of symptoms or an unconcern about the consequences of symptoms. It forms a core criterion of frontotemporal dementia (Neary 1998); the prevalence of frontotemporal dysfunction in ALS implies that insight is thus decreased in a significant number of patients. This may be another mechanism by which patients with ALS have reduced capacity to make decisions regarding healthcare or financial circumstances. It also impairs the ability to engage competently in end-of-life decisions and interventions such as non-invasive ventilation and gastrostomy feeding tubes.

Given that measures of neuropsychological performance may predict capacity for treatment decisions in individuals with mild to moderate dementia (Gurrera 2006) this preliminary study aimed to explore capacity in patients with ALS. The recent consensus guidelines (Strong 2009) have allowed broad classification of ALS patients into “unimpaired” versus “impaired” based upon cognitive and behavioural assessment. This study was hence able to compare capacity in ALS subgroups as well as in patients with ALS compared to controls.
8.3 Hypotheses

8.3.1 Medical decision-making capacity in patients with ALS compared to controls.
This study predicted that medical decision-making capacity would be decreased in patients with ALS compared to controls given the prevalence of frontotemporal and executive dysfunction and loss of insight in ALS.

8.3.2 Medical decision-making capacity in ALS subgroups
It was also hypothesised that there would be heterogeneity across ALS groups so that capacity would be further compromised in patients with cognitive and/or behavioural impairments compared to those with “pure ALS”.

8.4 Methodology

8.4.1 Participants
This study was part of a large scale analysis of cognition and behaviour in ALS. Patients in this study were recruited from a population-based cohort through the Irish Register of ALS. Control recruitment and inclusion and exclusion criteria are as described in Chapter Three. The first 25 patients who partook in home-based cognitive and behavioural testing were also asked to participate in this capacity analysis. Three patients were interviewed during their hospital admission.

This project had full ethical approval from Beaumont Hospital Research Ethics Committee. Methods of data protection are described in Chapter Three.

Given the potential for deceased capacity in some participants, it was anticipated that the low potential of adverse events of the study would not compromise incompetent patients in any way. Participants were informed through information sheets / verbal information about the nature of the study. It was emphasised they could withdraw from the study at any time with no explanation required and no impact on their subsequent care. If they declined to take part, their consent form was archived in a secure filing cabinet.
8.4.2 Measures

8.4.2.1 Neuropsychological Assessment

Full neuropsychological assessment was conducted as described previously (Chapter Three) and encompassed the domains of executive function, memory and language. Neuropsychological assessment was conducted within four months of capacity evaluation.

8.4.2.2 Capacity

The Capacity to Consent to Treatment Instrument (CCTI) is a conceptually based, reliable, and valid instrument for the assessment of MDC in healthy and cognitively impaired older adults (Marson 1995; Griffiths 2005). Two clinical vignettes presented in both written and oral formats describe hypothetical medical problems and their accompanying symptoms—firstly a brain tumour and secondly a coronary artery blockage. These vignettes have a low syntactic complexity and a moderate information load (Marson 1997). In both cases, participants are asked choose between two treatment options (e.g. medications versus surgery in the second case); each has its benefits and risks.

The questions are designed to test consent capacity under consent standards (LSs) derived from legal and medical literature (Tepper 1984).

These are described by Marson et al (1995) as follows:

- LS1, expressing a treatment choice (expressing choice).
- LS2 making the reasonable choice (although this not a clinically accepted consent standard).
- LS3, appreciating the consequences of a treatment choice (appreciation).
- LS4, providing rational reasons for a treatment choice (reasoning).
- LS5, understanding the treatment situation, treatment choices, and respective risks/benefits (understanding).

Comprehension of questions was ensured through the use of explicit instructions; face-to-face administration by a trained interviewer; the use of written and oral formats; and finally assessment of the respondent’s comprehension by prompts as suggested by the authors of the CCTI.
Inter-rater reliability is high: $r = 0.83$ for interval scales, and $r > 0.96$ for categorical scales (Marson 2000).

8.4.3 Statistical Methods

ALS groups ($n=21$) and controls ($n=11$) were compared on demographic data, neuropsychological data.

This analysis defined impaired capacity in a similar fashion to other studies (Marson 1995; Okonkwo 2007) Participants' scores on each CCTI legal standard were summed across vignettes A and B to create a composite variable (except for [LS2], which is unique to vignette A). Comparisons of group performance on these composite LS variables were performed using one-way analysis of variance (LS1, LS3, LS4, and LS5) or two-way analysis [S2]. To identify CCTI outcome status (capable, or incapable), psychometric cut-off scores were derived from control performance. An incapable outcome was defined for legal standards LS3, LS4 and LS5 as a score greater than 2 SD below the control group mean on that legal standard. For the fourth interval level data (S1), which has a maximum possible score of 4, a capable outcome was defined as a score of 4; and incapable as a score 2. Because [S2] is a dichotomous variable, there were only two possible outcomes: capable (1 point) or incapable (0 point).

ALS-impaired encompassed the diagnostic categorisations of ALS-cognitive impairment, ALS-behavioural impairment, ALS-frontotemporal dementia and ALS-comorbid dementia, as defined in recent consensus guidelines (Strong 2009). Cognitive and behavioural results for these patients groups were compared to those of controls who completed the same neuropsychological and capacity testing.

All collected data was scored and entered into Statistical Package for the Social Sciences (SPSS) version 15.

8.5 Results

25 patients were invited to participate in this study. 3 declined citing a lack of time as the reason for doing so. The fourth was unwell at the time of assessment.
11 controls also participated. 2 other control participants opted not to continue with capacity evaluation as they had relatives with brain tumours (as in the case described in Vignette One) and found the interview too distressing.

8.5.1 Demographics
Patients under study (n=21) had a mean age of 61.41 (9.88); years of education on average was 11.15 (3.45). Mean HADS scores for depression and anxiety were 3.31 (4.51) and 6.44 (5.03) respectively – these means are not indicative of moderate to severe mood disorder.

Controls (n=11) had a mean age of 59.20 (10.19); years of education on average was 13 (3.97). Mean HADS scores for depression and anxiety were 1.2 (1.79) and 5.6 (5.37) respectively; these values did not meet criteria for moderate-to severe mood disorder.

8.5.2 CCTI performance results
CCTI results were compared between patients and controls between pure ALS versus ALS-impaired and between ALS subgroups (Tables 38, 39, 40).

8.5.2.1 MDC in patients versus controls
Table 38 compares legal standards between patients and controls. Patients had lower mean scores than controls on all legal standards representing expressing choice, reasonable choice, appreciation, reasoning and understanding.

Capacity outcomes are also reported.

1 Making a choice (LS1): One patient was found to be incapable (as defined in section 8.4.3). This patient has no accompanying cognitive and / or behavioural impairment. No controls were deemed incapable - all scored the maximum possible score of 4.

2 Reasonable choice (LS2): One patient was incapable. This patient was cognitively impaired at the time of testing. No control was incapable as per the same definition

3 Appreciation (LS3): 33% (n=7) of patients were impaired (2SD below control norm). 9% (n=1) of controls were impaired (2SD below control norm).
4 Reasoning (LS4): capacity could not be assessed on this measure; the limited range with wide standard deviations precluded meaningful interpretation.

5 Understanding (LS5): 33% (n=7) of patients were impaired (2SD below control norm). No controls were impaired.

Table 38. Group performance on CCTI consent standards

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>Std. Dev</th>
<th>SEM</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expressing choice (0-4)</td>
<td>Patient</td>
<td>21</td>
<td>3.76</td>
<td>0.54</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>11</td>
<td>4.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Reasonable choice (0-1)</td>
<td>Patient</td>
<td>21</td>
<td>Dichotomous variable</td>
<td>Capable=1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>11</td>
<td>Dichotomous variable</td>
<td>Incapable=0</td>
<td></td>
</tr>
<tr>
<td>Appreciation (0-8)</td>
<td>Patient</td>
<td>21</td>
<td>5.52</td>
<td>2.21</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>11</td>
<td>6.27</td>
<td>1.01</td>
<td>0.30</td>
</tr>
<tr>
<td>Reasoning (0-48)</td>
<td>Patient</td>
<td>21</td>
<td>5.47</td>
<td>2.18</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>21</td>
<td>6.73</td>
<td>3.41</td>
<td>1.03</td>
</tr>
<tr>
<td>Understanding (0-134)</td>
<td>Patient</td>
<td>21</td>
<td>46.14</td>
<td>17.47</td>
<td>3.97</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>11</td>
<td>56.45</td>
<td>9.81</td>
<td>2.96</td>
</tr>
</tbody>
</table>

Legal Standard = LS. LS1, expressing choice; LS2, reasonable choice; LS3, appreciation; LS4, reasoning; LS5, understanding.

*Value represents mean of two standard deviations below the control norm.

8.5.2.2 MDC in ALS subgroups

Legal standards were compared between ALS subgroups as defined by the consensus criteria (Strong 2009).

Table 39 outlines differences between legal standards in patients with behavioural and cognitive impairment and patients with no such impairments. Mean scores for patients with impairments were lower on all standards except LS1 (expressing choice). Comparison within small ALS-impairment subgroups (Table 40) also demonstrated that lowest scores on all legal standards except LS1 were found in those with ALSbi, ALSci or ALSFTD. This implies (with the caveat that these are exploratory analyses) that patients with ALS may have varied levels of capacity but that this cannot be predicted by nature of impairment (e.g. cognitive vs. behavioural) alone.
### Table 39. Consent standards in "pure ALS" versus "ALS-impaired"*

<table>
<thead>
<tr>
<th>ALS Groups</th>
<th>N</th>
<th>Mean</th>
<th>Std. Dev</th>
<th>SEM</th>
<th>Impairment</th>
<th>No impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expressing choice (0-4)</td>
<td>11</td>
<td>3.91</td>
<td>0.30</td>
<td>0.09</td>
<td>Impairment</td>
<td>No impairment</td>
</tr>
<tr>
<td>Reasonable choice (0-1)</td>
<td>11</td>
<td>0.91</td>
<td>0.30</td>
<td>0.09</td>
<td>Impairment</td>
<td>No impairment</td>
</tr>
<tr>
<td>Appreciation (0-8)</td>
<td>11</td>
<td>4.55</td>
<td>2.50</td>
<td>0.76</td>
<td>Impairment</td>
<td>No impairment</td>
</tr>
<tr>
<td>Reasoning (0-48)</td>
<td>11</td>
<td>4.36</td>
<td>2.01</td>
<td>0.61</td>
<td>Impairment</td>
<td>No impairment</td>
</tr>
<tr>
<td>Understanding (0-134)</td>
<td>11</td>
<td>36.82</td>
<td>18.58</td>
<td>5.60</td>
<td>Impairment</td>
<td>No impairment</td>
</tr>
</tbody>
</table>

*Impairment refers to the presence of cognitive impairment, behavioural impairment, or dementia as described in Chapter Four. Legal Standard - LS. LS1, expressing choice; LS2, reasonable choice; LS3, appreciation; LS4, reasoning; LS5, understanding.

