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White matter integrity, executive dysfunction, and processing speed in Amyotrophic Lateral Sclerosis

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Abstract

Cognitive impairment in amyotrophic lateral sclerosis (ALS) is characterized by deficits on tests of executive functions however the contribution of processing speed is unknown. By contrast, multiple sclerosis (MS) is a disorder in which slowed processing speed is regarded as the core deficit, however, methodology is often confounded by tasks which depend on motor speed. MRI studies have revealed multi-system cerebral involvement in ALS, with evidence of reduced white matter volume and integrity in predominantly frontotemporal regions. The current study had two aims. Firstly, to investigate whether cognitive impairments in ALS and MS are due to executive dysfunction or slowed processing speed, independent of motor dysfunction. Secondly, to investigate the relationship between specific cognitive impairments and the integrity of distinct white matter tracts in ALS. Twenty-nine ALS patients, twenty-five MS patients, and matched healthy control groups were administered a dual task paradigm and processing speed tasks in which stimulus presentation times were manipulated. In addition background measures of executive functioning, working memory, verbal memory, and language were administered. White matter integrity was investigated using region-of-interest (ROI) and tract based spatial statistics (TBSS) analyses of diffusion MRI data. ALS patients did not show impairments in tests of processing speed, but deficits were revealed in the dual task, as well as background tests of executive functioning, working memory, and verbal memory. MS patients also exhibited deficits in the dual task as well as background tests of executive functioning, working memory, and verbal memory. However, in contrast to ALS patients, a processing speed deficit was also observed in MS. ROI analyses revealed significant differences in fractional anisotropy (FA) and mean diffusivity ($\langle D \rangle$) between ALS patients and healthy controls. Reduced integrity was observed in the corticospinal tracts and prefrontal and temporal white matter tracts including uncinate fasciculus, inferior longitudinal fasciculus,

and regions of the cingulum. Significant differences also emerged in the white matter underlying the superior, medial and inferior frontal gyri, and the temporal gyri. Similar group differences were found in the TBSS analyses; ALS patients displayed prominent changes in the corticospinal tract and corpus callosum as well as extensive changes in prefrontal and temporal tracts and association fibres. Correlations between task performance and ROI parameters revealed that dual task performance was associated with FA in the middle frontal gyrus white matter while letter fluency indices correlated with FA in the corpus callosum and corticospinal tracts. Furthermore, verbal memory performance correlated with FA in the inferior longitudinal fasciculus and working memory performance correlated with ⟨D⟩ in uncinate fasciculus and hippocampal portion of the cingulum. Correlations with TBSS revealed significant associations between letter fluency indices and FA in the corticospinal tracts and anterior corpus callosum. The current study demonstrates that cognitive impairment in ALS is not due to slowed processing speed. Moreover dual task deficits are related to distinct prefrontal tract involvement in ALS, whilst fluency deficits may reflect decreasing callosal integrity. Deficits in working memory and verbal memory are related to white matter changes in fibre bundles connecting prefrontal, temporal, and limbic structures.

Prior publications

Prior to the completion of the current thesis, two publications related to this body of work have been submitted to peer-reviewed journals. The first is an imaging methods paper concerning the sensitivity of a novel tractography protocol for detecting white matter abnormalities in ALS:

Bastin, M. E., Pettit, L. D., Bak, T. H., Gillingwater, T. H., Smith, C., & Abrahams, S. (2013). Quantitative tractography and tract shape modeling in amyotrophic lateral sclerosis. *Journal of Magnetic Resonance Imaging.* Article first published online: 28 Feb 2013. doi: 10.1002/jmri.24073

The second concerns the white matter region-of-interest analysis and correlations with cognitive performance described in Chapter 6. The ALS group investigated for the purpose of this publication included an additional patient who met the criteria for ALS-FTD and thus the data, although similar, are not identical to that described in the current thesis.

Pettit, L. D., Bastin, M. E., Smith, C., Bak, T. H., Gillingwater, T. H., & Abrahams, S. (2013). Executive deficits, not processing speed relates to abnormalities in distinct prefrontal tracts in ALS. *Brain, 136,* 3290–3304.

Declaration

I, the author and candidate, hereby declare that:

a) The thesis has been composed by the candidate.

b) The work is the candidate's own.

c) The work has not been submitted for any other degree or professional qualification except for the publications detailed previously.

Signed: Date:

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Chapter 1. Literature review

1.1 Disease description

Amyotrophic lateral sclerosis (ALS) is the most common form of a group of neurodegenerative disorders which encompasses primary lateral sclerosis and progressive muscular atrophy, and which collectively fall under the bracket of motor neuron disease. Originally described by Charcot (1869; 1874), ALS is a fatal disorder of the human motor system which causes progressive degeneration of pyramidal motor neurons in the brain (upper motor neurons), and anterior horn cells in the spinal cord (lower motor neurons). The resultant disruption of the motor system causes progressive muscle weakness and wastage as well as spasticity and fasciculations, eventually leading to death usually through respiratory failure (Anderson et al., 2007).

The physiological mechanisms underlying neurodegeneration in ALS are not fully understood, although are likely to be multifactorial in nature and include factors such as glutamate excitoxicity, the formation of protein aggregates, DNA/RNA processing, mitochondrial dysfunction, and disruption to axonal transport processes (Keirnan et al., 2011). There is still debate as to whether the disease begins in the upper motor neurons or lower motor neurons. The "dying-forward" hypothesis (Eisen, Kim & Pant, 1992) proposes that pathology begins in the pyramidal motor neurons and spreads to the anterior horn cells via glutamate excitoxicity, whereas the "dying-back" hypothesis proposes that pathology begins in the neuromuscular junction where depleted levels of neurotrophic hormone result in disruption to functioning of the upstream neuronal cell (Chou & Norris, 1992 Fischer et al., 2004). However, the possibility remains that upper and lower motor neuron pathology develops independently as physiological and pathological studies have predominantly

reported a lack of association between degeneration in the respective anatomical areas (Kiernan & Hudson, 1991; Attarian, Vedel, Pouget & Schmied, 2008).

1.2 Diagnosis and progression

The diagnosis of ALS presents a challenge as there is no definitive diagnostic test for the disease. Instead clinicians must rely on observations, nerve conduction analyses (electromyography), neuroimaging, and biopsies to identify a combination of upper and lower motor neuron pathology, as well as evidence of disease spread from one body region to another. Diagnosis is usually made based on the revised El Escorial criteria (Miller, Munsat, Swash & Brooks, 1999) which provides different levels of diagnostic certainty based on the extent and distribution of observed pathology, and the presence or absence of genetic components.

Further complexity arises in the variation of clinical phenotypes. Disease onset is focal in ALS and reflects the involvement of upper and lower motor neuron regions which subserve the same anatomical area. Typically, patients may present with limb-onset (approx 70%), bulbar onset (approx 25%), or trunk or respiratory involvement (approx 5%) which are focal in nature before spreading to other areas of the body (Vucic, Burke & Kiernan, 2007). Atypical forms of onset include, weight loss, emotional lability and cognitive dysfunction (Ferguson & Elman, 2007). Disease spread in ALS is thought to be predominantly contiguous, with degeneration spreading to adjacent areas in both the upper and lower motor neuron anatomy (Brooks, 1991; Ravits, Paul & Jorg, 2007). However, in the lower motor neurons spread may move in a rostral to caudal direction, whereas in the upper motor neurons spread is medial to lateral in nature (Ravits & La Spada, 2009). This process,

coupled with rapid disease progression and the fact that the relative involvement of upper and lower motor neuron pathology is highly heterogeneous, may explain why there is such variation in clinical phenotype from one patient to another. Progression in ALS is relentless and survival statistics are harrowing with approximately 50% of patients dying within 30 months of symptom onset, and only 20% surviving to between 5 and 10 years after symptom onset. Poor survival is predicted by older onset age, early respiratory dysfunction, and bulbar-onset whereas younger age at onset, diagnostic delay and limb-onset are predictors of longer survival (Talbot, 2009).

1.3 Intervention and management

Currently, drug intervention in ALS is restricted to Riluzole, a glutamate release inhibitor, which has been shown in randomised control trials to increase survival by 3 – 6 months (Miller, Mitchell, Lyon & Moore, 2007). In the absence of effective disease modifying drugs, management of ALS and its progression becomes paramount. Optimal care is provided by multidisciplinary teams encompassing physiotherapists, occupational therapists, speech therapists, respiratory physicians, gastroenterologists and social workers; support of this kind not only benefits the patient in terms of well being and alleviation of symptoms, but can also improve survival significantly (Van den Berg et al., 2005).

Respiratory and nutrition management are the most vital components of palliative care as both are significant predictors of prognosis and survival (Miller et al., 2009). Respiratory weakness can be present from the onset of symptoms, and as the disease progresses ALS patients can suffer from nocturnal hypoxia as well as inspiratory and diaphragmatic weakness. Intervention comes in the form of non-invasive ventilation (NIV) which can

prolong survival and also improve quality of life by alleviating the associated symptomology of respiratory dysfunction (Bourke, Tomlinson, Williams, Bullock, Shaw & Gibson, 2006). Invasive ventilation is also an option and does significantly improve survival, but the reality of drastically reduced quality of life and financial costs mean that this strategy is rarely implemented. Malnutrition in ALS can be a result of weakened swallow and choking (dysphagia), or due to an increase in metabolic rate that affects approximately 50% of patients (Bouteloup et al., 2009). The associated weight loss can be mediated by the implementation of a feeding tube, either by percutaneous endoscopic gastrostomy (PEG) or radiologically inserted gastrostomy (RIG) depending on the patient's symptoms. However as ALS progresses, palliative care is the main requirement as patients require careful monitoring of physical symptoms and emotional distress to make the end stage of the disease as easy as is possible.

1.4 Epidemiology and genetics

Although ALS has been reported throughout the world, precise global incidence is as yet unknown. However, population based studies in Europe have indicated a relatively stable incidence rate of 2.16 per 100,000 person-years (Logroscino et al., 2009), with men having a slightly higher incidence (3.0 per 100,000 person-years) than women (2.4 per 100,000 person-years). Risk of disease onset increases with age; peak incidence in the sporadic form is between 58 – 63 years old although it is considerably lower in familial forms (47 – 52 years old).

Although ALS appears to be a predominantly sporadic disease, approximately 10% are familial and follow a Mendelian pattern of inheritance (Kiernan et al., 2011). Currently,

fourteen genetic loci have been identified in familial forms of ALS with advancements in genomic techniques allowing new discoveries in recent years. Indeed, the proportion of ALS cases with a genetic component may be larger than is currently estimated as new discoveries continue to be made. Although the proportion of familial cases in ALS is relatively small, genetic studies remain a crucial line of investigation as the familial and sporadic phenotypes are virtually indistinguishable suggesting that there may be common pathways underpinning the observed pathology (Ravits & La Spada, 2009).