### Table 40. Consent standards in ALS subgroups

<table>
<thead>
<tr>
<th>ALS Groups</th>
<th>N</th>
<th>Mean</th>
<th>Std. Dev</th>
<th>SEM</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expressing choice (0-4)</td>
<td>ALS-FTD</td>
<td>4.00</td>
<td>0.00</td>
<td>0.00</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>ALS - comorbid dementia</td>
<td>4.00</td>
<td>0.00</td>
<td>0.00</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ALS</td>
<td>3.67</td>
<td>0.58</td>
<td>0.33</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ALSbi</td>
<td>4.00</td>
<td>0.00</td>
<td>0.00</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pure ALS</td>
<td>3.56</td>
<td>0.73</td>
<td>0.24</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3.75</td>
<td>0.55</td>
<td>0.12</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Reasonable choice (0-1)</td>
<td>ALS-FTD</td>
<td>0.67</td>
<td>0.58</td>
<td>0.33</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ALS - comorbid dementia</td>
<td>4.00</td>
<td>0.00</td>
<td>0.00</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ALS</td>
<td>3.67</td>
<td>0.58</td>
<td>0.33</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ALSbi</td>
<td>4.00</td>
<td>0.00</td>
<td>0.00</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pure ALS</td>
<td>3.56</td>
<td>0.73</td>
<td>0.24</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.95</td>
<td>0.22</td>
<td>0.05</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Appreciation (0-8)</td>
<td>ALS-FTD</td>
<td>2.00</td>
<td>2.00</td>
<td>1.15</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>ALS - comorbid dementia</td>
<td>4.33</td>
<td>1.53</td>
<td>0.88</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>ALS</td>
<td>5.33</td>
<td>2.31</td>
<td>1.33</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>ALSbi</td>
<td>7.50</td>
<td>0.71</td>
<td>0.50</td>
<td>7</td>
<td>8</td>
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</table>

186
### ALS Groups

<table>
<thead>
<tr>
<th>ALS Groups</th>
<th>N</th>
<th>Mean</th>
<th>Std. Dev</th>
<th>SEM</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure ALS</td>
<td>9</td>
<td>6.44</td>
<td>1.24</td>
<td>0.41</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>5.40</td>
<td>2.21</td>
<td>0.49</td>
<td>0</td>
<td>8</td>
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</table>

#### Reasoning (0-48)

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<tr>
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<th>N</th>
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<th>Std. Dev</th>
<th>SEM</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS-FTD</td>
<td>3</td>
<td>4.33</td>
<td>2.08</td>
<td>1.20</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>ALS - comorbid dementia</td>
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<td>4.33</td>
<td>1.53</td>
<td>0.88</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>ALSci</td>
<td>3</td>
<td>4.67</td>
<td>3.06</td>
<td>1.76</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>ALSbi</td>
<td>2</td>
<td>4.00</td>
<td>2.83</td>
<td>2.00</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Pure ALS</td>
<td>9</td>
<td>6.56</td>
<td>1.74</td>
<td>0.58</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>5.35</td>
<td>2.16</td>
<td>0.48</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

#### Understanding (0-134)

<table>
<thead>
<tr>
<th>Understanding</th>
<th>N</th>
<th>Mean</th>
<th>Std. Dev</th>
<th>SEM</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS-FTD</td>
<td>3</td>
<td>27.67</td>
<td>9.24</td>
<td>5.33</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>ALS - comorbid dementia</td>
<td>3</td>
<td>34.67</td>
<td>11.02</td>
<td>6.36</td>
<td>24</td>
<td>46</td>
</tr>
<tr>
<td>ALSci</td>
<td>3</td>
<td>27.67</td>
<td>16.26</td>
<td>9.39</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>ALSbi</td>
<td>2</td>
<td>67.50</td>
<td>10.61</td>
<td>7.50</td>
<td>60</td>
<td>75</td>
</tr>
<tr>
<td>Pure ALS</td>
<td>9</td>
<td>56.33</td>
<td>8.93</td>
<td>2.98</td>
<td>39</td>
<td>66</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>45.60</td>
<td>17.74</td>
<td>3.97</td>
<td>10</td>
<td>75</td>
</tr>
</tbody>
</table>

*FTD* = frontal temporal dementia. *ALSci* = ALS with cognitive impairment. *ALSbi* = ALS with behavioural impairment. These entities are described as per consensus criteria (Strong 2009) described in Chapter Three. Legal Standard = LS. LS1, expressing choice; LS2, reasonable choice; LS3, appreciation; LS4, reasoning; LS5, understanding.

### 8.6 Discussion

This study predicted that medical decision-making capacity would be decreased in patients with ALS compared to controls given the prevalence of frontotemporal and executive dysfunction and loss of insight in ALS.

Patients scored lower than controls on all legal standards representing expressing choice, reasonable choice, appreciation, reasoning and understanding.

In terms of incapacity, this was only seen in one patient for each of the minimal consent standards (making a choice; expressing a choice). However for the more stringent and clinically relevant consent standards including appreciation of decision impact and understanding (Okonkwo 2007; Tepper 1984), levels of impaired capacity were seen in 35% of patients. It is worth mentioning however that the greater part of participants were not impaired on these standards. Hence an assumption should not be made that ALS patients...
particularly those with cognitive and/or behavioural impairment lack medical decision-making capacity.

As predicted there was heterogeneity across ALS groups so that capacity appeared to be compromised in patients with cognitive and/or behavioural impairments compared to those with “pure ALS”. This implies (with the important caveat that these are exploratory analyses) that patients with ALS may have varied levels of capacity but that this cannot be predicted by nature of impairment (e.g. cognitive vs. behavioural) alone.

The rational for capacity compromised in ALS might be explained by the broad range of cognitive and behavioural deficits reported in Chapter Four. Measures of neuropsychological performance may predict capacity for treatment decisions (Jones 1995; Gurrera 2006). More specifically the patterns of impairment seen in this population-based analysis might explain capacity compromise. 18% of patients had frontotemporal dementia, predominantly frontal variant FTD and 24% of patients had cognitive impairment (with or without behavioural impairment but not meeting criteria for ALS-frontotemporal dementia). Domains involved were executive function, memory and language.

Executive functions facilitate problem solving; thus deteriorating cognitive or executive function could compromise capacity to make decisions about health care or financial circumstances, capacity to use and comply with interventions and the ability to engage competently in end-of-life decisions (Phukan 2007). Indeed previous work has showed that appreciation of decision impact and rational reasons for a decision (as tested by LS3 and LS4) are highly influenced by executive function (Massur 1994; Dymek 1999).

This current project also discovered a range of memory deficits, beyond those encoding deficits associated with frontotemporal dementia. Temporal lobe pathology may be more prevalent in ALS than earlier recognised (Kato 1993; Okamoto 1998; Papps 2005; Schmolck 2007). Memory deficits are associated with diminished capacity, particularly with relation to capacity to understand treatment situation choices which draws heavily on short term verbal memory (Marson 1995; Griffith 2005; Okonkwo 2007). It has also been reported that verbal retrieval is the strongest single predictor of decisional ability (Gurrera 2006).
Although medical-decision making capacity cannot be solely assessed by functional assessment (see section 8.7), this preliminary analysis suggests that patients with ALS may have compromised capacity.

8.7 Limitations

Although this is the first exploratory study of its kind to examine medical decision-making capacity in ALS, there are some caveats worthy of mention. These findings represent just a snapshot view of capacity in ALS; they do not take into account that capacity can change over the course of an illness. A recent three-year longitudinal study of capacity (as measured by the CCTI) demonstrated that compared to controls, MCI patients experienced progressive decline in the ability to understand consent information (Okonkwo 2008). This decline accelerated after conversion to Alzheimer disease, highlighting the need for clinicians and researchers to focus attention particularly to the informed consent process around the time of this conversion. The same process might be true for those with ALS with behavioural and/or cognitive impairment i.e. health care professionals need to be alert to be compromised capacity with progression of the disease. However this study found that cognition remained relatively stable over a six month period (Chapter Seven); thus the progression of cognitive impairment in MCI may not be applicable to ALS where progression is not inevitable and where such evolution is difficult to identify simply given its life expectancy.

Capacity instruments such as the CCTI are effective, reliable, and valid for the assessment of MDC (Marson 1995; Griffiths 2005); however they do not necessarily take into account the real-life decisions facing patients with ALS. Being asked to make decisions in hypothetical situations such as having a coronary artery blockage may not be representative of decisions made in a terminal illness where cure is not an option. There is also a lack of consensus regarding which capacity instruments are most suited to assess MDC (Appelbaum 2007; Gurrera 2007) and concerns that cut-off scores, although useful in the clinical setting, are arbitrary and may or may not reflect societal values (Kim 2006). Capacity instruments demand a high degree of verbal memory, rather than the real-world availability of memory aids such as notes,
diagrams and social support; verbal memory is not synonymous with decision-making ability (Moye 2004).

Likewise although measures of neuropsychological performance may predict capacity for treatment decisions (Jones 1995; Gurrera 2005), executive dysfunction and decreased insight do not equate to a lack of capacity and may imply that capacity is a general rather than task-specific ability (Sutherby 1996).

Functional assessment of capacity is useful but other factors such as attitudes of patients to their own functional limitations, strategies developed to deal with these limitations and cultural decision-making influences should also be examined (Moore 1999; Calcedo-Barba 2004).

Assessing clinical and legal competence is thus a multidimensional longitudinal process that encompasses patient input, clinical judgment of healthcare professionals, collateral from family members, capacity evaluation instruments, and neuropsychological evaluation. Ultimately qualitative observations from daily interactions must supplement quantitative data (Workman 2004).

8.8 Implications

8.8.1 Clinical

Among the domains of functional activity, there is arguably no area of greater ethical and legal importance than MDC (Okonkwo 2008). Diminished capacity in ALS can compromise the ability of patients to make important choices about healthcare or financial circumstances. It also impairs the ability to engage competently in end-of-life decisions and interventions such as non-invasive ventilation, gastrostomy feeding tubes and tracheostomy which may have a complex risk-benefit ratio (Phukan 2007).

Impaired judgement, attention, abstraction, insight, motivation, planning, making voluntary decisions, and response inhibition / generation occur frequently in ALS. However the high prevalence of frontotemporal dysfunction identified in this study does not equate to a high prevalence of incapacity. Evaluation of capacity instead requires a multidisciplinary approach in
This study also highlights the need for better recognition by physicians of impaired / intact capacity that is not biased by the diagnosis of specific conditions, severity of illness, or by personal opinions. McKinnon et al (1989) noted that in capacity assessments performed by psychiatrists, evaluation was often incomplete, rarely addressed the treatment decision, and may have overestimated incapacity to make treatment decisions. Grisso et al (1989) assessed competence to consent to treatment asked five physicians to review videotapes of capacity assessments and to rate the competence of patients. The rate of agreement between physicians was no better than chance (kappa statistic, 0.14) suggesting that clarification of the applicable criteria and the use of a systematic approach to assessment would be of benefit. Improvement in interrater reliability is additionally facilitated by imparting knowledge of specific legal standards that are important for legal competency (Marson 2000). However although education improves decisional capacity, there is an endpoint beyond which additional educational intervention does not result in measurable improvement in decisional capacity (Lapid 2003).

Patients with ALS can be helped to participate in decision making through adequate time spent providing unambiguous information and allowing time for questions; evaluating the social and situational context for the health-care decision; strategies to compensate for problems with verbal recall, complex simultaneous processing, and intentional planning (Moye 2004; Moye 2006); targeted questioning to verify adequate comprehension (Taub 1991); and reinforcement.

Where incapacity is identified, a clinician can immediately treat to preserve life, and if the patient has a more persistent lack of capacity, (s)he be treated using the best interests criteria (Raymont 2002). These measures should be supplemented with a search for secondary or reversible causes of apparent fluctuating cognition such as sepsis, hypercarbia / hypoxia, medications; a second opinion; clear documentation of the situation; disclosure of information to relatives; and frequent reassessment of capacity.

This analysis demonstrated that the greater part of participants were not impaired on several legal standards. Hence an assumption should not be made
that ALS patients, particularly those with cognitive and/or behavioural impairment, lack medical decision-making capacity.

Patients with ALS should be able to maintain autonomy despite the presence of fronttemporal dysfunction if a multidisciplinary and multidimensional approach confirms the presence of competency.

8.8.2 Research
Consequences of this study's findings also extend to research trials which many of our patients are involved in. There may be a conflict of interest between researchers and potential participants. Several guiding and/or legal frameworks exist for research participants who lack capacity (e.g. Declaration of Helsinki (last revision, 1989); the Nuremberg Code (1947; amended at 59th WMA General Assembly, Seoul, October 2008); the International Covenant on Civil and Political Rights of the United Nations (1966); The Mental Capacity Act for England and Wales - Department of Health (2005); and the European Clinical Trials directive 2001/20/EC. These all require free and informed consent of research participants. However assessing capacity in cognitively impaired research participants is a complex process that should balance appropriate risk-benefit judgments and preserve respect for autonomy of research participants (Buckles 2003; Oldham 1999). This becomes even more challenging with research studies that employ procedures that have no expectation of direct benefit to the participants or in studies whose focus is on testing safety rather than efficacy (Kim 2002). Establishing capacity in the research domain can be facilitated through adequate, clear information for potential participants with regular feedback, targeted questioning to verify adequate comprehension (Taub 1991) and reinforcement; appropriate measures to assess capacity/ability to provide informed consent where available; longitudinal assessment of capacity to evaluate if this changes over the course of the study; input from research ethics committees; and consideration of proxy consent in some situations although the latter may lack legal authority (Kim 2002). At a national and international level, uniformity, written policies and harmonisation of procedures for the assessment of informed consent by central national bodies (Cahill 2000; Karlawish 2002; Rikkert 2005) would be welcome.
8.9 Future research

There is scope to tailor capacity evaluations for patients with ALS. These assessments should allow for the limb and bulbar of ALS by providing written and oral formats (as per the CCTI), and provide hypothetical situations that are more relevant to patients with ALS (rather than vignettes about coronary artery blockages and brain tumours where surgery is an option). Validity, normative values and reliability should be established for these evaluations.

As described in Chapter Three, neuropsychological evaluation in ALS has been clarified by the recent the consensus criteria for frontotemporal syndromes in ALS (Strong 2009). However these are still subject to shortcomings. ALSbi and ALSci are not mutually exclusive; patients may change diagnostic categories as the disease progresses; there are inherent inadequacies associated with cognitive tests and behavioural questionnaires that are unmodified for use in patients with ALS; and finally a focus on executive function may be at odds with emerging evidence of memory involvement in ALS. The consensus guidelines helped however to stratify patients in this study to those with "pure ALS" and "ALS-impaired" and in turn capacity could be contrasted between these two groups. However further optimisation of cognitive evaluation in ALS will help categorise these two groups accurately and allow improved determination of capacity in ALS subgroups.

Future research should also explore the evolution of competence in ALS as well as predictors of incapacity. Progressive decline in the ability to understand consent information was demonstrated in a longitudinal capacity study in patients with amnestic mild cognitive impairment (Okonkwo 2008) but the progression of ALS may be very different.

The ultimate aim is to find ways to support the autonomy and dignity of our patents whilst protecting those whose incapacity renders them vulnerable.
Chapter 9  Dysregulation of plasma and CSF angiogenin levels in patients with sporadic ALS

Note re contribution: I was involved in all plasma and CSF angiogenin quantification, conducted by enzyme-linked immunosorbent assay, in the Human Science Research Unit, Faculty of Education and Health Sciences, University of Limerick under the supervision of Professor Phil Jakeman. Additional statistical analysis was conducted by the Statistical Consulting Unit, University of Limerick; additional genotyping and related analysis was conducted by Russell McLaughlin Trinity College Institute of Neuroscience, Trinity College Dublin. Plasma and CSF samples were provided by our own clinic at Beaumont Hospital; the Swedish samples were provided by the Department of Pharmacology and Clinical Neurosciences, Umeå University Hospital, Sweden led by Professor Peter Andersen.

9.1 Introduction

Chapter Two (Section 2.2.3) explored in detail the exciting new developments in the field of genetics supporting mechanistic overlaps between ALS and other neurodegenerative diseases.

This chapter focuses on angiogenin, the 14.1-kDa product of ANG on chromosome 14. Its potential role in the development of dementia in ALS is discussed below. Angiogenin is an hypoxia-responsive protein which is part of a larger RNAse superfamily and is expressed in a wide variety of normal tissues, including the brain and spinal cord, (White 2004; Greenway 2006). It promotes angiogenesis and regulates vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF1) (Kisomoto 2005), both of which have neuroprotective properties (Oosthuyse 2001; Storkebaum 2004). It also seems that angiogenin is an important neurodevelopmental protein with neuroprotective properties, and that mutant ANG impairs neurite outgrowth (Subramanian 2007; Wu 2007; Gellera 2008). There is thus evolving evidence to suggest that angiogenin is an important neuromodulatory peptide.

The link between angiogenin and ALS was realised when the functional similarities between it and two other proteins linked to ALS were observed.
1 VEGF: Angiogenin is functionally similar to VEGF and is involved in its regulation; dysregulation of the VEGF gene has been associated with ALS (Oosthuyse 2001; Rosenstein 2004). 'At risk' promoter haplotypes in VEGF, which predict reduced expression of bioavailable isoforms, have been described in some European ALS populations (Lambrechts 2003) and combined with evidence from animal models, the data suggest that VEGF isoforms have, like angiogenin, a neuromodulatory and neuroprotective role in the CNS.

2 Progranulin: Both angiogenin and progranulin are hypoxia-responsive proteins; both are growth factors and angiogenic; and both are regulated by an siRNA (small interfering RNA), at an allelic site that is associated with an increased risk for frontotemporal dementia. Meanwhile, mutations in the progranulin (GRN) gene cause dementia in patients with non-tau, chromosome 17-linked ALS-FTD (Baker 2006; Cruts 2006).

Thus it seemed that since functionally similar proteins play a key role in ALS (+/- FTD), angiogenin merited further investigation. As predicted, mutations in the ANG gene coding for angiogenin, including loss-of-function mutations, have now been associated with classical ALS in populations that include Irish, Scottish, Scandinavian, US, Italian and German patients (Greenway 2006; Wu 2007; Gellera 2008; Paubel 2008; Conforti 2008; Fernández-Santiago 2009; van Es 2009). To date, 15 different ANG missense variants have been identified in patients with ALS but not in controls. ANG mutations predict loss of RNAse and angiogenic function (Greenway 2006). Recently, the K171 mutation was shown to segregate with disease in a FALS patient negative for SOD mutations. This segregation has been reported with familial ALS, frontotemporal dementia and parkinsonism (van Es 2009). A link between angiogenin and cognitive impairment has also been supported by a study that identified a SALS patient with angiogenin mutation and frontal lobe dysfunction (Gellera 2008).

Despite the functional similarity between angiogenin and VEGF and progranulin, there have been few studies to date that have investigated angiogenin expression and regulation in ALS. Given the functional similarity of angiogenin to progranulin (the latter being associated with chromosome 17-linked ALS-FTD) and the preliminary association of angiogenin with
frontotemporal dysfunction (Gellera 2008; van Es 2009), there exists the possibility that angiogenin could be used as a biomarker for ALS and FTD. However such research would require evaluation of angiogenin levels in plasma and CSF, and elucidation of population-specific differences on angiogenin expression.

One previous study has shown that serum angiogenin levels in ALS differ from controls (Cronin 2006). However, the biological implications of this finding remain to be determined. Furthermore, the patterns of plasma and cerebrospinal fluid (CSF) angiogenin expression have not previously been investigated, and there have been no studies to determine whether ANG haplotypes modulate protein expression.

9.2 Aims

The aims of this project were as follows:

1. To determine whether angiogenin is expressed in cerebrospinal fluid (CSF).
2. To test the population specificity of angiogenin levels in serum.
3. To determine whether there is a consistent relationship between plasma and CSF angiogenin levels.
4. To determine whether genetic variations in the ANG locus control angiogenin expression.
5. To determine whether, as has been reported for VEGF and progranulin (Devos 2004; Ilzecka 2004; Nygren 2002; Baker 2006; Cruts 2006), there is a dysregulation of angiogenin in ALS compared to controls.

9.3 Materials and Methods

9.3.1 Participants in the SNP genotyping studies

The demographics of the Irish and Swedish study populations are outlined in Table 41. All patients fulfilled the El Escorial criteria for clinically definite or probable sporadic ALS. Patients with atypical phenotypes were excluded. Unrelated control subjects with no family history of ALS were drawn from the same populations. For the SNP genotyping study, 661 Irish and Swedish SALS patients and 580 controls were genotyped. All Swedish patients tested negative for genes known to cause ALS. Informed consent was obtained and
the study approved was by the Beaumont Hospital and Umea University medical ethics committees.

Table 41. Characteristics of the Irish and Swede populations genotyped for ANG variants

<table>
<thead>
<tr>
<th>Study Populations</th>
<th>Total</th>
<th>M / F</th>
<th>Mean age at onset (±SD)</th>
<th>Spinal onset (%)</th>
<th>Bulbar onset (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IRELAND</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SALS</td>
<td>227</td>
<td>119/108</td>
<td>58 (12.8)</td>
<td>76</td>
<td>24</td>
</tr>
<tr>
<td>Control</td>
<td>215</td>
<td>114/101</td>
<td>53 (13.8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>SWEDEN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SALS</td>
<td>434</td>
<td>159/132</td>
<td>66 (12.9)</td>
<td>66</td>
<td>33</td>
</tr>
<tr>
<td>Control</td>
<td>365</td>
<td>132/128</td>
<td>63 (11.0)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

9.3.2 Participants in the plasma and CSF angiogenin level studies

Plasma and CSF samples were drawn from Swedish SALS patients and controls matched for age, gender and ethnicity. Plasma samples with known genotype were available from 111 patients with SALS and 144 control subjects. CSF samples were available from 105 SALS patients and 100 healthy Swedish controls. The characteristics of these participants are given in Table 42.

Table 42. Characteristics of Swedish participants with available plasma and/or CSF

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Gender (M:F)</th>
<th>Age (y) [mean (SD)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma (genotype known)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SALS</td>
<td>111</td>
<td>65:46</td>
<td>65.6 (13.2)</td>
</tr>
<tr>
<td>Control</td>
<td>144</td>
<td>76:68</td>
<td>61.7 (13.7)</td>
</tr>
<tr>
<td><strong>CSF (genotype known)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SALS</td>
<td>105</td>
<td>57:48</td>
<td>66.4 (12.8)</td>
</tr>
<tr>
<td>Control</td>
<td>100</td>
<td>54:46</td>
<td>61.0 (12.9)</td>
</tr>
</tbody>
</table>

9.3.3 Genotyping of SNPs across the ANG locus

DNA was isolated from peripheral blood according to standard protocols. Data from the CEPH panel of the International HapMap Project were used to select 5 informative haplotype tagging SNPs (htSNPs) (inter-marker $r^2$ below 0.8, minor allele frequency above 5%) covering the ANG gene (SNPs 1-5, Table 43) (International HapMap Consortium 2003). Among these, only SNP5, rs11701, is directly included on or tagged efficiently by the SNPs represented
on the Illumina 317K genotyping arrays which have been utilized for the recent genome-wide studies of ALS (van Es 2009). Genotyping was performed commercially by KBiosciences (Herts, UK) using KASPar assays. Quality-control criteria were that genotypes formed three distinct clusters, water controls were negative and minor allele frequency was greater than 5%. All samples were blinded prior to screening and were de-coded following genotyping.

9.3.4 Quantification of angiogenin in CSF and plasma

Samples were stored at -80°C until assay. Concentration of angiogenin was measured by enzyme-linked immunosorbent assay (ELISA), (Quantikine Duoset, R&D Systems Abingdon, UK) according to manufacturer's guidelines. All samples were assayed in duplicate and calibrated against serially diluted standards of known mass. Pooled CSF and plasma quality control (QC) samples were both assayed in duplicate on each microtiter plate. These data set the precision of the assay across all microtiter plates. An inter-assay CV of 6% and 8% was obtained for the high and low plasma QC respectively. An inter-assay CV of 9% was obtained for the CSF QC.

9.3.5 Statistical Analysis

Statistical assessments of allele and genotype frequencies were made using Haploview software (Barrett 2005). Allelic association statistics per SNP were computed using the chi-squared test. We report uncorrected p values in the Irish study population, and correct for multiple testing through replication in the Swedish cohort.