Until recently, the most common known genetic mutation was *SOD1* which accounts for 20% of familial ALS and up to 5% of cases thought to be sporadic. *SOD1* encodes for copper-zinc superoxide dismutase and is responsible for toxic gain of function (Rosen et al., 1993). Other important genetic markers discovered in recent years are *TDP-43* (or *TARDBP* which encodes TAR DNA binding protein) and *FUS* (which encodes fusion in sarcoma). Both of these genes are multifunctional but play an important role in RNA processing suggesting that this may be a key feature of ALS molecular pathology (Sreedharan et al., 2008; Vance et al., 2009).

In addition to the Mendelian inheritance of familial forms of ALS itself, epidemiological studies in relatives of ALS sufferers have revealed above average incidences of other neurodegenerative diseases (Fallis & Hardiman, 2009), suggesting that there may be susceptibility genes which increase overall risk of neurodegeneration. Indeed, pathology studies have revealed that *TDP-43* pathology is present in almost all ALS cases and more than 50% of frontotemporal dementia (FTD) cases providing strong evidence for a link between the two disorders (Neumann et al., 2006). Moreover, the most recent and

potentially significant genetic mutation, the hexanucleotide repeat expansions in *C9orf72*, has been shown to account for up to 41% of familial ALS cases, and is also present is a significant proportion of FTD patients (Byrne et al., 2012; Snowden et al., 2012).

1.5 Overlap with FTD

Frontotemporal dementia (FTD) is a progressive neurodegenerative disease which causes focal atrophy of the frontal or anterior temporal lobes, or both, depending on the variant. Incidence and prevalence rates are variable, but the highest rates are in people of 60 – 69 years old (prevalence 9.4 per 100,000; Knopman, Petersen, Edland, Cha & Rocca, 2004, incidence 8.9 per 100,000 person-years; Rosso & Kaat, 2003) and it is the second most common form of dementia in people under 65 years old (Ratnavalli et al., 2002). Three variants of FTD are recognised; behavioural variant (bvFTD), semantic dementia (SD) and progressive non-fluent aphasia (PNFA), and each have a different cognitive and behavioural profile.

BvFTD is the most common variant and is characterised by profound behavioural and personality disturbances including disinhibition, impulsivity, emotional blunting, stereotyped behaviour, changes in appetite, lack of insight, and apathy (Neary et al., 1998). Cognitive changes may also be present at onset, or may develop as the disease progresses, with impairments observed in tests of executive functioning (goal-directed behaviours such as planning, strategy formation, mental flexibility, and inhibition), but relative sparing of episodic memory and visuospatial abilities (Rascovsky et al., 2011). Presentation in bvFTD is relatively heterogeneous, but typical pattern of atrophy associated with the syndrome is primarily of orbitofrontal and medial frontal cortex, with involvement of more dorsolateral

prefrontal areas as the disease spreads in an anterior – posterior direction (Weder, Aziz, Wilkins & Tampi, 2007). SD is characterised by a profound loss of semantic knowledge resulting in word finding difficulties (anomia), as well as poor conceptual knowledge and recognition of words, objects, and faces. As semantic networks are lost, speech becomes increasingly empty with a paucity of nouns although grammatical structure is preserved (Weder et al., 2007). Behavioural changes may also be present in SD, but compared to bvFTD, patients with SD are less likely to be apathetic and more likely to be compulsive (Boxer & Miller, 2005). As in bvFTD, episodic memory and visuospatial skills are typically spared, however, in contrast to bvFTD problem solving ability and executive functioning tends to remain intact, at least in the earlier stages of the disease (Lillo & Hodges 2009). Atrophy associated with SD is consistently within the anterior and inferior temporal lobes, and often asymmetrical with a left hemispheric bias (Hodges & Patterson, 2007). PNFA predominantly affects the language abilities, but in contrast to SD, impairments are present in grammar and phonology (speech sounds) resulting in speech which non-fluent, poorly articulated and agrammatical (Wender et al., 2007). Like SD, patients with PNFA may also present with word finding difficulties, however they can be differentiated from SD patients by the presence of intact comprehension and recognition of words and objects (Knibb, Kipps & Hodges, 2006). Unlike either bvFTD or SD, behavioural changes do not occur in PNFA until later into disease progression, and the associated atrophy is observed in insular and inferior frontal regions (Nestor et al., 2003).

The association between ALS and cognitive and psychiatric symptoms has been documented in some of the earliest descriptions of the disorder; Marie (1892) stated that psychic disturbances were relatively common in ALS, and subsequent clinicians noted patients with personality and behavioural changes, failure of memory, and intellectual

impairment (Westphal, 1925; Meyer, 1929; Ziegler, 1930). Further investigations revealed that ALS was associated with a higher incidence of frontotemporal lobar dementia than in the normal population (e.g. Brion et al., 1981, and see Hudson, 1981 for a review), and seminal work by Neary et al. (1990) described patients with cognitive, behavioural, and cerebral hallmarks of FTD with co-occurring ALS. In spite of this, the traditional view of FTD assumed that the syndrome was clinically and pathologically separate from other neurodegenerative disorders (Lillo & Hodges, 2009). Likewise the prevailing view adopted by neurologists and scientist alike was that ALS was purely a motor disorder. However, with the discovery of shared *FUS* and *TDP-43* pathology in both disorders as mentioned above, a plausible biological link between ALS and FTD was tentatively established. Further evidence was provided by families in which members developed ALS or FTD, or both, with linkage identified on chromosome 9 (Vance et al., 2009; Pearson et al., 2011).The recent discovery of the mutation in *C9orf72* has consolidated this relationship (Renton et al., 2011), and the overlap between the FTD and ALS is now well recognised. In FTD populations, there is now consistent evidence that a significant minority of patients also have ALS with some studies suggesting that co-incidence is as high as 15% (Lomen-Hoerth, Anderson & Miller, 2002; Hodges et al., 2003). Incidences of ALS patients developing or presenting with FTD (ALS-FTD) have been subject to more investigation; the percentage of patients meeting FTD criteria in small scale studies have ranged from 22% to 52% (Murphy, Henry, Langmore, Kramer, Miller & Lomen-Hoerth, 2007; Lillo, Savage, Mioshi, Kiernan, & Hodges, 2012; Lomen-Hoerth, Murphy, Langmore, Kramer, Olney & Miller, 2003). However, larger clinic-based studies have shown that the true overlap is likely to be smaller; the largest study to date of 279 consecutive ALS patients found that 15% also met criteria for FTD (Ringholz et al 2005), whilst a more recent population-based study of 186 ALS patients reported that 14% met criteria for FTD (Phukan et al., 2012). ALS-FTD patients predominantly present with the behavioural variant of the disease,

although cases of ALS-SD or ALS-PNFA have been reported (Lomen-Hoerth et al., 2003). Patients exhibit the same behavioural and cognitive sequelae that characterise the pure FTD syndromes. For example, patients with ALS-FTD have been shown to exhibit behavioural abnormalities such as aggression, impulsivity, and apathy (Neary et al., 1990), as well as showing more formalised changes on the Frontal Systems Behaviour Scale (Woolley, Moore & Katz, 2010). Executive deficits have been reported in letter and category fluency tests (Lepow et al., 2010), and on the Stroop Interference Test (Lomen-Hoerth et al., 2003), and linguistic impairment have been reported in confrontation naming (Lomen-Hoerth et al., 2003). Moreover, investigation of ALS-FTD patients by structural magnetic resonance imaging (MRI) has revealed atrophy in corresponding frontotemporal regions, although to a lesser extent than patients with FTD in isolation (Lillo, Mioshi, Burrell, Kiernan, Hodges, & Hornberger, 2012).

The clinical and pathological overlap between ALS and FTD discussed above had led to the suggestion that the two syndromes exist on a single continuum (Murphy et al., 2007). Neuroimaging studies have shown that although ALS, ALS-FTD and FTD have discrete and dissociable structural changes, there is overlapping structural pathology in frontotemporal grey and white matter structures between all the disorders (Chang et al., 2005; Lillo et al., 2012). Further support for this idea is provided by the growing evidence base of studies which have demonstrated cognitive and behavioural impairments in ALS patients who do not meet FTD criteria, implying that a proportion of patients lie somewhere on the spectrum between pure ALS and ALS-FTD (see Goldstein & Abrahams, 2013 for a review). Large scale studies have shown that detailed neuropsychological testing can detect cognitive impairments in a high proportion of patients, with estimates between 35% and 50% (Massman, Sims, Cooke, Haverkamp & Appel, 1996; Ringholz et al., 2005). Recently, a

consensus criteria was proposed in which characteristics of cognitive impairment (ALSci) and behavioural impairment (ALSbi) were defined (Strong et al., 2009). ALSci patients are defined as those performing below the 5th percentile on two or more tests that are sensitive to executive functioning, and several large population-based studies have reported that significant proportion of patients (21 – 25%) meet this criteria (Phukan et al., 2012; Taylor et al., 2012; Elamin et al., 2013). Indeed, the most consistently reported cognitive impairments in non-demented ALS patients are in the domain of executive functioning (Massman et al., 1996; Frank, Haas, Heinze, Stark & Münte, 1997; Ringholz et al., 2005; Gordon et al., 2010). However, some have argued that language deficits are equally prevalent (Taylor et al., 2012), and memory impairment is also an increasingly recognised feature of this disorder (Ringholz et al., 2005; Christidi, Zalonis, Smyrnis & Evdokimidis, 2012). These impairments will be discussed in more detail in the following sections.

1.6 Cognition in non-demented ALS

1.6.1 Executive functions

Executive functions can be defined as high-level cognitive processes that facilitate new ways of behaving, and optimise one's approach to unfamiliar circumstances (Gilbert & Burgess, 2008). Executive functions can be based upon internally or externally driven goal-directed behaviours, and are highly involved in self-enhancing behaviours and social interaction (Anderson, Jacobs, & Anderson, 2008). The precise nature, and number of discrete cognitive functions that fall under the bracket of "executive functions" is highly debated (Jurado & Roselli, 2007), however most models agree that they play a crucial role in adaptive behaviour by facilitating processes such as: selective attention, planning, problem solving, initiation of action, mental flexibility, monitoring and inhibition, and

working memory (the ability to temporarily hold and manipulate information "in mind"). In Chapter 3 a detailed discussion of models of executive functions are given in order to provide a foundation for the methodological design of the current thesis. The literature investigating executive functions in ALS has not typically been related to specific models of executive processes but rather has been described in relation to specific tests, most commonly standard assessments used in clinical neuropsychology, the results of which are summarised in Table 1.

Table 1. Studies investigating executive functions in ALS

Study	Group/Case analyses	Impaired performance	Normal performance
Gallassi et al., 1985	Group: 22 ALS	Letter fluency, visual attention (Barrage test)	Working memory (verbal and spatial memory spans)
David et al., 1986	Group: 14 ALS	Concept formation (WCST)	Working memory (digit span)
Ludolph et al., 1992	Group: 18 ALS	Verbal fluency	Concept formation (WCST), cognitive inhibition (Stroop), working memory (digit span), visual attention (D2 test)
Hartikainen et al., 1993	Group: 24 ALS	Attention (Digit symbol substitution test), processing speed/switching (TMT A, TMT B, TMT B-A)	Category fluency
Kew et al., 1993	Group: 16 sporadic ALS	Letter fluency (written)	Inhibition (Stroop), concept formation (WCST), sustained attention
Abrahams et al., 1996	Group: 12 sporadic ALS	Letter fluency impaired subgroup (n = 6); letter fluency *fi* (written + spoken) WCST (trials to first criterion), random joystick movement	WCST (no. of categories, errors, perseverations)
Massman et al., 1996	Case: 146 sporadic ALS	Letter fluency (spoken), attention (VSAT, SDMT), concept formation (WCST)	NOTE: 35.6% showed cognitive impairment (2 tests). Dysarthric patients more impairment (48.5%) than limb onset (27.4%).
Abrahams et al., 1997	Group: 52 ALS; bulbar subgroup (n = 24)	All ALS patients: Letter fluency *fi* (written), planning + working memory (computerised Tower of Hanoi), concept formation (WCST),	Inhibition (Stroop errors and reaction time)

		inhibition (Stroop negative priming – trend). Bulbar patients only; random movement joystick test	
Frank et al., 1997	Group: 74 sporadic ALS	Letter fluency, inhibition (Stroop) – both correlated with age. Visual attention (D2 test), concept formation (WCST).	
Rakowicz & Hodges, 1998	Group: 18 ALS	Verbal fluency (letter and category), working memory (reverse digit span)	Working memory (digit span)
Strong et al., 1999	Group: 13 ALS; 8 longitudinal	Letter fluency (spoken +written) BULBAR only: Concept formation (WCST), working memory (consonant trigrams test).	Concept formation (WCST), working memory (consonant trigrams test) NOTE: Impaired = < 1SD in this paper.
Abrahams et al., 2000	Group: 22 sporadic ALS	Fluency *fi* (written letter, category, design), Working memory (letter strings)	Letter fluency *fi* (spoken)
Newsom-Davis et al., 2001	Group: 19 ALS; hypoventilation subgroup (n = 9)	Hypoventilation patients only: Letter fluency *fi* (written). NOTE: All improved after nocturnal ventilation.	Working memory (digit span)
Hanagasi et al., 2002	Group: 20 sporadic ALS	Verbal fluency (letter + category), attention (continuous performance test), working memory (reverse digit span, SDLT, delayed recognition test), inhibition (Stroop), processing speed/switching (TMT A, TMT B, TMT B-A)	Working memory (digit span)
Moretti et al., 2002	Group: 14 ALS	Verbal fluency, concept formation (WCST), cognitive inhibition (Stroop), attention (PASAT)	Working memory (digit span)
Lomen-Hoerth	Case: 100 ALS; full	Verbal fluency screen (31% impaired). Full	NOTE: 50% bulbar patients had VF impairment vs

et al., 2003	assessment subgroup (n = 44)	neuropsych; Inhibition (Stroop interference), concept formation (WCST + California card sort) most sensitive	25% limb Of 44; 17 had VF deficit, 12/17 met FTLD criteria. Of 44; 27 had no VF deficit, 6/27 met FTLD criteria
Abrahams et al. 2004	Group: 28 Sporadic ALS	Letter fluency *fi* (written + spoken), working memory (letter span)	Category fluency *fi*, design fluency *fi*, concept formation (WCST)
Kilani et al., 2004	Group: 18 ALS; longitudinal	Switching (TMT B-A) NOTE: no change over 12 months	Concept formation (WCST), working memory (digit span)
Abrahams et al., 2005	Group: 23 sporadic ALS; fluency impaired subgroup (n = 11)	Subgroup only: Fluency *fi* (written letter and category), working memory (letter span)	Fluency *fi* (design), concept formation (WCST)
Ringholz et al., 2005	Case: 279 sporadic ALS	Cluster analysis 32% mild impairment, 13% moderate impairment, 15% FTD. Sensitive tests: Attention (VSAT), letter fluency	Cluster analysis: 49% patients cognitively intact
Abrahams et al., 2005	Group: 20 ALS; longitudinal	Letter fluency *fi* (written and spoken), computerised sentence-completion task (at time point 2).	Fluency *fi* (category and design), attention (PASAT), working memory (letter span), concept formation (WCST).
Schreiber et al., 2005	Group: 52 sporadic ALS; longitudinal	Fluency (letter and design), concept formation (WCST), interference (colour word interference test – bulbar only), attention (phasic and tonic alertness RTs), divided attention (dual task RTs)	NOTE: only bulbar patients showed some evidence of longitudinal deterioration (interference, design fluency, recognition memory)
Robinson et al., 2006	Case: 19 sporadic ALS; longitudinal	Z scores: (37%) had abnormalities at 6 month follow up. Sensitive tests: concept formation (WCST)	

Mezzapesa et al., 2007	Group and case: 16 sporadic ALS	ALS vs controls: Attention/processing speed, (SDMT). Z scores: 50% of patients were ALSi; 2SD below normative data on 2 tests.	ALS vs controls: Working memory (Brown-Peterson interference test), letter fluency, interference (stroop)
Kim et al., 2007	Group: 16 ALS; low FVC subgroup (n = 8)	Low FVC vs High FVC: letter fluency *fi* (spoken) NOTE: no healthy control group	Low FVC vs High FVC: letter fluency *fi* (written), category fluency *fi*
Lule et al., 2007	Group: 13 sporadic ALS	Verbal fluency (letter and alternating)	Fluency (design), concept formation (WCST-computerised), attention/processing speed (SDMT)
Pinkhardt et al., 2008	Group: 20 sporadic ALS	Fluency (letter and design), selective attention (incompatibility task)	Fluency (category), inhibition (Stroop).
Bartels et al., 2008	Case: 22 ALS	Z-scores; most sensitive tests = verbal fluency (57%), working memory (digit span – 40%), delayed recall (33%). 12/22 impaired on 2 or more tests.	
Wicks et al., 2009	Group: 58 ALS; 41 sporadic, 7 SOD1 familial, 10 non-SOD1 familial	Non-SOD1 familial ALS patient: written letter fluency *fi*, inhibition (Hayling test - trend)	Sporadic and SOD1 ALS patients were unimpaired in all tests of executive functioning: letter fluency *fi*, category fluency, concept formation (WCST), inhibition (Hayling test)
Stukovnik et al., 2010	Group: 22 ALS	Letter fluency *fi*, switching (trail making task B), ecological executive planning task (Medication scheduling task).	Fluency *fi* (category, switching), inhibition (Stroop), planning and working memory (Tower of London)
Gordon et al., 2010	Case: 50 ALS; longitudinal	28% ALSi. Most sensitive tests were: fluency (letter and category), concept formation (WCST).	NOTE: only category fluency performance decreased over time. ALSi patients had shorter survival times.

Witgert et al., 2010	Case: 141 sporadic ALS; longitudinal	Cluster analysis: 43% with mild cognitive impairment and 17% with moderate to severe cognitive impairment. Most sensitive tests; letter fluency, attention (VSAT), processing speed/switching (TMT A, TMT B)	Least sensitive test; delayed verbal recall (Logical Memory II)
Meier et al., 2010	Group and case: 18 ALS	ALS vs Controls; fluency *fi* (letter and category), planning (One-touch Stockings of Cambridge – similar to tower of London). Z scores; 28% impaired letter fluency, 39% impaired category fluency, 22% impaired stockings of Cambridge.	
Sterling et al., 2010	Group: 355 sporadic ALS; 31% bulbar 94/175 dysarthric NOTE: no controls	Dysarthric patients performed worse on inhibition (Stroop), attention (VSAT) and switching (TMT A + B), only Stroop remained significant after motor control condition.	Bulbar patients performed worse than limb onset patients on inhibition (Stroop) and attention (VSAT) but not after motor control.
Lepow et al., 2010	Group: 49 ALS; 13 ALSu, 17 ALSi, 7 ALS-FTD	All ALS patients vs controls: verbal fluency (letter and semantic) ALSu vs ALSi vs ALS-FTD: group differences in the number of switches made in the letter fluency test, and the clustering indices in the semantic test.	
Hammer et al., 2011	Group and case: 20 ALS patients	ALS vs controls: fluency (letter, figural) Z scores: letter fluency (35%), digit span (25%)	ALS vs controls: working memory (digit span, reading span), concept formation (WCST), attention (tone alertness), inhibition (go/no-go)
Sarro et al., 2011	Case: 16 sporadic ALS	Z scores: processing speed (TMT A, 6%), inhibition (Stroop, 19%), concept formation (WCST, 19%), letter fluency (12%), category	Z scores: attention/switching (TMT B, TMT B-A, 0%)

		fluency (6%)	
Libon et al., 2012	Case: 41 ALS	Cluster analysis: 20% impaired, 45% average, and 34% above average on concept formation; DKEFS card sort performance (free recall and recognition). DKEFS scores were related to letter fluency scores	DKEFS card sort performance was not related to performance in working memory and switching (oral trail making task)
Phukan et al., 2012	Case and group: 160 ALS; cognitive subgroups	ALS vs controls: ALS higher incidence of executive impairment. ALSi vs ALSu: category fluency and inhibition (Stroop). Z-scores: 14% ALS-FTD, 21% ALSci. Letter fluency *fi* most sensitive (94%)	NOTE: 14% non executive impairment (language, memory, visuospatial), 47% intact. ALS vs Controls: no group difference in incidence of memory, language or visuospatial impairment.
Jelsone-Swain et al., 2012	Group and case: 22 ALS	ALS vs Controls: Verbal fluency (letter and category). Z scores: 36% executive dysfunction (Strong criteria).	ALS vs controls: Switching (oral trail making test), working memory (digit span forward and backward). NOTE: depression not associated with cognitive impairment but physical decline.
Taylor et al., 2012	Group and case: 51 ALS	ALS vs controls: concept formation (DKEFS), letter fluency *fi*, rule detection (Brixton errors). Z scores: 31% executive impairment (25% ALSci).	ALS vs controls: inhibition (Hayling test), category fluency.
Zalonis et al., 2012	Group: 48 sporadic ALS; bulbar subgroup (n = 18)	Attention/switching (TMT B-A), inhibition (Stroop), perseveration (WCST).	Concept formation (WCST). NOTE: no differences on executive measures between spinal and bulbar onset patients.
Lillo et al., 2012	Group: 20 ALS	ALS vs controls; Working memory (reverse digit span), inhibition (Hayling test). NOTE: 25% were ALS-FTD	Decision making (Iowa gambling task). NOTE: rasch analysis showed ALS and FTD patients share same profile (continuum)

Elamin et al., 2013	Case: 186 ALS; longitudinal	Z scores: at baseline 12% ALS-FTD, 25% ALSci NOTE: 12% ALS with non-executive impairment.	NOTE: baseline cognitive dysfunction associated with ALS severity, death, and development of further impairment.
Mioshi et al., 2013	Group and case: 22 ALS	ALS vs controls: verbal fluency (letter and category). Z scores: 32% ALSci	ALS vs controls: inhibition (Hayling test errors), switching (TMT B-A).