The data for angiogenin levels are shown as the mean and standard deviation (SD). The Shapiro-Wilks and Kolmogorov-Smirnov tests were used to assess the normality of data distribution. Comparison between patient and control groups was by the Mann-Whitney test owing to the non-parametric distribution of the data. Multivariate (ANCOVA) analysis was applied to examine the known influence of age and sex over angiogenin levels (Pantsulaia 2006). Log-transformation of nonparametric data was conducted for the multivariate analyses.
9.4 Results

9.4.1 ANG tagging SNPs

The mean genotyping call rate was 98.2%. Included polymorphisms did not deviate significantly from Hardy-Weinberg equilibrium for the study populations. Table 43 shows the allele frequencies and allelic association p values for each of these SNPs in the Irish and Swedish cohorts. LD between markers is shown in the supplementary figure. All five htSNPs showed significant association with risk for SALS in the Irish case-control group. Among these, one marker (SNP4, rs17114699) was also replicated in the Swedish cohort (T allele at SNP4; Ireland, p = 0.03; Sweden, p = 0.002).

Table 43. Allele frequencies and p values for ANG tgSNPs genotyped in the Irish and Swedish case-control populations

<table>
<thead>
<tr>
<th>SNP</th>
<th>Alleles</th>
<th>Risk allele frequency</th>
<th>Risk allele</th>
<th>Allelic association†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SALS; control</td>
<td>p value</td>
</tr>
<tr>
<td>rs9322855</td>
<td>A&gt;C</td>
<td>0.557, 0.549</td>
<td>A</td>
<td>0.86</td>
</tr>
<tr>
<td>rs8004382</td>
<td>G&gt;A</td>
<td>0.553, 0.493</td>
<td>G</td>
<td>0.18</td>
</tr>
<tr>
<td>rs4470055</td>
<td>G&gt;A</td>
<td>0.232, 0.231</td>
<td>A</td>
<td>0.96</td>
</tr>
<tr>
<td>rs17114699</td>
<td>G&gt;T</td>
<td>0.135, 0.080</td>
<td>T</td>
<td>0.04*</td>
</tr>
<tr>
<td>rs11701</td>
<td>T&gt;G</td>
<td>0.143, 0.128</td>
<td>G</td>
<td>0.62</td>
</tr>
</tbody>
</table>

†None of the SNPs deviated significantly from HWE
*Significant p value

Figures from Haploview for LD between the five SNPs in the Swedish are shown below in Figure 3. The red figure represents D' × 100 between the SNPs and the grey figure represents r² × 100.
9.4.2 Plasma angiogenin levels

Plasma angiogenin levels were 17% lower in the patients with sporadic ALS versus control group (p < 0.001, Mann-Whitney test (Table 44; Figure 4). The median value in the control group was 378 ng/ml and 312.5 ng/ml in patients (Table 44). Plasma angiogenin was higher overall in males vs. females (mean plasma angiogenin 378.8 in males vs. 346.9 ng/ml in females, p = 0.01) and increased with age (p = 0.02). Plasma levels in ALS patients remained lower than controls after multivariate analysis correcting for age and gender (p = 0.001, ANCOVA).

Table 44. Plasma angiogenin levels in ALS patients and controls

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Plasma angiogenin</th>
<th>Plasma Angiogenin</th>
<th>© Relative to control group (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>[mean (SD)]</td>
<td>[median]</td>
<td>Univariate (Mann Whitney) Multivariate (Adjusted for age and sex)</td>
</tr>
<tr>
<td>Controls (Ω)</td>
<td>160</td>
<td>389 (111)</td>
<td>378</td>
<td>61.8 (13.4)</td>
</tr>
<tr>
<td>Sporadic ALS (Σ)</td>
<td>128</td>
<td>332 (122)</td>
<td>312.5</td>
<td>65.5 (12.6)</td>
</tr>
</tbody>
</table>

Ω - Normal dist.
Σ - Not normal dist.
* significant p value below 0.05
9.4.3 CSF angiogenin levels

Angiogenin was expressed at detectable levels in CSF. Angiogenin levels in CSF range from 72.98ng/ml to 2284ng/ml. The median value was not significantly different between control and patient groups (p=0.66, Mann-Whitney U). CSF angiogenin was 13% higher in males than females (p<0.003) and increased with age (p<0.01), Levels were not significantly different between control and patient groups after accounting for these co-variates (p = 0.83, ANCOVA; Table 45).

Table 45. CSF angiogenin levels in ALS patients and controls

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>CSF Angiogenin ng/ml [mean (SD)]</th>
<th>CSF angiogenin ng/ml [median (range)]</th>
<th>Age (y), [mean (SD)]</th>
<th>Univariate (Mann Whitney)</th>
<th>Multivariate (Adjusted for age and sex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Population (Σ)</td>
<td>123</td>
<td>7.2 (2.3)</td>
<td>7.0 (11)</td>
<td>61.3 (12.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporadic Population (Σ)</td>
<td>130</td>
<td>7.3 (3.1)</td>
<td>7.0 (29)</td>
<td>65.5 (12.4)</td>
<td>0.659</td>
<td>0.828</td>
</tr>
</tbody>
</table>

Ω - Normal dist.
Σ - Not normal dist.
* significant p value below 0.05

Figure 4. Box-plots illustrating plasma and CSF [ANG] levels of patient subgroups and control group

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9.4.4 Effect of genetic variation on angiogenin expression

In total, data for both plasma angiogenin and ANG genotypes was available for 111 participants; data for CSF angiogenin and ANG genotypes was available for 105 participants.

Table 46 shows angiogenin levels in plasma and CSF stratified by genotype at each htSNP.

**Table 46. Plasma and CSF angiogenin levels stratified by genotypes for each tagging SNP.**

<table>
<thead>
<tr>
<th>SNP</th>
<th>rsID</th>
<th>Genotype n</th>
<th>Mean (ng/ml)</th>
<th>Comparison of means n</th>
<th>Mean (ng/ml)</th>
<th>Comparison of means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Plasma angiogenin</td>
<td>CSF angiogenin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SALS v control</td>
<td>SALS v control</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SALS Control</td>
<td>Control</td>
<td>p value</td>
<td>SALS Control</td>
</tr>
<tr>
<td>1</td>
<td>rs9322855</td>
<td>AA 86</td>
<td>346.1 382.5</td>
<td>70 7.12 6.97</td>
<td>0.03*</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 105</td>
<td>316.1 396.0</td>
<td>81 7.08 7.85</td>
<td>&lt;0.0001*</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CC 60</td>
<td>388.9 400.5</td>
<td>51 7.07 7.08</td>
<td>0.31</td>
<td>0.006*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p value</td>
<td>0.04* 0.63</td>
<td>0.47 0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>rs8004382</td>
<td>AA 60</td>
<td>342.4 368.6</td>
<td>43 7.53 6.92</td>
<td>0.09</td>
<td>0.02*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GA 120</td>
<td>326.3 391.7</td>
<td>99 7.09 7.45</td>
<td>&lt;0.0001*</td>
<td>0.008*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG 70</td>
<td>376.9 424.0</td>
<td>58 7.17 7.78</td>
<td>0.05*</td>
<td>0.01*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p value</td>
<td>0.09 0.08</td>
<td>0.76 0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>rs4470055</td>
<td>AA 14</td>
<td>296.3 326.7</td>
<td>12 7.06 5.72</td>
<td>0.44</td>
<td>0.04*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GA 88</td>
<td>343.4 380.3</td>
<td>73 6.83 7.82</td>
<td>0.03*</td>
<td>0.0002*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG 149</td>
<td>349.9 407.2</td>
<td>117 7.20 7.28</td>
<td>0.0002*</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p value</td>
<td>0.62 0.03</td>
<td>0.85 0.02*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>rs17114699</td>
<td>GG 204</td>
<td>334.9 384.3</td>
<td>156 7.18 7.27</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GT 48</td>
<td>383.3 437.0</td>
<td>48 7.09 7.91</td>
<td>0.10</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TT 1</td>
<td>- 450.6</td>
<td>0 -</td>
<td>0.05*</td>
<td>0.49 0.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p value</td>
<td>0.05* 0.24</td>
<td>0.49 0.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>rs11701</td>
<td>TT 186</td>
<td>337.5 379.8</td>
<td>4 7.68 8.46</td>
<td>0.001*</td>
<td>0.05*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GT 63</td>
<td>377.9 422.3</td>
<td>48 7.09 7.43</td>
<td>0.005*</td>
<td>0.004*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG 4</td>
<td>469.2 590.1</td>
<td>151 7.07 7.34</td>
<td>0.004*</td>
<td>0.92 0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p value</td>
<td>0.40 0.004*</td>
<td>0.92 0.90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Comparison of SALS patients vs. controls using ANCOVA of log transformed angiogenin levels with age and gender as co-variates

b Comparison of genotypes using ANCOVA of log transformed angiogenin levels with age and gender as co-variates

In the plasma of controls, a graded, allele-dose dependent increase in plasma angiogenin concentration was observed in heterozygotes and homozygotes for
the G allele at SNP2 (p = 0.005) and the G allele at SNP 5 (p = 0.04). However, the greatest single increase when comparing the heterozygous state to wild-type was at SNP4 (GT vs. GG genotypes, 82.6 ng/ml or 20.5% increase in plasma angiogenin, p = 0.12), although the lack of a TT homozygote group at this SNP meant that the trend did not reach significance. In plasma from patients with SALS, a trend for increased plasma angiogenin levels was observed for the same alleles at SNP2, SNP4 and SNP5. However, the association between angiogenin levels with SNPs 2 and 5 was absent in heterozygote ALS patients. Furthermore, plasma angiogenin levels, when stratified by genotype at each SNP, were consistently lower in ALS patients than controls in eight of the 12 comparisons (Table 46).

In control CSF, a similar graded, allele-dose dependent increase in CSF angiogenin concentrations was observed for heterozygotes and homozygotes for the G allele at SNP2, the T allele at SNP4 and the G allele at SNP 5, although the differences do not reach significance. Again, this trend was absent in ALS patient CSF. Furthermore, CSF levels were lowest in patients heterozygous for the "at risk" T allele at SNP4, (mean CSF angiogenin in ALS vs. control 6.99 vs. 9.54 ng/ml, p = 0.03; Table 46).

Limited individuals homozygous for at risk haplotypes across ANG precluded the analysis of the effect of haplotypes over ANG expression.

9.4.5 Correlation between plasma and CSF angiogenin levels
A moderate correlation was found between CSF angiogenin and plasma angiogenin concentrations in all participants (r=0.277, p<0.0005). This correlation was more in evidence in the control group (r² = 0.21), than in the patient group (r² = 0.01) (Figure 3).
Mutations in \textit{ANG} are associated with ALS. 5 informative haplotype tagging SNPs (htSNPs) covering the \textit{ANG} gene were selected and tested for association in Irish and Swedish ALS patients and controls. Multiple independent htSNP associations with sporadic ALS (SALS) were found in the Irish population, with replication of association at rs17114699 in the Swedish cohort. This study confirms the previously observed association between \textit{ANG} variants and ALS in the Irish population (Cronin 2006). Observation of association at all 5 unlinked ($r^2 < 0.8$) htSNPs across \textit{ANG} supports this chromosomal region as important in SALS risk in Celtic nations, and is consistent with reports of increased genetic homogeneity in the general Irish population (Cronin 2008). These data are consistent with the observations that homogenous populations are most useful to identify key susceptibility genes operating in a particular ancestral population, and that re-testing in other populations with alternative founder haplotypes is more useful for fine mapping (Wright 1999). In this study the T allele at SNP4 (rs17114699) replicates in a Swedish population, supporting the conjecture that SNP4 confers increased susceptibility to SALS in a wider population. This variant has not been tagged by the commercial genotyping arrays used in recent GWA studies of ALS (based on data from the HapMap Project).