FVC = forced vital capacity. WCST=Wisconsin card-sorting test. VSAT=verbal series attention test. PASAT=paced auditory serial addition test. TMT = trail making test, parts A TMT B = trail making test, part B, TMT B-A = trail making test, part B minus part A. SDLT = serial digit learning test. SDMT = symbol-digit modality test. DKEFS = Delis-Kaplan executive function system. FrSBe = Frontal systems behaviour scale. ALSi = patients with cognitive impairment. ALSu = patients without cognitive impairment. ALSci = patients meeting consensus criteria (Strong et al., 2009) for cognitive impairment. FTD = frontotemporal dementia. *fi* = fluency index.

1.6.1.1 Fluency

The most striking deficits in ALS are in tests of verbal fluency, and in particular letter (phonemic) fluency (e.g. Gallassi et al., 1985; Abrahams et al., 1996; Rakowicz & Hodges, 1998; Abrahams, Leigh & Goldstein, 2005; Lepow et al., 2010; Phukan et al., 2012). Letter fluency tasks require participants to generate as many words as possible beginning with a specified letter, and within a time limit. Intrinsic generation is required for these tasks as participants cannot rely heavily on external or environmental cues. Lesion studies have suggested that category fluency tasks are more sensitive to temporal lobe damage whereas letter fluency is more sensitive to frontal lobe lesions (Baldo, Shimamura, Delis, Kramer & Kaplan, 2001; Baldo, Schwartz, Wilkins & Dronkers, 2006), although parietal regions have been implicated in both types of task. The specificity of fluency tests has been brought into question by studies demonstrating that patients with non-frontal lesions can perform as badly as those with frontal lesions (Perret, 1974). However, other studies have shown that letter fluency tasks are particularly sensitive to left dorsolateral and inferior frontal lesions (Stuss et al., 1998; Robinson, Shallice, Bozzali & Cipolotti, 2012), which supports the results of functional imaging studies reporting higher activation in dorsolateral and inferior frontal gyri of the left hemisphere during letter fluency tasks (Frith et al., 1995; Phelps, Hyder, Blamire & Shulman, 1997; Warkentin & Passant, 1997; Abrahams et al., 2004).

A recent meta-analysis of cognitive impairments in ALS reported that letter fluency tests were the most common deficit reported in the literature and produced medium effect sizes (Raaphorst et al., 2010). This is reflected by the fact that virtually every study in which letter fluency has been investigated have reported impairments, either at the group level, or in a significant proportion of cases (see Table 1). However, letter fluency tasks have an inherent motor component as responses must be spoken or written which presents an

obvious confound when testing populations with compromised motor functioning. This problem has been overcome by the introduction of a motor control condition in which participants simply repeat or copy the words that they produced during the fluency test. This information can then be used to work out a Fluency Index (*Fi* – Abrahams et al., 1996); a measure of the average time to *think* of a word which is independent of motor slowing. Not all studies investigating fluency performance in ALS have employed motor control measures (Frank et al., 1997; Ringholz et al., 2005; Witgert et al., 2010; Jelsone-Swain et al., 2012), casting some doubt over the validity of the findings. However, studies in which fluency indices were employed have invariably found deficits in letter fluency (Abrahams et al., 2000; Abrahams, Leigh & Goldstein, 2005; Kim et al., 2007; Meier, Charleston & Tippett, 2010; Phukan et al., 2012), and the necessity for controlling for motor dysfunction when assessing cognition in ALS is now well recognised (Raaphorst et al., 2010; Goldstein & Abrahams, 2013). Of note, letter fluency tests are repeatedly reported as the most sensitive tests in studies investigating the prevalence of cognitive impairments in ALS populations, with one study reporting that 94% of patients had impaired letter fluency (Gordon et al., 2010, Witgert et al., 2010; Taylor et al., 2012; Phukan et al. 2012).

Thus, letter fluency tests appear to be particularly sensitive to cognitive dysfunction in ALS even when motor dysfunction is controlled for. However, the underlying reasons for this sensitivity are not fully resolved. It has been suggested that fluency performance can be divided into dissociable components of clustering and switching (Troyer, Moscovitch & Winocur, 1997), with clustering being more sensitive to temporal lobe damage affecting semantic retrieval, and switching more sensitive to frontal lobe damage and executive dysfunction (Troyer, Moscovitch, Winocur, Alexander & Stuss, 1998). Lepow and colleagues (2010) investigated clustering and switching performance in a heterogeneous

group of ALS patients, some of which had mild cognitive impairment and some which had ALS-FTD. The authors reported that all ALS patients performed worse than controls in both measures of clustering and switching. Moreover, patients with cognitive impairment and ALS-FTD were worse again than cognitively intact patients in both measures, suggesting progressive involvement of both frontal and temporal regions in the ALS continuum. In addition, letter fluency performance has been found to be correlated with picture naming and verbal memory performance (Robinson et al., 2012). Thus, although letter fluency tasks are assumed to be measures of executive functioning, they may also rely on an efficient lexical network implicating basic linguistic processes such as simple word retrieval and subvocal rehearsal.

Attempts have been made to elucidate the underlying processes that contribute towards fluency deficits in ALS by investigating performance in terms of the multiple component model of working memory (Baddeley & Hitch, 1974; Baddeley, 2000 – see Chapter 3, Section 3.3.1 for a review). Abrahams et al. (2000) investigated fluency performance in a number of domains including letter, category and design (non-verbal fluency). Phonological loop and store components of working memory were assessed by testing for the word length effect and phonological similarity effect; reliable cognitive phenomena in which longer words are more difficult to remember than shorter words, and phonologically similar words are harder to recall than phonologically dissimilar ones (Baddeley & Wilson, 1988). In addition, basic word retrieval was assessed through confrontation naming and sentence completion tasks. Impairments were found in fluency tasks, including letter fluency, in the absence of basic linguistic deficits. Moreover, the investigation of word length and phonological similarity effects revealed that word span was significantly lower in ALS patients compared to controls, although normal word length and phonological

similarity effects were observed. Taken together, the results indicated that executive dysfunction and reduced short-term memory capacity are more likely to contribute towards poor verbal fluency performance in ALS than basic linguistic and verbal abilities.

Fluency tasks are thought to recruit several discrete executive processes including; initiation, strategy formation, sustained attention, set-shifting, working memory and inhibition (Troyer, Moscovitch & Winocur, 1997; Azuma, 2004; Abrahams et al., 2000; Rende, Ramsberger & Miyake, 2002). Robinson and others (2012) have postulated that letter fluency tasks impose a particular demand on selective attention as there is a high degree of competition amongst potential responses for any given letter. Selective attention has been argued to be a key function of the left inferior frontal gyrus (Thompson-Schill, D'Esposito, Aguirre & Farah, 1997; Robinson, Shallice, Bozzali & Cipolotti, 2010), and is thought to be particularly relevant to letter fluency tasks as these tasks impose fewer constraints than semantic fluency tasks therefore inducing higher response competition. Divided attention may also play an important role in fluency tasks as it has been demonstrated in healthy populations that fluency performance is reduced when concurrent tasks are employed – especially those requiring set-shifting (Rende, Ramsberger & Miyake, 2002). However, these processes have not been sufficiently investigated in ALS. It has also been suggested that processing speed plays an important role in fluency tasks. Performance in measures such as the Digit Symbol Substitution Test and Letter Comparison task have been found to be strong predictors of fluency performance in populations with traumatic brain injury (Bittner and Crowe, 2007) and Parkinson's disease (McDowd et al., 2011), as well as in normal ageing (Bryan, Luszcz & Crawford, 1997). Indeed, ALS patients have also been shown to be impaired on the Symbol Digit Modalities Test (Mezzapesa et al., 2007) which was adapted to control for motor impairment. Thus, the diversity of processes

required by letter fluency tasks may be the key to their sensitivity in ALS as disruption to any of the above processes could potentially lead to impaired performance.

1.6.1.2 Working memory

Working memory can be defined as a system responsible for the active maintenance of information in the face of ongoing processing and/or distraction (Conway et al., 2005). Working memory is an integral component of many tasks that purportedly assess executive functioning as information must be held in mind in order to form a strategy or monitor, inhibit, or update responses (Miyake et al., 2000, 2002; Engle, 2002). Although executive functioning is the most commonly reported deficit in ALS, only a few tasks have been employed in the study of cognition in ALS that purportedly isolate working memory capacity, the most common of which are digit span and reverse digit span. There is some debate as to whether digit span tasks are true measures of working memory capacity as they only require the storage and maintenance of information in absence of any additional processing (Baddeley, 1997; Conway et al., 2005). As such digit span may be a better representation of short-term memory capacity (Engle, Tuholski, Laughlin & Conway, 1999), or even attention (Lezak, 1995; Sattler, 2001). By contrast, reverse digit span tasks do require additional processing as digits must be transformed from their original sequence into the reverse order – indeed reverse digit span tasks have been shown to correlate highly with well validated measures of working memory capacity such as reading/sentence span (Oberauer, Süß, Wilhelm & Wittmann, 2003). Studies investigating digit span in ALS cohorts have predominantly reported that ALS patients perform normally in this measure (see Table 1), although two studies have reported deficits (Bartels et al., 2008; Hammer et al., 2011), with both studies reporting that impairments were exhibited by a significant proportion of patients (40% and 25% respectively). Moreover, Abrahams and colleagues

(2000) reported that ALS patients exhibited impaired short-term memory span for letters and words. Although fewer studies have investigated reverse digit span, the majority of studies have reported deficits in ALS patients (Rackowicz & Hodges, 1998; Hanagasi et al., 2002; Lillo et al., 2012). However, Mezzapesa at al., (2007) employed the Brown-Peterson task which utilizes distracter tasks such as backward counting during 10 or 30 second delay periods between the presentation and recall of verbal trigrams. The authors reported no performance difference between patients and controls, suggesting that ALS patients in this cohort at least, exhibited normal performance in a working memory tasks which required considerable additional processing.