In addition to an age- and gender- effect, this study also demonstrates that angiogenin expression in control plasma and CSF is modulated by at least 3

\textbf{Figure 5.} Correlation between plasma [angiogenin] and CSF [angiogenin]
htSNPs. In the samples used for the International HapMap Project, SNPs accounted for 76% of the variability of mRNA expression by genes (Stranger 2007). The SNPs modulating expression of each gene were found within 2kb upstream or downstream of the relevant transcription start site. In this study, the allele with greatest influence per individual copy on angiogenin was the T allele at SNP4. This clear allele-dose dependent relationship was not seen in patients, suggesting a dysregulation of angiogenin expression in the disease. Failure of the normal genetic upregulation in those carrying risk alleles may also attenuate the neuroprotective effect of angiogenin. The mechanism by which regulation fails is unclear, but could involve other key proteins in the hypoxia-response pathway. The dysregulation of angiogenin in ALS echoes similar findings for the functionally-related hypoxia–responsive proteins VEGF and progranulin (Oosthuyse 2001; Rosenstein 2004; Lambrechts 2003; Baker 2006; Cruts 2006). The link between progranulin and ALS-FTD begs the question whether angiogenin expression may also be altered in patients with ALS and cognitive impairment. Preliminary evidence suggests that this might be the case. Gellera et al (2008) identified a SALS patient with an angiogenin mutation and frontal lobe dysfunction. In addition, van Es et al (2009) reported segregation of K171 mutation in angiogenin with familial ALS (non-SOD), frontotemporal dementia and parkinsonism.

The present study demonstrated that angiogenin is expressed in detectable levels in CSF. Whilst there was no significant difference in CSF angiogenin levels between patients with sporadic ALS (SALS) and controls, plasma angiogenin levels were significantly lower in patients than in controls. A moderate correlation was found between CSF angiogenin and plasma angiogenin concentrations in all participants. The finding of lower plasma levels of angiogenin in Swedish individuals contrasts with a previous report of elevated serum angiogenin levels in an Irish patient with ALS (Cronin 2006). The difference in these observations may have related to artifactual changes generated during sample preparation and storage. This seems unlikely however; the stability of angiogenin in serum over an extended period of time has been shown previously (Cronin 2006). Furthermore, both studies used matched controls, and patient and control samples were handled in an identical manner. Another possible explanation for the seemingly contradictory results may lie in the ancestral origin of the samples. The prior study (Cronin
2006) was undertaken in samples from a homogenous Irish population, and the present larger study was using samples from a Swedish population of different ancestral origin. It also seems that lower plasma angiogenin levels exist in the Polish population (personal communication). Since all 5 htSNPs associate with ALS in the Irish population, whereas only SNP4 associates with ALS in the Swedish, it is plausible that population-based differences in association may account for the variability in findings as seen with VEGF (Van Vught 2005). These population-based differences may also affect the regulation of angiogenin expression in different directions, and imply that in some cases of ALS the expression of angiogenin may be dysregulated. If this is indeed the case, the disrupted levels in patients might be higher or lower, reminiscent of the previously published conflicting reports of VEGF levels in ALS.

In summary, multiple htSNP associations exist with sporadic ALS in the Irish population. This study thus confirms the previously observed association between ANG variants and ALS in the Irish population. Replication in the Swedish suggests that SNP4 confers increased susceptibility to SALS in a wider population. Although angiogenin expression in CSF does not differ between ALS patients and controls, angiogenin levels may be modulated by various SNPs, and regulation of angiogenin expression may be disrupted in some patients with sporadic ALS. Indeed treatment with angiogenin protein in order to modulate angiogenin levels and activity in the spinal cord may be beneficial for patients with ALS (Kishikawa 2008). These findings support the hypothesis that angiogenin is a biologically important protein in ALS.

The next step in this investigation will be to evaluate if angiogenin levels correlate with cognitive function and if at-risk angiogenin haplotypes predict cognitive impairment. This will require a large scale study of well characterised-patients who have undergone standardised neuropsychological evaluation as described in Chapter Three. Such a project is now underway in our research group. Ultimately angiogenin and functionally similar proteins may be used as a biomarker for ALS and FTD but there is much work to be done before this can be explored.
Chapter 10 General Discussion

10.1 Introduction

Amyotrophic Lateral Sclerosis is a progressive neurodegenerative disease without a cure.

The presence of cognitive and behavioural impairment in ALS has far-reaching implications for patients, their families, and for research into the pathogenesis and potential treatments of this devastating condition.

This study was designed to determine for the first time the population prevalence, evolution and impact of cognitive and behavioural impairment in ALS. It involved 200 home visits. A comprehensive and validated neuropsychological battery was utilised for all patients with adaption as required for limb and bulbar disability. Cognitive and/or behavioural categorisation of patients was facilitated by the recently published consensus criteria (2009) and thus the present analysis also tested the utility of the guidelines as a research tool.

This chapter presents a summary of findings from the project; the implications and limitations of the study; and finally suggests potential directions for future research.

10.2 Summary of Findings

10.2.1 The frequency and evolution of cognitive decline in ALS in a population-based cohort

10.2.1.1 Cross-sectional study: cognitive impairment

It was hypothesized that cognitive decline primarily affecting the executive domain would be present in up to 50% of the Irish ALS population, that a smaller number of patients would have overt dementia, and that a proportion of patients with cognitive or behavioural impairment would progress to develop full-blown frontotemporal dementia.

The consensus criteria (Strong 2009; Appendix 2) define the following frontotemporal syndromes in ALS: ALS; ALS-cognitive impairment (ALSci), ALS-behavioural impairment (ALSbi), ALS-comorbid dementia and ALS-frontotemporal dementia (ALS-FTD).
18% (16 patients) of this population-based sample of ALS patients (n=87) had frontotemporal dementia at Time One, predominantly frontal variant FTD. 13 patients (15%) had ALSci affecting executive function, memory and language. 13 patients (15%) had behavioural impairment alone (ALSbi). 8 patients (9%) had both ALSci and ALSbi concomitantly. 37% of patients did not have cognitive or behavioural impairment.

These findings met the hypothesis that cognitive decline would be present in up to 50% of patients with ALS (42% in the current study) and that a smaller number of patients would have overt dementia (18% in this analysis).

Several factors strengthen the conclusions of the present study. Population-based recruitment and home visits meant that the findings are more representative of ALS patients since selection bias was minimised; the clinical features and natural history of prevalent cohorts differ significantly from incidence-based cohorts (Lee 1995; Traynor 2003; O'Toole 2007).

Compared to matched patients and controlling for differences in IQ, patients had lower scores on a number of executive measures, verbal memory and confrontation naming. Although executive dysfunction has been consistently noted in studies of ALS (see Chapter Two), the memory deficits in this analysis were not all related to encoding problems. However clinical, neuropathological and neuroimaging studies (Kato 1993; Okamoto 1998; Papps 2005, Schmolck 2007) have implicated more extensive temporal lobe involvement in ALS. It might be that although ALS and FTD show an overlap in terms of clinical presentation, genetics, pathology and imaging (Wright 2005; Ringholz 2005; Phukan 2007), that dementia in ALS does not represent an absolute FTD syndrome.

10.2.1.2 Cross-sectional study: behavioural change and patient insight in ALS

It was predicted that behavioural changes would be detected in patients with ALS. Cognitive impairment was hypothesized to correlate with such behavioural manifestations. It was also hypothesised that patient and carer reports of patient behaviour would differ, indicating a deficit of insight in some patients with cognitive impairment.

The analysis discovered a crucial discrepancy in the prevalence of behavioural impairment (ALSbi) depending on the definition used with limited overlap
between the two sets of defining criteria. Behavioural impairment as measured
by the Frontal Systems Behavioural Scale (FrSBe), occurred in 31% (13 of 42
patient/carer pairs) whilst the consensus criteria (Neary supportive criteria)
found that only 7 patients (8%) patients fulfilled the diagnostic criteria for
ALSbi.

This inconsistency has two implications. Firstly the FrSBe and similar
behavioural questionnaires should be amended to consider the physical
disability and terminal nature of ALS so that behavioural impairment is not
overestimated. Furthermore, the Neary supportive criteria may underestimate
the prevalence of behavioural variant (frontal) FTD (Piguet 2009) and the
same underestimation may apply to ALSbi.

Caregivers reported apathy as the most common behavioural change. This
high incidence contrasts Starkly to the frequent disinhibition seen in
frontotemporal dementia. Nonetheless this may be attributable to behavioural
questionnaires tending towards questions on the disinhibition scale about
actions that are often precluded in ALS due to its associated limb and bulbar
disability.

The absence of behavioural change in up to 37% of patients endorses previous
opinion that there might be extremes where some are free of behavioural
changes and others have prominent impairment (Gibbons 2008). This opinion
would require neuroimaging and post-mortem studies for confirmation.

The absence of correlation between self and carer-reported disinhibition
change is suggestive of patients’ diminished awareness of the presence of
disinhibition. The limitations of comparing patient and self-rating and proxy
responses are discussed in Chapter Four. Nonetheless if such loss of insight is
present in some patients with ALS it could contribute to increased stress and
caregiver burden (Seltzer 1997) and also to poor patient–caregiver interaction
(Hutchinson 1997). Poor compliance with medication and performing
dangerous or difficult activities has also been associated with loss of insight
(McGlynn 1989; Cotrell 1999).

Thus in summary the hypotheses relating to behavioural change were
confirmed but an important inconsistency was observed between different
definitions of behavioural impairment.
10.2.1.3 Longitudinal study

Cognitive and behavioural impairment did not inevitably evolve to dementia over the course of this study. A baseline diagnosis of "pure" ALS (i.e. absence of cognitive and behavioural impairment) favoured an absence of dementia at follow-up. An ongoing longitudinal analysis is underway to confirm these findings. Misclassification (incorrect "caseness") was observed in up to 22% of patients who had an initial diagnosis of ALSbi or ALSci but were found to have no such impairments at follow-up.

10.2.2 The impact of cognitive and / behavioural impairment in ALS

This study predicted that executive dysfunction and loss of insight in some patients with ALS would have a number of implications.

The potential impact of cognitive and behavioural impairment in ALS was examined via three methods:

1 Medical decision-making capacity
2 Utilisation and compliance with interventions
3 Burden and mood in caregivers

1 Capacity in ALS has not been systematically examined to date. Patients scored lower than controls on all legal standards representing expressing choice, reasonable choice, appreciation, reasoning and understanding. Lack of capacity was demonstrated in one third of patients for the more stringent legal standards of appreciation and understanding. 5% were deemed incapable with respect to the legal standards of making a choice and expressing a choice (minimal consent standards). Preliminary results suggested that those with cognitive and/or behavioural impairment were more likely to lack capacity. Although assessing clinical and legal competence is a multidimensional longitudinal process, this suggestion of impaired capacity in a subset of ALS patients has important ramifications discussed in the Implications section below.

2 There were no significant differences in cognitive and/or behavioural impairment between the ALS patients who used non-invasive ventilation
and those who did not. There was no difference in the number of NIV hours between patients with and without impairment. This analysis was limited by small "n" but will be interesting to examine in larger population-based cohort since it has been postulated that patients with ALS plus dementia are twice as likely to be noncompliant with non-invasive ventilation; shorted survival times for these patients may be partly linked to this non-compliance (Olney 2005).

3 Although a high level of burden was seen in almost a third of carers, the presence of cognitive and/or behavioural impairment in patients did not confer higher burden, depression or anxiety upon caregivers. This conflicts with studies of other dementia types in which patients' cognitive and behavioural disturbances are associated with higher levels of stress and carer burden (Grasel 1997; Coen 1999; González-Salvador 1999; Mafullul 2000; Thommessen 2002; Hecht 2003; Pinquart 2003). However our results may be attributable to the unique features of ALS-FTD. Apathy was the most common behavioural change identified in this study which might be less burdensome to carers than some of the behaviours seen in later Alzheimer's such as perseveration, paranoia, aggression and wandering. The disinhibition normally associated with fronttemporal dementia may be absent in ALS due to the rapid physical decline which precludes some of its characteristic behavioural manifestations including aggression, swearing, compulsions and impulsivity.

10.2.3 Quality of life and Mood in ALS

It was hypothesised that physical status was not the only relevant factor in determining QoL.

This hypothesis was confirmed. Significant negative correlations were found between some QOL subscales and depression as well as cognitive and / or behavioural impairment. Self-perceived burden also influenced QOL.