Further evidence for working memory impairments in ALS patients is derived from studies which have investigated cognition by combining neuropsychological and event-related potentials (ERP) methodologies. Volpato and collaborators (2010) reported that ALS patients had deficits on several working memory tasks including digit span and spatial span (Corsi blocks). Moreover, the study replicated the results of an earlier investigation (Paulus et al., 2002) by showing that performance in these tests correlated with abnormal ERP characteristics in an auditory "odd-ball" paradigm in which target tones must be detected within a presentation consisting primarily of distracter tones. The authors concluded that the data suggested that an attentional impairment was influencing poor working memory performance. A more direct investigation of working memory performance was carried out by Hammer et al. (2011) who collected ERP data during an n-back working memory tasks for figural and spatial stimuli. N-back tasks require participants to decide whether each stimulus in a sequence matches the one that appeared n items ago, and have been shown to be a valid test of working memory capacity (Kane, Conway, Miura & Colflesh, 2007) as they require the continuous monitoring and updating of information (Conway et al., 2005).

A significant proportion of the patients were unable to complete the n-back paradigms, and those who did were impaired relative to controls in the spatial version of the task. ALS patients also exhibited abnormally exaggerated ERP response to targets in the n-back working memory. Of note, there were no group differences between patient and controls in digit span leading the authors to suggest that n-back paradigms are more sensitive to working memory impairment than span tasks. Despite the somewhat inconsistent results between different studies described above, there is evidence to suggest that at least a proportion of ALS patients present with impairments in short-term memory capacity with more convincing evidence of impairments in working memory capacity. Thus, potential deficits in working memory should be considered in the interpretation of deficits in tests of executive functioning described subsequently.

1.6.1.3 Concept formation and planning

Another component of executive functioning that has come under investigation in the ALS literature is concept formation by way of tests such as the Wisconsin Card Sort Test (WCST) and Delis-Kaplan Executive Functions System (D-KEFS) sorting test. The WCST requires participants to sort cards based upon simple visuoperceptual rules of colour, shape, or number. However, the sorting rule changes regularly requiring participants to update their responses accordingly. The D-KEFS sorting test (formally known as the California Card Sort Test) shares similarities with the WCST as it requires participants to find different ways to sort a set of cards based on visuoperceptual and verbal cues. Such tasks require multiple executive processes as participants must first have the ability to generate sorting strategies, as well as switch strategy (i.e. set-shifting) in response to rule changes or generate alternative sorting strategies, and inhibit previous responses (Nyhus & Barceló, 2009; Fine et al., 2010). Both tests have the advantage of providing untimed measures of

executive functioning. However the D-KEFS sorting test has the added advantage of explicitly testing abstract reasoning as participants are required to provide a description of each sort they make, allowing easier differentiations to be made between conceptual and perseverative errors (Delis et al., 2001).

Historically, the WCST has been reported to be sensitive to frontal lobe damage and in particular to lesions in dorsolateral prefrontal cortex (Milner, 1963), and functional imaging studies have largely supported the involvement of this area as part of a larger network of brain regions involved in WCST outside performance (Nyhus & Barceló, 2009). However, more recent studies have questioned the specificity of the WCST by demonstrating that performance is also affected by lesions to different sites in the prefrontal cortex (e.g. medial prefrontal cortex; Drewe, 1974; Stuss et al., 2000), and even lesions in regions outside of prefrontal cortex such as hippocampus (Igarashi et al., 2002), and other non-frontal lesions (Mukhopadhyay et al., 2008). The D-KEFS sorting test is a relatively recent addition to neuropsychological assessment and so has received less scrutiny. Nevertheless, deficits in the sorting test have been associated with focal frontal lesions (Dimitrov et al., 1999), Parkinson's disease (Beatty & Monson, 1990), and Multiple Sclerosis (Parmenter et al., 2007). A recent study employing volumetric structural imaging showed a correlation between left frontal lobe volume and performance in the D-KEFS sorting test (Fine et al., 2010). However, in the same study, performance on the D-KEFS sorting test was unable to differentiate between patients with Alzheimer's disease (AD), FTD, SD, or PNFA, once again casting doubt as to whether deficits on tests of this nature are specific to frontal lobe pathology. That said, involvement of dorsolateral prefrontal cortex pathology is not always observed in these disorders (Weder et al., 2007) which may explain the lack of sensitivity in these patient groups.

In ALS, deficits have been shown in both the WCST (e.g. David & Gillham 1986; Massman et al., 1996; Schreiber et al., 2005) and the D-KEFS sorting test (Libon et al., 2012; Taylor et al., 2012), although almost as many studies have reported intact performance in the WCST (e.g. Kew et al., 1993; Abrahams et al., 2005; Lule et al., 2007; Wicks et al., 2009). The inconsistent findings in the WCST may be explained to some extent by heterogeneity in the ALS cohorts between the different studies. For example, Lomen-Hoerth and colleagues (2003) reported that WCST was one of the most sensitive tests for detecting cognitive impairment in a study in which 18/44 of ALS patients met criteria for FTD. By contrast, Wicks and others (2009) did not find a deficit in a cohort of patients, a proportion of which were SOD1 familial cases which are reported to have very low incidences of cognitive impairment (Battistini et al., 2005), and none of whom met FTD criteria. Despite the inconsistencies, the WCST has proved useful in detecting cognitive impairments, with some investigators reporting that it was the most sensitive test (Robinson , 2006; Gordon et al., 2010), and others reporting deficits in 19% of patients (Sarro et al., 2011). Similar results have been reported for the D-KEFS sorting test, with reports of high sensitivity and impairment in 27% of ALS cases (Taylor et al., 2012). Another aspect of D-KEFS sorting test performance was investigated by Libon and colleagues (2012) who used cluster analysis to differentiate an ALS cohort into patients with impaired, average, and above average performance on the test – see Table 1. The authors reported that a significant proportion of patients showed impaired performance in the sorting test, the scores of which correlated with letter fluency performance. By contrast D-KEFS sorting test scores were not related to performance on an oral trail making test leading the authors to suggest that performance was related to mental search and semantic memory, and not set-shifting (Libon et al., 2012).

Planning ability has also been investigated in ALS, albeit to a lesser extent than other processes. Some studies have employed tasks based upon the Tower of London paradigm (Shallice, 1982) which typically require participants to arrange a set of coloured balls spread across three wells into a specified configuration in the minimum number of moves possible. These tasks impose high demands on problem solving and spatial planning and manipulation, and have been shown to be sensitive to frontal lesions (Unterrainer & Owen, 2006) and disorders of fronto-striatal dysfunction such as Parkinson's disease (Owen et al., 1992). Moreover, functional imaging studies have implicated right dorsolateral and rostrolateral prefrontal activation (Van den Heuvel et al., 2003; Wagner, Koch, Reichenbach, Sauer & Schlosser, 2006) in Tower of London tasks. The employment of Tower of London paradigms in ALS cohorts is problematic due not only to the motor requirements of the task itself, but also because the performance measures are typically time-based meaning that the results are difficult to interpret. However, investigators have employed computerized versions which minimize the motor component of the tasks (Abrahams et al., 1997; Meier et al., 2010), with the former study also employing a motor control condition. Abrahams and colleagues (1997) reported that ALS patients were impaired relative to controls, whilst Meier and others (2010) reported impairment in 22% of ALS patients. A recent study employed a motor independent naturalistic test of planning which required patients to plan a hypothetical medication schedule based on different rules that ranged in complexity (Stukovnik, Zidar, Podnar & Repovs, 2010). ALS patients performed poorly in the Medication Scheduling task whilst performance in motor independent measures of Tower of London was normal. The authors suggested that the naturalistic properties of the Medication Scheduling task provide a more sensitive test of self-initiated planning and online manipulation of information than standard neuropsychological tests, and may be a better reflection of everyday cognitive problems in ALS. However, unlike other ecological tests of executive functioning such as the Multiple

Errands Task (Shallice & Burgess, 1991), the Medication Scheduling task has yet to be validated and standardised. Another test assessing spatial planning and inductive reasoning is the Brixton Spatial Anticipation Test (Burgess & Shallice, 1996a) which has been shown to be particularly sensitive to lesions in lateral regions of left prefrontal cortex (Reverberi, Lavaroni, Gigli, Skrap & Shallice, 2005). The test requires participants to predict the spatial position of a target based on patterns derived from its previous position; patterns change regularly requiring participants to learn the new pattern quickly and adapt their predictions accordingly. The Brixton test also has the advantage of allowing responses to be made manually or verbally and providing an untimed measure of performance, making it particularly useful for the assessment of ALS patients. Despite this, only one study has investigated Brixton test performance in ALS patients (Taylor et al., 2012); the authors reported that there was a significant difference between the patient and control group in terms of the number of errors made on the test, with 25% of patients exhibiting impaired performance suggesting that the test is sensitive to executive deficits in ALS.

1.6.1.4 Attention and processing speed

Attention can be defined as a top-down, effortful set of processes which control non-routine behaviours or functions (Stuss, Shallice, Alexander & Picton, 1995). Control of attention is postulated to be a crucial aspect of executive functioning as cognitive resources must be allocated to the appropriate operations in order to complete a task effectively (Stuss et al., 1995; Baddeley, 1996; Shallice, Burgess & Robinson, 1996). Processing speed can be defined as the maximum rate at which elementary cognitive operations can be executed (Salthouse, 1985, 1992), and will impact upon performance in executive tasks as elementary operations must be completed within certain temporal limits to facilitate the processing of more complex operations. Models of attention and processing speed are discussed in more

detail in Chapter 3 (Sections 3.3.2 and 3.1 respectively). As can be seen in Table 1, attention has been evaluated in ALS by way of a variety of tasks over the past 25 years, although the distinction with processing speed is not always clear. An early investigation into cognition in ALS reported deficits in visual attention assessed by a digit cancellation task (Gallassi et al., 1985). However, a subsequent study by Ludolph and others (1992) failed to show impairment in a similar test of character cancellation. ALS patients have also exhibited impairment in a computerised visual search task assessing focussed attention (Chari, Shaw & Sahgal, 1996). However, tests of this nature may be a better reflection of basic visuoperceptual speed (i.e. simple processing speed; Chiaravalloti, Christodoulou, Heath & Deluca, 2003; Bates & Lemay, 2004) than high order attention.

Mixed results have also been reported in other purported tests of attention such as the Symbol Digit Modalities (SDMT) test in which impairments were reported by Massman et al. (1996) and Mezzapesa et al. (2007), but not by Lule and colleagues (2007). The SDMT measures the time and accuracy with which participants can match abstract symbols with specific numbers, and is particularly sensitive to cognitive impairment in Multiple sclerosis (Huijbregts, Kalkers, Sonneville, De Groot, Reuling, & Polman, 2004) and mild traumatic brain injury (DeMonte, Geffen, May & MacFarland, 2009). Although commonly employed as a test of sustained attention, the SDMT also has an inherent visuomotor component and is highly correlated with processing speed measures (Crowe et al., 1999). Thus, although efforts were made to control for motor slowing in the SDMT by using an oral version of the test (Mezzapesa et al., 2007) or only recording response accuracy (Lule et al., 2007), the findings are still likely to be affected by processing speed. The Paced Auditory Serial Addition Test (PASAT) has also been employed to assess sustained attention, with one study reporting impairment in ALS patients relative to controls (Moretti et al., 2002), whilst

a subsequent study found no group differences (Abrahams et al., 2005). The PASAT requires participants to keep track of a sequence of numbers presented at a constant rate so that the last two numbers can be summed. Once again, interpretation of results is ambiguous as factor analysis studies have associated the PASAT with various cognitive constructs including attention (Bate, Mathias & Crawford, 2001), working memory (Robertson et al., 1996), and processing speed (Larrabee & Curtiss, 1995), and performance in the test is now widely regarded as multifactorial (Madigan et al., 2000).

The verbal series attention test (VSAT) has been employed by several large scale studies to measure attention in ALS and all reported that a significant proportion of patients were impaired either in terms of the time taken to complete the test (Massman et al., 1996; Witgert et al., 2010), or the number of errors made (Ringholz et al., 2005; Witgert et al., 2010). In the largest study, Ringholz and collaborators (2005) concluded that the VSAT was the most sensitive test and stated that the majority of ALS patients in a cohort of 279 exhibited impairments. The VSAT is comprised of several subtests such as reciting the alphabet and months of the year backwards, alternatively saying letters and numbers in ascending order, and counting backwards from 100 by threes. Massman and colleagues (1996) reported that bulbar patients were significantly more impaired in the VSAT than those with limb-onset which is likely to be a reflection of the high demands placed on speech production by this particular test. Indeed, another study comparing dysarthric to non-dysarthric patients found that impairments in the VSAT were mediated when a motor control condition was taken into account (Sterling et al., 2010). Moreover, as has been acknowledged by some investigators (Ringholz et al., 2005), the VSAT is another example of a test of attention that is multifactorial in nature and has been shown to be particularly related to working memory (Sanchez-Cubillo et al., 2009).

Another task which shares similarities with those discussed above is the Trail Making Test (TMT). This task is typically administered as a paper and pencil test, although oral versions have also been developed, and comprises two sections; TMT A requires participants to draw a continuous line (i.e. trail) linking numbers from 1 to 25 which are randomly arranged on the page. TMT B increases the complexity by adding letters into the arrangement and participants must link numbers and letters in alternate and ascending order, e.g. 1-A, 2-B, 3-C etc. Performance is typically measured in terms of time to completion for TMT A and TMT B, and a derived measure comprising of the time for Part B minus Part A which is meant to control for motor speed (Lezak, 1995). A recent study investigating the construct validity has shown that TMT A is related to visuomotor speed, TMT B to working memory and switching, and TMT B-A isolates the switching component (Sanchez-Cubillo et al., 2009). Some studies utilising the TMT in ALS have reported intact performance (Palmieri et al., 2009) or impairment in TMT A only (Sarro et al., 2011). Others have found impairments in TMT A and TMT B (Witgert et al., 2010), as well as TMT B-A (Hartikainen & Soininen, 1993; Hanagasi et al., 2002). However, the most convincing evidence of an attention deficit comes from investigators that have found an isolated deficit in TMT B-A indicative of a specific problem with attentional switching (Kilani et al., 2004; Zalonis et al., 2012), although others have failed to replicate this finding (Mioshi et al., 2013).

Some studies have employed tasks in which the putative process is more defined. Pinkhardt and collaborators (2008) utilised the incompatibility subtest of the Test battery for Attentional Performance (TAP; Zimmermann & Fimm, 2002); this stimulus- response paradigm required participants to respond to compatible visual stimuli and inhibit responses to incompatible stimuli. The authors reported that ALS patients had slower reaction times

than controls in this test, suggesting that this result reflected a deficit in selective attention. Moreover, ERP recording during a dichotic listening task showed that patients had attenuated responses to target and increased responses to irrelevant stimuli, providing more evidence for an attentional impairment.

A different approach to the investigation of attentional control can be seen in studies which employ dual tasks to assess divided attention. Dual task ability has been postulated to be a key process in complex human behaviour (Baddeley, Della Sala, Papagno & Spinnler, 1997, Engle, 2002), and has been shown to be sensitive to executive dysfunction in FTD (Perry & Hodges, 2000; Sebastian & Hernandez-Gill, 2010), and in particular Alzheimer's disease (Logie, Cocchini, Della Sala & Baddeley, 2004). Functional imaging studies have suggested that a network of areas are activated during dual tasking (Erickson et al., 2005), with particular importance placed on dorsolateral and inferior prefrontal regions (MacDonald, Cohen, Stenger & Carter, 2000; Wager & Smith, 2003). The only study to investigate dual tasking in ALS employed the divided attention subtest from the TAP in which participants are required to react to sequences of simultaneously presented visual and auditory cues. The authors reported that ALS patients had impaired reaction times in comparison to normative data (Schreiber et al., 2005) indicative of a deficit in divided attention. However, the true extent of the deficits in selective and divided attention reported by the above studies is difficult to evaluate as reaction times in ALS cohorts are likely to be affected by motor dysfunction.

Inhibition is a process which refers to the ability to suppress or reject a prepotent or learned response in an inappropriate situation and has been postulated to be a crucial component of

theories of executive and attentional control alike (Miyake et al., 2000; Stuss, Shallice, Alexander & Picton, 1995). The Stroop colour-word interference test (Stroop, 1935) is one of the most commonly used tests of selective attention and inhibition (MacLeod, 1991). It has been shown to be sensitive, if not specific, to lesions in lateral and medial prefrontal cortex, and functional imaging studies have highlighted the involvement of distributed networks in Stroop performance with particular emphasis placed on anterior cinglulate cortex (Alvarez & Emory, 2006). The Stroop test requires participants to name the colour of ink in which colour-words are presented in and induces increased response times for incongruent trials (i.e. when the word "RED" is presented in blue ink) compared to when congruent trials (i.e. when the word "GREEN" is presented in green ink). Although the Stroop test is a timed measure, the interference condition remains relatively independent of motor slowing as it is derived from the time taken to complete the congruent subtracted from the time taken to complete the incongruent condition. Studies investigating the Stroop test in ALS patients have found relatively inconsistent results – see Table 1. Early investigations (e.g. Kew et al., 1993) reported intact Stroop performance, although a subsequent study showed a trend towards impairment in the Negative Priming condition (Abrahams et al., 1997). More recent studies have reported deficits in the interference condition (e.g. Lomen-Hoerth et al., 2003) while others have shown impairments in a significant proportion of patients (e.g. Sarro et al., 2011). However some investigations, including one large scale study, did not report impairment in the Stroop test (Ringholz et al., 2005; Pinkhardt et al., 2008; Stukovnik et al., 2010). Inconsistencies between studies may reflect the heterogeneity of ALS impairment in different cohorts; for example two of the studies in which Stroop impairment was reported included a proportion of FTD patients (Moretti et al., 2002; Lomen-Hoerth et al., 2003) which may have exaggerated group effects. The Hayling Sentence Completion Test (Burgess & Shallice, 1997) is another purported test of cognitive inhibition which is dissociable from other tests of executive

functioning and has been shown to distinguish patents with frontal lesions from those with posterior lesions (Burgess & Shallice, 1994; Burgess & Shallice, 1996). The Hayling test requires participants to inhibit stereotypical and context-dependent responses when completing simple sentences. With regards to ALS, a relatively small number of studies have employed the Hayling test, and once again results have been inconsistent; some studies have reported that ALS patients exhibit normal performance (Taylor et al., 2012; Mioshi et al., 2013), whereas another reported that ALS patients were impaired (Lillo et al., 2012) although 25% of the ALS cohort met criteria for FTD. Moreover, Wicks et al. (2009) reported that only patients with bulbar disease onset were impaired in the Hayling test. Thus, it would appear that the Stroop test may be more sensitive to impairments in inhibitory control, although results from this test are by no means clear-cut. Of note, a key difference between the Hayling and Stroop tests is in the sensory domain that is under investigation; the Stroop test requires inhibition of perceptual prepotent responses, whereas the Hayling test requires inhibition of auditory/semantic responses. Whether this a determining factor in the sensitivity of either test for detecting impairments in ALS remains to be seen.

1.6.1.5 Executive functioning in ALS summary

The last 20 years has seen a considerable rise in the number of studies including cognitive assessment as part of their investigations into ALS, with the main focus on executive functions. Deficits in letter fluency remain the most consistently reported executive impairment, with several recent population-based studies confirming that it is one of the most sensitive tests in ALS. Attempts have been made to investigate the underlying cause of dysfunction in this complicated test, and it would seem that basic linguistic processes are not responsible, placing emphasis back on high-order executive processes. Further

impairments have been commonly although not consistently found in tasks of concept formation, planning, and working memory suggesting that executive dysfunction in ALS is not restricted to letter fluency. Inconsistencies within the literature may in part be explained by the heterogeneous nature of cognitive impairment in ALS. Cognitive impairments are typically present in 30 – 50% of patients, with a smaller proportion presenting with ALS-FTD and the relative number of impaired patients is likely to differ between studies and affect group comparisons. Studies investigating attention have also reported deficits in a range of attentional processes including selective attention, divided attention, and inhibition. However, inconsistencies among results are common in this domain, and may reflect the nature of the tasks used to assess them which are often confounded by involvement of additional processes such as working memory, processing speed and motor ability; indeed, a commonality between many purported neuropsychological tests of attention is that they are also employed as measures of processing speed. Thus the challenge remains to explicitly delineate the constructs of executive functioning, attention, and processing speed, as well as develop tests which can assess these functions independently while controlling for motor dysfunction.

1.6.2 Language

Historically, reports of language dysfunction in ALS have been documented, although these were typically restricted to clinical observations and case studies (Bak, 2010). More recently, language dysfunction has been reported in ALS patients who present with co-morbid primary progressive aphasia syndromes associated with frontotemporal lobar degeneration; patients have been described with language deficits that appear consistent with progressive non-fluent aphasia and semantic dementia, lending support to the proposed

continuum between ALS and FTD (Casselli et al., 1993; Doran, Xeureb & Hodges, 1995; Bak, O'Donovan, Xuereb, Boniface & Hodges, 2001; Catani et al., 2003).

However, language deficits have also been found in non-demented ALS patients. Confrontation naming has been the most widely employed method of assessing language ability in ALS; measures such as the Graded Naming Test (GNT) or Boston Naming Test (BNT) which require participants to name pictures of objects of increasing difficulty (i.e. decreasing frequency) have been used by numerous studies with relatively inconsistent findings. For example, some relatively early investigations reported intact confrontation naming (Ludolph et al., 1992; Kew et al., 1993), whereas others reported impairments (Hartikainen & Soinenen, 1993; Rakowicz & Hodges, 1998). More recent investigations have predominantly reported deficits in confrontation naming (e.g. Kilani et al., 2004; Wicks et al., 2008; Gordon et al., 2010), but see Abrahams et al. (2000, 2005a), and a recent meta-analysis has suggested that language dysfunction (primarily assessed by confrontation naming) *is* present in non-demented ALS patients although the authors warn of a publication bias in this domain (Raaphorst et al., 2010). The same authors suggested that inconsistencies in confrontation naming findings may be a reflection of small heterogeneous samples typically recruited in most cross-sectional studies. Indeed population based studies reporting case incidences as opposed to group findings have shown that a significant proportion of ALS patients (between 11% and 23%) exhibit deficits in confrontation naming tests (Ringholz et al., 2005; Phukan et al., 2012) suggesting that these measures are reasonably sensitive to language dysfunction in ALS.