As predicted, mood disorders (as measured by a self-report questionnaire) were not found to be an inevitable consequence of ALS perhaps due to a response shift away from physical domains, the use of denial as a psychological defence, or altered emotional responses towards positive valence (Moore 1998; Lulé 2005). Nonetheless up to 15% of patients had
moderate-severe mood disorder although overall mood was stable or even improved over a six month period.

The implications of changes in QOL and mood are discussed below.

10.3 Implications
The population-based study uniquely compromised of almost 200 home visits and incorporated a validated neuropsychological and behavioural test battery adapted for the disability of ALS. It is the largest study of its kind.

This study has provided clarification regarding the population-based frequency and risk of cognitive impairment in patients with ALS as well as the evolution of these impairments; this is crucial for patients and caregivers, for disease management, and for service development.

In addition the utility of the consensus criteria for diagnosis of frontotemporal cognitive and behavioural syndromes in ALS (Strong 2009) have been explored. These guidelines have facilitated to an extent categorisation of subgroups, albeit with some overlap, that can be followed over time to explore if cognitive and behavioural impairment progress to frontotemporal dementia. Potential areas for clarification and improvement include

1 Redefining behavioural impairment in ALS given the discrepancy between supportive Neary criteria versus self-rated and carer-rated measure of the FrSBe.

2 The consideration of memory evaluation in defining ALSci given this study’s discovery that temporal involvement in ALS patients is more common that perceived heretofore.

3 The refinement of subgroup definitions given that misclassification occurred in 22% of patients who were originally reported to have impairment and then not to have such impairment six months later. This might be due to confounding factors but and validation of the criteria before making this assumption.

4 The pitfalls of combining executive measures to create a global measure which fails to recognise that various executive tests reflect independent, dissociated networks.
Adaptation of self-report measures, which the consensus criteria suggest as supportive tools, to account for physical disability in ALS.

Consideration of the overlap of ALSbi and ALSci. These syndromes are not mutually exclusive and whilst creation of subgroups is useful in the research setting, this can be difficult to apply to clinical practice.

Diminished capacity and loss of insight as identified in some patients in this study can compromise decision-making about healthcare, finances, advance directives, and treatment. These results underline the importance of functional capacity assessments in all patients but with an accompanying multidisciplinary approach and neuropsychological evaluation.

Lower QOL and mood, and higher self-perceived burden in patients with ALS are of concern. These factors are implicated in patients' decisions to refuse treatment and in some physicians' decisions to withhold or withdraw life-sustaining medical treatment. Lower QOL and mood are correlated with suffering, poor social support, sense of burden, fatigue and increasing hopelessness (Jonsen 1992; Ganzini 1999; Lou 2003; Chio 2004). Patients with psychological distress have a greater risk of mortality than those with psychological well-being (McDonald 1994; Tedman 1997; Johnston 1999; Badger 2001; Lou 2003; Chio 2004). Up to one third of caregivers in this study described a high degree of burden. Ameliorating psychological well-being requires a multidisciplinary approach that addresses psychological factors as well as physical ones.

Meanwhile, this study has added to the important genetic aspects of frontotemporal dysfunction in ALS. The patterns of angiogenin dysregulation in ALS have been elucidated and an association between ANG gene variants and ALS have been confirmed in the Irish population. The next step is to evaluate if angiogenin levels correlate with cognitive function, if at-risk angiogenin haplotypes predict cognitive impairment, and ultimately if angiogenin and functionally similar proteins may be used as a biomarker for ALS and FTD.

The recognition that other neurodegenerative conditions can overlap with ALS has been an important step in our understanding of the pathogenesis of ALS and FTD. From a genetic viewpoint, it is anticipated that this study will ultimately provide the knowledge to identify novel gene(s) that increase the risk
of cognitive decline in ALS, and therefore provide further valuable insights into the pathogenesis of the neurodegenerative process. To this aim, our research group is using the population based data generated by this study to correlate genetic risk with clinical phenotype, as the genetic structure of the Irish population has been well characterised, and is comparatively homogenous.

10.4 Limitations

The cross-sectional study of cognition and behaviour in ALS recruited 65.4% of 133 eligible patients. Although participants and non-participants demonstrated no differences in demographic and clinical variables, there is no assurance that non-participants may have had early insight into their cognitive / behavioural changes and opted out on that basis or conversely that they felt that their normal cognition / behaviour diminished the need for them to participate.

As regards the longitudinal study, attrition rates were high as noted in all studies of ALS due to the progressive and devastating nature of the illness (Strong 1999; Abrahams 2005). It is thus impossible to comprehensively describe progression of frontotemporal dysfunction in all patients tested at baseline. Missing data occurred due to disability precluding certain tests, even though all tests were adapted if possible. Nonetheless almost 60% of eligible patients were assessed at both baseline and six-month follow-up and data was available for a further 20% who already had a diagnosis of dementia. This analysis was thus the largest study of its kind to date.

One of the greatest limitations to this work was the difficulty posed by the inability of the consensus criteria to classify patients at baseline and at later evaluation (Chapter Seven). Patients who met criteria for cognitive and/or behavioural impairment were, in several cases, categorised as having no impairment six months later. Although this could be assumed to due to confounding factors, these classification inconsistencies highlight the need for validation of the consensus criteria for use in clinical practice.

The number of participants in the QOL / mood / burden sections limited the statistical power of findings. This analysis was thus subject to selection bias since patients and carers with lower mood and QOL were perhaps less willing to participate. The same could apply to those patients with cognitive and / or behavioural impairment. Conversely participants may have been more likely to
engage in this study because of a desire to discuss concerns surrounding mood and QOL.

10.5 Future

This project was designed to allow definition of distinct subgroups of ALS patients with different profiles of cognitive impairment. It has facilitated initiation of several future projects in our research group:

1 Correlation of these subgroups with a corresponding genetic risk.

2 Exploration of whether presence of cognitive decline should be adopted as important variable for stratification within clinical trials.

3 Clarification whether the presence of cognitive decline in patients, coupled with a strong family history of neurodegeneration can be used to segregate patients and kindreds for sub-characterization using neuroimaging and genetic analysis.

4 Combination of the dataset with a similar cross-sectional data from Scotland, as a robust population-based preliminary dataset for a larger population-based European study of the genetics of cognitive decline in ALS.

5 Evaluation of correlation of angiogenin levels with cognitive function and examining if at-risk angiogenin haplotypes predict cognitive impairment. This analysis will depend upon a large scale study of well characterised-patients who have undergone standardised neuropsychological evaluation as initiated by this project.

Research in our group and many others will continue to examine the utility of consensus criteria and neuropsychological tests batteries to identify areas for improvement. Future studies should focus on creating reliable, standardised screening tools modified for those with ALS, taking into account communication difficulties, impaired mobility potential fatigue and progressive disability.

Investigation is also needed regarding the effect of elevated self-perceived burden on crucial decision-making. Further research may also clarify which strategies are best for addressing burden in ALS patients and their caregivers to alleviate psychological distress.
In addition large-scale studies should explore the evolution of competence in ALS, as well as predictors of incapacity and the impact of incapacity on real-world complex decisions that face patients with ALS. The ultimate aim is to find ways to support the autonomy and dignity of patients whilst protecting those whose incapacity renders them vulnerable.

Prospective longitudinal, population-based clinicopathological correlative studies are essential to accurately define the evolution of cognition and behaviour in ALS over time and to improve diagnostic accuracy. Definition of pure ALS is essential in future therapeutic trials in ALS owing to the difference in prognosis with ALS alone versus ALS with frontotemporal impairments (Strong 2008).

Stimulating advances in genomics, proteomics and bioinformatics, neuropathology, and neuroimaging bring us ever closer to understanding whether ALS, ALSci, ALSbi and FTD represent a continuous spectrum of ubiquitin-associated neurodegenerative disease (Talbot 2006) or instead whether they symbolise distinct entities.

Exploration of functionally related proteins (e.g. progranulin, angiogenin, TDP-43, FUS / TLS) should uncover mechanisms of neurodegeneration in ALS and related conditions. There is a possibility that such proteins could be used as biomarkers for ALS and FTD with the caveat that population-specific differences may affect expression.

All the above endeavours will add greater insights into ALS and related frontotemporal syndromes. This understanding will lead to better care for patients with ALS and their families, and provide further valuable understanding of the pathogenesis of neurodegeneration.

10.6 Conclusion

This thesis examined cognitive and behavioural impairment in a population-based cohort of patients with ALS and the impact of these changes on psychological well-being and clinical decision-making in both patients and their caregivers. I hope that the insights gained from this work and others will forward, even in a very small way, an understanding of ALS that ultimately benefits whole families affected by this devastating condition.
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Appendices

1. El Escorial Criteria
2. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis
3. Ethics Approval
4. Patient Information Sheet
5. Patient Consent Form
6. Carer Information Leaflet
7. Recruitment Advertisement
8. Control Recruitment Information Leaflet
9. ALS Functional Rating Scale
10. Fixed Test Order
Appendix 1  El Escorial Criteria

Clinically Definite ALS: defined on clinical evidence alone by the presence of UMN, as well as LMN signs, in three regions (bulbar region and at least two spinal regions or in three spinal regions).

Clinically Probable ALS: defined on clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.

Clinically Probable - Laboratory-supported ALS: defined when clinical signs of UMN and LMN dysfunction are in only one region, or when UMN signs alone are present in one region, and LMN signs defined by EMG criteria are present in at least two regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.

Clinically Possible ALS: defined when clinical signs of UMN and LMN dysfunction are found together in only one region or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of Clinically Probable - Laboratory-supported ALS cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiologic, neuroimaging or clinical laboratory studies. Other diagnoses must have been excluded to accept a diagnosis of Clinically Possible ALS.

Clinically Suspected ALS may be suspected in many settings, wherein the diagnosis of ALS could not be regarded as sufficiently certain to include the patient in a research study. Hence, this category is deleted from the revised El Escorial Criteria for the Diagnosis of ALS.

UMN: Upper motor neurone. LMN: Lower motor neurone

ALS and other motor neuron disorders 2000 1, 293–299 © 2000 ALS and other motor neuron disorders.
### Appendix 2  Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis.

<table>
<thead>
<tr>
<th>ALS-FTD</th>
<th>ALS-dementia (ALS-D)*, FTD-MND</th>
<th>ALS patient meeting either the Neary criteria (51) or Hodge’s criteria (2) for FTD</th>
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<tr>
<td>ALS-PNFA</td>
<td>ALS patient meeting Neary criteria for PNFA</td>
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<tr>
<td>ALS-SD</td>
<td>ALS patient meeting Neary criteria for SD</td>
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<th>ALSbi</th>
<th>ALS patient meeting at least two non-overlapping supportive diagnostic features from either the Neary criteria or Hodge’s criteria for FTD</th>
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<td>ALSci</td>
<td>Evidence of cognitive impairment at or below the 5th percentile on at least two distinct tests of cognition that are sensitive to executive functioning</td>
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<th>A neuropathological diagnosis in which FTLD is the primary diagnosis but in which there is neuropathological evidence of motor neuron degeneration, but insufficient to be classified as ALS</th>
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<td>ALS-dementia (ALS-D)*</td>
<td>ALS with dementia, not typical of FTLD</td>
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<tr>
<td>ALS-AD</td>
<td>ALS in association with AD</td>
</tr>
<tr>
<td>ALS-vascular dementia</td>
<td>ALS in association with vascular dementia</td>
</tr>
<tr>
<td>ALS-mixed dementia</td>
<td>ALS in association with a mixed dementia (e.g. AD-vascular dementia)</td>
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</table>

**ALS-Parkinsonism-dementia complex**

| Western Pacific variant of ALS; lytico bodig. | ALS concurrent with dementia and/or Parkinsonism occurring in hyperendemic foci of the western Pacific |

*Note that the term 'ALS-dementia' has been used generically within the literature to imply the presence of any clinical or neuropathological evidence of cognitive or behavioural impairment and thus appears in two synonymous categories. The participants recommend restriction of the use of 'ALS-dementia' to refer to specific dementias.*
### Appendix 3 Ethical Approval

**Ethics (Medical Research) Committee - Beaumont Hospital**

**Notification of ERC/IRB Approval**

**Investigator:** Dr. O. Hardiman  
**Protocol No.:** 06/79  
**Protocol Title:** A population-based survey of cognitive decline in ALS: Genetic determinants within a population isolate  
**Ethics Committee Meeting Date:** 29th September 2006  
**Final Approval Date:** 21st November 2006  
**From:** Ethics (Medical Research) Committee - Beaumont Hospital, Beaumont, Dublin 9

#### Documents Reviewed

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Appendix 4 Patient/Study Information Leaflet

Beaumont Hospital Ethics (Medical Research) Committee
Patient/Study Information Leaflet

Protocol Title:

* A population based survey of cognitive decline in Motor Neurone Disease
* Principal Investigator: Doctor Orla Hardiman

Beaumont Hospital

You are being asked to take part in a clinical research study carried out at Beaumont Hospital. Before you decide whether or not you wish to take part, you should read the information provided below carefully and if you wish discuss it with your family, friends or GP. Take time to ask questions - do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you – this process is known as Informed Consent.

You may change your mind at any time (before the start of the study or even after you have commenced the study) for whatever reason without having to justify your decision and without any negative impact on the care you will receive from the medical staff.

**WHY IS THIS STUDY BEING DONE?**

You have been asked to participate in a study to determine whether some people with Motor Neurone Disease (MND) develop problems with thinking and memory (cognitive impairment) and decision-making. The study also collects DNA from patients and controls to look for genes that associate with MND and cognitive impairment.

**WHO IS ORGANISING AND FUNDING THIS STUDY?**

This study is being performed by Dr. Julie Phukan, a Specialist Registrar in Neurology under the supervision of Doctor Orla Hardiman, who is a consultant neurologist at Beaumont Hospital in Dublin. The work is being done in
collaboration with Doctor Niall Pender who is a Consultant Neuropsychologist at Beaumont Hospital.

**HOW WILL IT BE CARRIED OUT?**

This study will start in October 2006 and will continue for the next 3 years until sufficient information has been collected. Everybody in Ireland who has been diagnosed with MND will be approached and asked to participate. Those who agree to do so will complete a series of psychological tests to measure memory and thinking, and a questionnaire about their family history. The psychological tests will be repeated after 6 and then 12 months. A blood sample will be taken at the time of the first test for genetic research. This sample will be coded so that you cannot be identified from it. It will be stored in a DNA bank at the National Centre for Medical Genetics at Crumlin Hospital.

The genetic research will be conducted in collaboration with Dr. Bryan Traynor, National Institute of Health, USA, who will provide facilities to undertake detail screening using a new technique called whole genome wide association scanning.

**WHAT WILL HAPPEN TO ME IF I AGREE TO TAKE PART?**

Dr. Phukan will arrange to visit you at home at a time that is convenient, and will perform the various tests with you. These tests are designed to identify subtle changes in memory, language and attention that have been reported to occur in MND. Dr. Phukan will also ask your spouse/partner some questions about your care. The tests will take approximately 1 hour. Selected patients will also be asked to answer some questions about decision-making; these will take another 20-25 minutes. These tests will be repeated after 6 months and 12 months.

At the time of the first test, Dr. Phukan will analyse the results and will contact you within 8 weeks to provide some feedback and advice.

At the time of the first test, Dr. Phukan will take a blood sample for genetic research. It will not be possible for you to receive any individual results from the genetic research.
WHAT ALTERNATIVE TREATMENTS ARE AVAILABLE TO ME?
The proposed study does not involve any change to your existing treatment plan. You may decide to withdraw consent from the study at any time without justifying your decision and your future treatment will not be affected.

POSSIBLE BENEFITS OF THE STUDY
The cause of MND is unknown. This study aims to determine whether people with Motor Neuron disease develop cognitive impairment, and if so, to what extent. We will also look for genes that make people more susceptible to the development of cognitive impairment.

You can obtain information about the results of the psychological testing from Dr. Phukan. If Dr. Phukan identifies serious difficulties with thinking and memory, or if you have any concerns in this regard, a referral to the Neuropsychology Department at Beaumont Hospital will be arranged for or appropriate follow-up and assistance.

POTENTIAL RISKS ASSOCIATED WITH THE STUDY
It is possible that identifying cognitive impairment such as memory loss may cause emotional distress. If this occurs, counselling services will be made available through the MND clinic at Beaumont Hospital.

WHAT IF SOMETHING GOES WRONG AS A RESULT OF MY PARTICIPATION IN THIS STUDY?
We do not anticipate that anything will go wrong. However, if at any time you feel that your participation in this study has become unduly stressful, you are free to discontinue. This will not affect in any way the quality of care that you receive at Beaumont Hospital, or the access that you will have to specialist services.

WILL THERE BE ANY ADDITIONAL COSTS INVOLVED?
No additional expenses will be incurred by the participating individuals as a consequence of participating in this research study.

YOUR RESPONSIBILITIES AS A PARTICIPANT
If you agree to participate in this study we request that you cooperate to the best of their ability. You can withdraw from the study at any stage without justifying your decision and your future treatment will not be affected.
OUR RESPONSIBILITIES TO YOU AS INVESTIGATORS

All data will be maintained in a strictly confidential manner. The information that you provide will be stored in a way that it cannot be accessed except by the named researchers. It will only be used for the research purposes to which you have explicitly agreed.

CONFIDENTIALITY ISSUES

Your GP will be notified of your participation in the study unless you request otherwise. The GP will not receive any of the details of the information that you provide unless you request that it be sent to him/her.

All the information obtained from participating individuals will be treated in a strictly confidential manner according to the stipulations of the Data Protection Act. All of the information obtained will be stored on a password-protected computer database to which only the named researchers will have access. Each individual entered on the database will be assigned a unique numeric identifier in order to ensure anonymity. The names of the individuals will be maintained in a separate password-protected encrypted database with access limited to the named researchers.

If you think you might be interested in participating in the study, please fill in the enclosed form and return it in the stamped addressed envelope to me by post. My group will then contact you by telephone to determine whether or not you are interested in learning more about participating in the study. You will be asked to sign a consent form, if you agree to participate in the study.

IF YOU REQUIRE FURTHER INFORMATION

If you have any further questions about the study or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be affected. For additional information now or any future time please contact:

Name: Doctor Orla Hardiman or Doctor Julie Phukan
Address: Department of Neurology, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland
Phone No: (01) 8093000 beeper 622 (Dr. Hardiman) or (01) 809 3874 (Dr. Phukan).
Appendix 5  Patient Consent Form

A population based survey of cognitive decline in Motor Neuron Disease

Principal Investigator: Prof. Orla Hardiman
Co-Investigators: Dr. Niall Pender, Dr. Julie Phukan

Please tick the appropriate answer.

I confirm that I have read and understood the Patient Information Leaflet dated ______________ attached, and that I have had ample opportunity to ask questions all of which have been satisfactorily answered.

☐ Yes ☐ No

I understand that my participation in this study is entirely voluntary and that I may withdraw at any time, without giving reason, and without this decision affecting my future treatment or medical care.

☐ Yes ☐ No

I understand that my records may be viewed by responsible individuals with delegated authority from the Beaumont Hospital ethics committee and by representatives of Health Authorities.

☐ Yes ☐ No

I understand that my identity will remain confidential at all times.

☐ Yes ☐ No

I am aware of the potential risks of this research project.

☐ Yes ☐ No

I have been given a copy of the Patient Information Leaflet and this Consent form for my records.

☐ Yes ☐ No

I agree that I will not restrict the use to which the results of this study may be put. I give my approval that anonymous data concerning my person may be stored or electronically processed for the purpose of scientific research and may be used in related or other studies in the future. (This would be subject to approval by an independent body that safeguards the welfare and rights of people in biomedical research studies - the Beaumont Hospital Ethics (Medical Research) Committee.)

☐ Yes ☐ No

Patient ____________________________________________________________________________________________

Signature and date Nanne in block capitals

Researcher __________________________________________________________________________________________

Signature and date Name in block capitals

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Appendix 6  Carer Information Leaflet

Beaumont Hospital Ethics (Medical Research) Committee

Carer Information Leaflet

Protocol Title:
A population based survey of cognitive decline in Motor Neuron Disease

Principal Investigator: Professor Orla Hardiman, Beaumont Hospital

We would like to invite you to take part in a clinical research study in which your relative has kindly agreed to participate: the Population based survey of cognitive decline in Motor Neuron Disease. This study is being conducted by Dr. Julie Phukan under the supervision of Professor Orla Hardiman. The aspect of the project we are inviting you to participate in examines the experience of carers of people with Motor Neuron Disease (MND). Before you decide whether or not you wish to take part, you should read the information provided below carefully and if you wish discuss it with your family or friends. Take time to ask questions - do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you - this process is known as Informed Consent.

Please note participation in this study is entirely voluntary and you may decline to participate or change your mind at any time (before the start of the study or even after you have commenced the study) for whatever reason without having to justify your decision and without any negative impact on the care you or your relatives will receive from the medical staff.

WHY IS THIS STUDY BEING DONE & WHAT WILL HAPPEN IF I AGREE?

This aspect of the project is designed to investigate the experience of caring for someone with MND and to examine the factors that may contribute to carer’s distress. Should you agree to take part, Laura Gallagher, a research assistant with the psychology department in Beaumont Hospital, will visit your
home at a time that is convenient for you and will help you to complete a number of questionnaires. These have been designed to provide information about your experiences of MND. These questionnaires will take approximately 30 minutes to complete.

POSSIBLE BENEFITS OF THE STUDY
The wider study aims to determine whether people with Motor Neuron disease develop cognitive impairment (also known as thinking impairment), and if so, to what extent. We will also look for genes that make people more susceptible to the development of cognitive impairment. The aspect of the study we're inviting you to participate in aims to investigate the factors that contribute to distress in carers of people with MND. We hope that this will highlight areas with which carers may need assistance.

POTENTIAL RISKS ASSOCIATED WITH THE STUDY
We understand that discussing your experience of caring for your relative may be difficult and upsetting. If this occurs, we will ensure that you receive appropriate assistance.

WHAT IF SOMETHING GOES WRONG AS A RESULT OF MY PARTICIPATION IN THIS STUDY?
We do not anticipate that anything will go wrong. However, if at any time you feel that your participation in this study has become unduly stressful, you are free to discontinue. This will not affect in any way the quality of care that you receive at Beaumont Hospital, or the access that you will have to specialist services.

WILL THERE BE ANY ADDITIONAL COSTS INVOLVED?
No additional expenses will be incurred by the participating individuals as a consequence of participating in this research study.

OUR RESPONSIBILITIES TO YOU AS INVESTIGATORS
All data will be maintained in a strictly confidential manner. The information that you provide will be stored in a way that it cannot be accessed except by the named researchers. It will only be used for the research purposes to which you have explicitly agreed.
CONFIDENTIALITY ISSUES

All the information obtained from participating individuals will be treated in a strictly confidential manner according to the stipulations of the Data Protection Act. All of the information obtained will be stored on a password-protected computer database to which only the named researchers will have access. Each individual entered on the database will be assigned a unique numeric identifier in order to ensure anonymity. The names of the individuals will be maintained in a separate password-protected encrypted database with access limited to the named researchers.

If you think you might be interested in participating in the study, please fill in the enclosed form and return it in the stamped addressed envelope to me by post. My group will then contact you by telephone to determine whether or not you are interested in learning more about participating in the study. You will be asked to sign a consent form, if you agree to participate in the study.

IF YOU REQUIRE FURTHER INFORMATION

If you have any further questions about the study or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be affected. For additional information now or any future time please contact:

Name:

Doctor Orla Hardiman Consultant Neurologist
Doctor Julie Phukan Specialist Registrar in Neurology
Doctor Niall Pender, Principal Clinical Neuropsychologist/Head of Psychology Department
Laura Gallagher, Research Assistant, Psychology Department
Bernie Corr, MND Clinical Nurse Specialist

Address:

Department of Neurology, Beaumont Hospital, Beaumont Road, Dublin 9 or
Department of Psychology, Beaumont Hospital, Beaumont Road, Dublin 9

Phone No: (01) 8093000 beeper 622 (Dr. Hardiman);
(01) 809 3874 (Dr. Phukan);
087 243 8309 (Bernie Corr);
(01) 809 2963 Laura Gallagher
Can you help us with our research?