Assessing language functioning in ALS is complicated by speech disruption that affects patients with bulbar symptoms and makes distinguishing dysarthria from dysphasia particularly problematic (Bak & Hodges, 2004; Abrahams, 2012). Indeed, the relationship between language impairment and these symptoms is not fully understood (Bak & Chandran, 2012), although some have suggested that dysarthric patients are more likely to exhibit cognitive dysfunction (Sterling et al., 2010). As such, in depth investigations of linguistic functioning have been relatively rare, but some investigators have demonstrated deficits in simple naming and word-picture matching as well as non-verbal semantic knowledge and syntactic comprehension in individual ALS cases (Rakowicz & Hodges, 1998). In a longitudinal study, Strong and colleagues (1999) reported that several ALS patients exhibited impairments in single-word vocabulary comprehension, as well as deficits in confrontation naming – moreover, when naming errors and were analysed, they revealed verbal paraphasias (e.g. "yell" when correct response was "funnel") and semantic paraphasias (e.g. "nut" instead of "acorn") although impairments did not decrease over time. However, another longitudinal study reported that ALS patients' ability to complete simple sentences became poorer over time, independent of motor slowing (Abrahams et al., 2005a) which may reflect progressive slowing of word retrieval processes. Moreover, an Italian study (Moretti et al., 2002) which employed the Bilingual Aphasia Test reported that non-demented ALS patients showed increasing numbers of paraphasias, morpheme substitutions, and semantically deviant sentences longitudinally, with bulbar patients exhibiting additional impairment in complex command execution and syntactic comprehension. Concordantly, a study of Japanese patients revealed writing errors in ALS with predominance for "kana" errors which are used primarily for syntactic meaning; although half of the patients met criteria for ALS-FTD, significant kana errors were also exhibited by non-demented patients (Ichikawa et al., 2010). A subsequent study by the same group demonstrated that writing errors correlated with frontal lobar atrophy on longitudinal brain imaging data which

suggested that writing errors may predict cognitive decline and ALS dementia (Ichikawa, Ohno, Murakami, Ohnaka & Kawamura, 2011).

Following on from findings reported in ALS-FTD/aphasia studies (Bak et al., 2001; Bak & Hodges, 2004) which demonstrated selective impairments for verbs over nouns, Grossman et al. (2008) investigated action knowledge in a cohort of 34 ALS patients some of which showed signs of cognitive impairment and FTLD. The authors reported that patients were impaired relative to controls in tests requiring knowledge of actions as opposed to knowledge of objects, and that those with cognitive impairment performed worse than those without impairment. Moreover action object and object knowledge were both correlated with syntactic performance indicating that the deficits in action knowledge were not caused by grammatical problems. The authors concluded that ALS patients exhibited a specific impairment in action knowledge which may reflect the neuronal degeneration of associative motor areas. However, performance in action knowledge was correlated with tests of executive functioning (category fluency and reverse digit span), making it difficult to determine whether the reported language deficits were a primary aphasic syndrome or a secondary symptom of executive dysfunction. Some investigators have proposed that the relationship between ALS patients with cognitive impairment or co-occurring FTLD syndromes and specific linguistic impairments in action and verb knowledge reflects the underlying neurodegenerative process. Bak and Chandran (2012) have suggested that impairments in verb and action processing reflect the degeneration of a wider network of motor and prefrontal areas responsible for movement control, speech production, and action knowledge, and that disease pathogenesis is able to spread along this functional network.

Some studies have attempted to delineate language impairment from executive dysfunction. In a functional imaging study, Abrahams et al. (2004) showed that ALS patients exhibited reduced activation in a network of areas during a confrontation naming task as well as a fluency task suggesting that functional abnormalities were not specific to executive tasks. A recent clinic-based study of 51 non-demented patients carried out a detailed investigation into language and executive functioning (Taylor et al., 2012). Tests of vocabulary, confrontation naming, syntactic and semantic comprehension, verb and noun naming, synonym judgement, and spelling, as well as standardised measures of executive functioning were employed to derive composite scores for language and executive functioning; the authors reported that relative to controls, 31% of patients were impaired in the executive composite whilst 43% were impaired in the language composite score. Moreover, although, there was a strong correlation between the two composite scores, a regression revealed that executive functioning performance only accounted for 44% of the variance in language scores suggesting that a large proportion of language deficits were independent of executive dysfunction. This is an important finding as it indicates that a) language impairment may not only be more common than previous reports, it may be the *most* common cognitive impairment in ALS and should be investigated more thoroughly by subsequent investigations, and b) language impairment may occur independently of executive dysfunction. The findings of Taylor et al. (2012) may also go some way to explaining the sensitivity of verbal fluency to cognitive deficits in ALS, as although predominantly tests of executive functioning, fluency measures undoubtedly require linguistic processing as well (Abrahams, 2012). Moreover, the pattern of higher prevalence of language impairment than executive impairment may indicate a departure from the purported continuum between ALS and FTD where executive and behavioural abnormalities are much more common than language dysfunction, although this needs to be replicated by further studies (Bak, 2010; Abrahams, 2012).

1.6.3 Memory

In comparison to the reports of executive dysfunction and more recently language impairment in ALS, investigations into memory have proved less consistent. Various memory paradigms have been employed and almost all have provided mixed results. For example, episodic memory has been investigated by story recall paradigms such as the Logical Memory subtest from the Wechsler Memory Scale. These paradigms require participants to listen to a short passage of prose, and then recall as much of the story as possible, either immediately, or after a delay (typically 20 – 30 minutes). Some investigators have reported intact immediate and delayed recall of stories (Newsom-Davis, Lyall, Leigh, Moxham & Goldstein, 2001) whereas others have reported impairments in both conditions (Mantovan et al., 2003; Christidi et al., 2012), and there have also been reports of impaired immediate recall but preserved delayed recall of prose passages (Hartikainen & Soinenen, 1993).

Other studies have employed so called Paired Associates paradigms in which participants are presented with a list of word pairs such as TRUCK-ARROW. At recall, participants are presented with one word from the pair (i.e. TRUCK) and are required to recall its match (i.e. ARROW), thus the task assesses cued verbal recall. Mixed findings have also been reported in this test with some investigators reporting impaired performance in ALS cohorts (David & Gillham, 1986; Abrahams et al., 1996) whilst other studies have reported a trend towards impairment (Abrahams et al., 2004) or impairments only in those patients with executive dysfunction (Abrahams et al., 2005b). However, other studies by the same group have failed to show impairments in Paired Associates paradigms (Kew et al., 1993, Abrahams et al.,

1997; Abrahams et al., 2005a), suggesting that verbal memory deficits may not be a core feature of cognitive impairment in ALS.

Other paradigms based on list learning have been employed in ALS investigations including the California Verbal Learning Test (CVLT) and the Rey Auditory Verbal Learning Test (RAVLT). These tests share similarities in that both require participants to learn lists of words over a number of trials to assess encoding efficiency as well as employing a delayed recall condition. The CVLT also assess the use of encoding organisation strategies as words in the list are split into semantically related chunks e.g. "fruits", "spices" etc. In addition, both tests can be used to assess interference by presenting another list of distracter words before recall or recognition of the original list. Deficits in these tasks have been predominantly reported in immediate recall conditions (Massman et al., 1996; Robinson et al., 2006; Hammer et al., 2011), although the reverse pattern of intact immediate recall and impaired delayed recall in the CVLT was reported by Hanagasi et al. (2002). However, as with Paired Associates paradigms, some studies have reported that ALS patients exhibit normal performance in these list learning measures (Strong et al., 1999; Lomen-Hoerth et al., 2003; Strutt et al., 2012).

Recognition memory for verbal and non-verbal stimuli has also been investigated in ALS patients, primarily through the use of the Warrington Recognition Memory Test (RMT). This test involves the presentation of 50 words or faces on individual cards at a rate of 1 every three seconds; subsequently participants are presented with word pairs or face pairs and asked to decide which word came from the original target list. Once again ALS performance in this test has been variable – impairments have been reported by some studies

(Abrahams et al., 1997; Strong et al., 1999) but others have failed to find deficits (Kew et al., 1993; Abrahams et al., 1996, 2004, 2005a), although it should be noted that the latter two studies only investigated recognition memory for words. Interestingly, Strong et al. (1999) reported no deficits on the RMT at initial testing but showed that deficits appeared in the RMT for faces longitudinally, although this was not replicated in another longitudinal study by Abrahams et al. (2005a). By contrast, Abrahams et al. (1997) reported impairment in the recognition of words, but not faces. Non-verbal memory has received less attention than verbal memory in ALS investigations, but some studies have employed paradigms such as the Kendrick Object Learning Test (KOLT) which assesses immediate non-verbal memory by presenting participants with pictures of common household objects and asking them to recall as many as possible. ALS performance in this test is also characterised by inconsistent findings; impairments have been reported by some studies (Kew et al., 1993; Abrahams et al., 1996; Newsom-Davis et al., 2001), although it should be noted that the latter study was in patients with poor respiratory functioning. Conversely, others have found intact performance in the KOLT (Abrahams et al., 1997, 2004, 2005a), suggesting that, like verbal memory, non-verbal memory impairment may not be a consistent feature of the ALS cognitive profile.

However, a recent meta-analysis of by Raaphorst et al. (2010) reported significant effects for immediate verbal memory and visual memory, and borderline significance for delayed verbal memory. Moreover, the effect sizes for immediate and delayed verbal memory were as large as those for fluency ($d = 0.5$), and the effect size for visual memory was only slightly smaller ($d = 0.4$) suggesting that memory impairment may in fact be a crucial component in ALS. Inconsistent memory findings may be explained by the inherent heterogeneity of cognitive impairment in ALS patients which can lead to different

proportions of impaired patients from one study to the next. This may be exacerbated in studies with small sample sizes which employ group analyses, particularly if impairments in the given domain are relatively rare. This point is highlighted by large-scale studies investigating the prevalence of cognitive impairment in ALS which have reported that a significant proportion of ALS patients exhibit memory impairment, but invariably less so than exhibit executive dysfunction (Massman et al., 1996; Ringholz et al., 2005; Phukan et al., 2012). Indeed, Massman et al. (1996) reported that 20% of patients were impaired in the CVLT and 22% in the continuous recognition memory test. More recent studies have employed a wider range of memory tests to produce a composite memory, for example Taylor et al. (2012) reported that 14% of ALS patients were impaired in a score which encompassed performance in story recall, the RMT and the KOLT, whereas the large population-based study by Phukan et al. (2012) reported memory impairment in 11% of patients as assessed by Logical Memory, Paired Associates, CVLT, and the Rey-Osterrieth complex figure test.