Title: A population based survey of cognitive decline in Motor Neuron Disease

Principal Investigator:
Dr. Orla Hardiman, Department of Neurology, Beaumont Hospital, Beaumont Rd. Dublin 9

Beaumont Hospital is conducting a study investigating whether some people with Motor Neurone Disease develop problems with thinking and memory. To do this we need people to participate as a 'control' to compare the overall results of those who have MND with those who do not.

We are looking for men and women aged between 50 and 80 with no history of neurological illness to complete paper and pen tasks examining memory and thinking. The tasks will last approximately 1 $\frac{1}{2}$ hours.

This will take place in the Psychology Department in Beaumont Hospital and travel costs will be reimbursed.

All data collected, in conjunction with Beaumont Hospital's ethics standards, is strictly confidential and all participants will solely be identified by a numerical value.

If you would like to find out more about participating in this study please contact:

- Laura Gallagher, Research Assistant, Department of Psychology: (01) 8092963

- Dr. Niall Pender, Principal Clinical Neuropsychologist, Head of Psychology Department: (01) 8092223

Address: Department of Psychology, Beaumont Hospital, Beaumont Rd. Dublin 9
Beaumont Hospital Ethics (Medical Research) Committee

Carer Information Leaflet

Protocol Title:
A population based survey of cognitive decline in Motor Neuron Disease

Principal Investigator: Professor Orla Hardiman, Beaumont Hospital

You are being asked to take part in a clinical research study carried out at Beaumont Hospital. Before you decide whether or not you wish to take part, you should read the information provided below carefully and if you wish discuss it with your family, friends or GP. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you – this process is known as Informed Consent.

You may change your mind at any time (before the start of the study or even after you have commenced the study) for whatever reason without having to justify your decision and without any negative impact on the care you or your relatives will receive from the medical staff.

WHY IS THIS STUDY BEING DONE?
You have been asked to participate in a study to determine whether some people with Motor Neurone Disease (MND) develop problems with thinking and memory (cognitive impairment). The study also collects information from controls (i.e. people without MND) to compare with the information obtained from people with MND.
WHO IS ORGANISING AND FUNDING THIS STUDY?
This study is being performed by Dr. Julie Phukan, a Specialist Registrar in Neurology under the supervision of Doctor Orla Hardiman, who is a Consultant Neurologist at Beaumont Hospital in Dublin. The work is being done in collaboration with Doctor Niall Pender who is a Consultant Neuropsychologist at Beaumont Hospital. Laura Gallagher, a Research Assistant at Beaumont Hospital, will be collecting data from the control group.

HOW WILL IT BE CARRIED OUT?
This study will start in October 2006 and will continue for the next 3 years until sufficient information has been collected. Everybody in Ireland who has been diagnosed with MND will be approached and asked to participate. So also will unrelated family members e.g. spouses/partners, who will thus act as "controls" in this study. The study will also be advertised to invite suitable members of the public to participate. Those who agree to act as controls will complete a series of psychological tests to measure memory and thinking, and a questionnaire about their family history

WHAT WILL HAPPEN TO ME IF I AGREE TO TAKE PART?
Laura Gallagher will arrange to conduct the study with you in the Department of Psychology in Beaumont Hospital at a time that is convenient. Laura Gallagher will perform the various tests with you. These tests are designed to identify subtle changes in memory, language and attention that have been reported to occur in MND. We do not routinely expect to find any such changes in those without MND. The tests will take approximately 1 hour and a half. At the time of the first test, Laura Gallagher will examine the results and will contact you within 8 weeks to provide some feedback and advice.

POSSIBLE BENEFITS OF THE STUDY
The cause of MND is unknown. This study aims to determine whether people with Motor Neuron disease develop cognitive impairment, and if so, to what extent. We will also look for genes that make people more susceptible to the development of cognitive impairment. Your participation as a 'control' allows us to compare the overall results of those who have MND with those who do not.
You can obtain information about the results of the psychological testing from Laura Gallagher. We do not expect that control participants will have serious difficulties with thinking and memory. However, if Laura Gallagher identifies these, or if you have any concerns in this regard, a referral to the Neuropsychology Department at Beaumont Hospital will be arranged for or appropriate follow-up and assistance.

**POTENTIAL RISKS ASSOCIATED WITH THE STUDY**

It is possible that engaging in these tasks and/or difficulty completing these tasks may cause emotional distress. If this occurs appropriate services will be made available.

**WHAT IF SOMETHING GOES WRONG AS A RESULT OF MY PARTICIPATION IN THIS STUDY?**

We do not anticipate that anything will go wrong. However, if at any time you feel that your participation in this study has become unduly stressful, you are free to discontinue. This will not affect in any way the quality of care that you receive at Beaumont Hospital.

**WILL THERE BE ANY ADDITIONAL COSTS INVOLVED?**

Any additional expenses incurred by the participating individuals as a consequence of participating in this research study (i.e. travel expenses) will be reimbursed.

**YOUR RESPONSIBILITIES AS A PARTICIPANT**

If you agree to participate in this study we request that you cooperate to the best of your ability. You can withdraw from the study at any stage without justifying your decision.

**OUR RESPONSIBILITIES TO YOU AS INVESTIGATORS**

All data will be maintained in a strictly confidential manner. The information that you provide will be stored in a way that it cannot be accessed except by the named researchers. It will only be used for the research purposes to which you have explicitly agreed.
CONFIDENTIALITY ISSUES

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IF YOU REQUIRE FURTHER INFORMATION

If you have any further questions about the study or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be affected. For additional information now or any future time please contact:

Name:

Doctor Orla Hardiman Consultant Neurologist
Doctor Julie Phukan Specialist Registrar in Neurology
Doctor Niall Pender, Principal Clinical Neuropsychologist/Head of Psychology Department
Laura Gallagher, Research Assistant, Psychology Department
Bernie Corr, MND Clinical Nurse Specialist

Address:

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Phone No: (01) 8093000 beeper 622 (Dr. Hardiman);
(01) 809 3874 (Dr. Phukan);
087 243 8309 (Bernie Corr);
(01) 809 2963 Laura Gallagher
Appendix 9  ALSFRS

Instructions for completing the ALSFRS-R (ALS Functional Rating Scale)
A. Comparisons are made with the patient’s status prior to the onset of the disease, not with status at the last visit.
B. Patient’s response (on a 5 point scale) is recorded in relation to the question "How are you doing at (...)? for each of the 12 functions listed in the ALSFRS-R

<table>
<thead>
<tr>
<th>SPEECH</th>
<th>DRESSING AND HYGEINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Detectable speech disturbance</td>
<td>3. Independent self care with effort or decreased efficiency</td>
</tr>
<tr>
<td>2. Intelligible with repeating</td>
<td>2. Intermittent assistance or substitute methods</td>
</tr>
<tr>
<td>1. Speech combined with non-vocal communication</td>
<td>1. Needs attendant for self care</td>
</tr>
<tr>
<td>0. Loss of useful speech</td>
<td>0. Total dependence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SALIVATION</th>
<th>TURNING IN BED AND ADJUSTING BEDCLOTHES</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Slight but definite excess of saliva in mouth, may have night time drooling</td>
<td>3. Somewhat slow or clumsy, needs no help</td>
</tr>
<tr>
<td>2. Moderately excessive saliva, may have minimal drooling</td>
<td>2. Can turn alone or adjust sheets with great difficulty</td>
</tr>
<tr>
<td>1. Marked excess of saliva with some drooling</td>
<td>1. Can initiate but cannot turn or adjust sheets</td>
</tr>
<tr>
<td>0. Marked drooling, requires constant tissue</td>
<td>0. Helpless</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SWALLOWING</th>
<th>WALKING</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Early eating problems, occasional choking</td>
<td>3. Early ambulation difficulties</td>
</tr>
<tr>
<td>2. dietary consistency changes</td>
<td>2. Walks with assistance</td>
</tr>
<tr>
<td>1. needs supplemental tube feedings</td>
<td>1. Non-ambulatory functional movement only</td>
</tr>
<tr>
<td>0. NPO (exclusively parental or enteral feedings)</td>
<td>No purposeful leg movement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HANDWRITING</th>
<th>CLIMBING STAIRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Slow or sloppy, all words legible</td>
<td>3. Slow</td>
</tr>
<tr>
<td>2. Not all words legible</td>
<td>2. Mild unsteadiness or fatigue</td>
</tr>
<tr>
<td>1. Able to grip pen, unable to write</td>
<td>1. Needs assistance</td>
</tr>
<tr>
<td>0. Unable to grip pen</td>
<td>0. Cannot do</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CUTTING FOOD AND HANDLING UTENSILS (patients without gastrostomy)</th>
<th>DYSPNOEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Normal</td>
<td>4. None</td>
</tr>
<tr>
<td>3. Somewhat slow and clumsy, needs no help</td>
<td>3. Occurs when walking</td>
</tr>
<tr>
<td>2. Can cut most foods, slow and clumsy, some help needed</td>
<td>2. Occurs with one or more: eating, bathing, dressing</td>
</tr>
<tr>
<td>1. Foods cut by someone else, can still feed slowly</td>
<td>1. Occurs at rest, either sitting or lying</td>
</tr>
</tbody>
</table>

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Instructions for completing the ALSFRS-R (ALS Functional Rating Scale)

A. Comparisons are made with the patient’s status prior to the onset of the disease, not with status at the last visit.

B. Patient’s response (on a 5 point scale) is recorded in relation to the question “How are you doing at (...)?” for each of the 12 functions listed in the ALSFRS-R

<table>
<thead>
<tr>
<th>Function</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. Needs to be fed</td>
<td>0. Significant difficulty, considering using mechanical support</td>
</tr>
<tr>
<td>CUTTING FOOD AND HANDLING UTENSILS (patients with gastrostomy)</td>
<td></td>
</tr>
<tr>
<td>4. Normal</td>
<td>4. None</td>
</tr>
<tr>
<td>3. Clumsy, able to perform all manipulations</td>
<td>3. Some difficulty sleeping, d/t shortness of breath, does not routinely use &gt;2 pillows</td>
</tr>
<tr>
<td>2. Some help needed with closures and fasteners</td>
<td>2. Needs extra pillows to sleep (&gt;2)</td>
</tr>
<tr>
<td>1. Provides minimal assistance to caregiver</td>
<td>1. Can only sleep sitting up</td>
</tr>
<tr>
<td>0. Unable to perform any aspect of task</td>
<td>0. Unable to sleep</td>
</tr>
<tr>
<td>ORTHOPNEA</td>
<td></td>
</tr>
<tr>
<td>RESPIRATORY INSUFFICIENCY</td>
<td></td>
</tr>
<tr>
<td>4. None</td>
<td></td>
</tr>
<tr>
<td>3. Intermittent use of BiPAP</td>
<td></td>
</tr>
<tr>
<td>2. Continuous use of BiPAP at night</td>
<td></td>
</tr>
<tr>
<td>1. Continuous use of BiPAP day and night</td>
<td></td>
</tr>
<tr>
<td>0. Invasive mechanical ventilation by intubation / tracheostomy</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 10 Fixed Test Order

Boston Naming Test (abbreviated version; 30 words)
Raven’s Standard Progressive Matrices
Logical Memory I
California Verbal Learning Test I
Verbal Paired Associates I
Rey Complex Figure Test
Stroop Test
Logical Memory II (25-35 minutes after LM I)
California Verbal Learning Test II (20 minute delay after part I)
Brixton Spatial Anticipation Test
Digit Span (forward and backward)
Verbal Fluency Index
Category fluency (one minute)
Verbal Paired Associates II (25-25 minutes after part I)
Rey Complex Figure Test (30-45 minutes after part I)
Wechsler Test of Adult Reading
Hospital Anxiety and Depression Scale
Frontal Systems Behavioural Scale