Although the evidence discussed above indicates that memory impairment is present in a proportion of ALS patients, the nature of these deficits may reflect executive dysfunction rather than memory impairment *per se*. Memory is a complicated process requiring processes of encoding, consolidation and retrieval, and moreover, the content and strength of memory can be affected by attention (Chun & Turk-Browne, 2007). Indeed, the predominant finding of impairments in immediate memory as opposed to delayed memory support the notion that executive dysfunction may be the underlying cause of memory impairments, as in general, immediate memory deficits are thought to reflect damage to prefrontal structures whereas delayed memory deficits are thought to reflect disruption to medial temporal areas (Lezak, Howieson & Loring, 2004; Köhler et al., 1998).

Several studies have provided further evidence of executive involvement in memory impairment in ALS. For example Hartikainen and Soinenen (1993) reported that, in a list learning test, ALS patients made more false-positive recognition errors suggesting that they may have impaired inhibitory control. Moreover, an ERP investigation (Munte et al., 1998) revealed that ALS patients had a dramatically attenuated ERP signature for recognising previously presented items after a 1 hour delay; a result which the authors proposed was due to the failure to lay down a strong memory trace during the initial encoding condition. A different approach was adopted by Mantovan et al. (2003) who investigated serial positioning recall in word lists and found that although ALS patients displayed a normal recency effect (better retention of items presented near the end of the list), unlike controls, they did not display a primacy effect (better retention of items at the start of the list) indicative of a long term memory deficit. A cued post-encoding condition in which participants were told which type of item to recall improved primacy recall in controls but not in patients, suggesting that the ALS patients may not be able to make effective use of strategies to enhance retrieval. Furthermore, ALS patients were impaired in logical memory, the scores of which correlated with verbal fluency performance which suggested that memory impairments may reflect executive dysfunction. A recent study by Christidi et al. (2012) applied an item specific deficit approach to a RAVLT list learning task which produces indices for encoding, consolidation and retrieval based on the type of omissions made during recall. The authors reported that ALS patients were impaired in both immediate and delayed condition of the RAVLT, and moreover, exhibited deficits in the encoding and consolidation indices but not the retrieval indices. In addition, the authors demonstrated that ALS patients were impaired in selective attention as measured by the Stroop test, and reported that performance in this test explained the largest amount of variance in RAVLT

performance (approx. 40%). This finding suggested that an executive impairment in selective attention affected encoding and consolidation processes in ALS and was responsible for poor memory performance in the RAVLT.

1.7 Social cognition, emotional processing and behaviour in ALS

In addition to executive dysfunction and language impairment discussed in previous sections, behavioural variant FTD patients can exhibit profound changes in behaviour and social cognition including theory of mind, emotional recognition, and affective decision making (Snowden et al., 2003; Lough et al., 2006; Torralva et al., 2007). Moreover, changes of this nature often occur before deficits are evident on standard neuropsychological test of executive functioning (Lough, Gregory & Hodges, 2001). In recent years increasing recognition of the link between ALS and FTD, and particularly bvFTD, has encouraged the growth of research into ALS which focuses on the cognitive and behavioural changes sensitive to bvFTD.

One of the first studies to investigate social cognition in non-demented ALS reported that patients failed to show the normal effect of enhanced recall for emotional words as opposed to neutral words, suggesting that changes may be present in limbic pathways affecting emotional memory (Papps, Abrahams, Wicks, Leigh & Goldstein, 2005). However, the same study showed that patients were unimpaired on tests of facial expression recognition as well as judging approachability and trustworthiness. By contrast, a subsequent study demonstrated that ALS patients with bulbar symptoms were impaired in the recognition of facial emotions, but could recognise embedded emotional tone in prosody (Zimmerman, Eslinger, Simmons & Barrett, 2007). Although some patients in this study showed signs of

dementia and depression, 50% of those exhibiting impaired facial expression recognition were otherwise intact. Furthermore, others have shown that ALS patients judged emotionally salient (ranging from unpleasant to pleasant) and arousing pictures (calm to exciting) differently to controls, with a follow up study associating this behaviour with reductions in brain activity in anterior insular regions, again suggesting that the processing of emotional stimuli is altered in ALS (Lulé et al., 2005, 2007). Further support for abnormal emotional processing has been provided by a study which demonstrated reduced right prefrontal activity during the selection of negative emotional words, and subsequent poor performance in the recognition of the negative words compared to controls (Palmieri et al., 2010). A recent study investigating emotional processing and recognition reported that ALS patients had attenuated responses to negative emotional words, and replicated the finding that patients fail to show enhanced recall of emotionally salient words (Cuddy, Papps, Thambisetty, Leigh & Goldstein, 2012). This relationship was only present in a subset of patients suggesting heterogeneity of performance in this type of test, and moreover, the subgroup performed poorly on immediate and delayed memory as measured by the CVLT, suggesting that general memory impairment may have influenced the observed pattern of results.

A study by Gibbons et al. (2007) investigated theory of mind, the ability to understand the thoughts and intentions of others, by assessing the interpretation of humorous cartoons and stories. Although group differences between ALS patients and controls were not evident, a subgroup of patients with bulbar signs did show abnormalities in ascribing mental states and errors were qualitatively similar to those produced by FTD patients. However, the findings of the study were difficult to interpret as a pure theory of mind deficit as performance on the tasks correlated with performance in the WCST and verbal fluency suggesting that an

underlying executive dysfunction may have been the root cause of the observed abnormalities. Cavallo et al. (2011) also employed a cartoon paradigm which distinguished between social contexts and non-social contexts in which participants had to choose an event to complete each cartoon. The authors reported that ALS patients were only impaired in the cartoon scenarios in which there was a social context suggesting that patients had particular difficulty interpreting social situations. Further investigations into theory of mind have been carried out using "faux pas" tests in which participants must identify socially inappropriate events within stories or scenarios. Meier et al. (2010) showed that ALS patients performed worse than controls at identifying faux pas events, even though they performed comparably in comprehension of the stories indicative of a specific deficit in theory of mind. In contrast the findings of Zimmerman et al. (2007), the same authors reported that ALS patients were impaired in the identification of emotional expression from prosody, and performance on this task correlated with faux pas task performance.

In an effort to control for the possible confounds of executive functioning, a very simplistic theory of mind task was employed by Girardi, MacPherson and Abrahams (2011) in which participants simply had to infer which of four objects a cartoon face liked best by following its eye-gaze. ALS patients made more errors than controls in this test suggesting that they had difficulty following the simple social cue of eye-gaze, and moreover, group differences were also evident in facial expression recognition and Reading the Mind in the Eyes tests (trend). Furthermore, approximately 50% of patients who performed abnormally in the eye-gaze task were not impaired in tests of executive functioning suggesting that deficits in theory of mind can occur independently. In addition to social cognition, tasks, Girardi et al. (2011) also investigated affective decision making with a version of the Iowa Gambling Task which assesses participants' ability to make rational reward-based decisions.

Participants are presented with four decks of cards which vary in their probability of producing a monetary reward and participants must try to accumulate as much money as possible through-out the task. ALS patients performed poorly in this task and exhibited poor decision making by choosing more disadvantageous decks than controls. However, ALS participants did not exhibit more risky strategies evidenced by patients with FTD and poor performance may have reflected difficulty in learning task rules as opposed to irrational decision making. Of note, an earlier study reported that ALS patients performed comparably to controls in a similar task of probabilistic reversal learning (Meier et al., 2010).

Despite some inconsitencies, tests of social cognition and emotional processing have demonstrated sensitivity to cognitive change in ALS, with some studies reporting that deficits in social cognition are more common than executive dysfunction in non-demented patients (Girardi et al., 2011). Results of this nature have implicated orbitofrontal involvement in ALS as social cognition tests are sensitive to damage to these regions (Eslinger & Damasio, 1985; Gregory et al., 2002). Moreover ALS patients have shown classical dissociations between deficits in social cognition and impairment in executive tests assumed to be more dependent on dorsolateral prefrontal regions (Meier et al., 2010). As such, the reported deficits in emotion and social cognition clearly support the postulated link between ALS and FTD, with further support derived from studies investigating behavioural change in ALS.

Profound behavioural abnormalities characterise patients with bvFTD and those patients with co-occurring ALS-FTD (Neary et al., 1990; Lillo et al., 2003) with associated atrophy

of the orbitomedial prefrontal cortex (Rosen et al., 2002). Recent investigations have shown that behavioural changes are also evident in non-demented ALS patients. Investigations employing standardised measures such as the Frontal Systems Behaviour Scale (FrSBe) and Frontal Behavioural Inventory have revealed self-reported and spouse/carer-reported increases in disinhibited, dysexecutive, and apathetic behaviour after disease onset, with apathy representing the most common behavioural change (Grossman, Wooley-Levine, Bradley & Miller, 2007; Witgert et al., 2010; Woolley, Moore & Katz, 2010; Lillo, Mioshi, Zoing, Kiernan & Hodges, 2011). Morever, apathy scores in the FrSBe have been correlated with reduced white matter integrity in anterior cingulum (Woolley, Zhang, Schuff, Weiner & Katz, 2011). However, a study employing an informant-based semi-structured interview concluded that self-centeredness and irritability were more common behavioural changes than apathy and loss of affect (Gibbons, Richardson, Neary & Snowden, 2008). In contrast to ALS-FTD patients, non-demented ALS patients are less likely to exhibit lack of insight into behavioural changes (Wooley et al., 2010).

Some criticism regarding the use of standard behavioural questionnaires for measuring apathy has been raised as these measures to do not take into account motor symptoms in ALS which inevitably effect patients' ability to participate in activities, and thus may confound apathy scores (Masellis, Zinman & Black, 2010) . Support for this notion has been provided by a large study which reported that a specifically developed behavioural questionnaire for ALS detected lower prevalence of apathy and other behavioural disturbances than did the FrSBe or Frontal Behaviour Inventory suggesting that these measures may indeed exaggerate behavioural dysfunction (Raaphorst et al., 2012). Another potential confound in the assessment of behaviour is ALS is the presence of co-occurring mood disorders which may reflect a psychological reaction to the diagnosis rather than a

disease specific state (Goldstein & Abrahams, 2013). However, the majority of studies investigating behaviour in ALS have reported that although levels of depression may be elevated in ALS patients (Lillo et al., 2011, cf. Jelsone-Swain et al., 2012), depression is not associated with apathy (Grossman et al., 2007; Woolley et al., 2011; Lillo, et al., 2011) or cognitive dysfunction (Jelsone-Swain et al., 2012).

The prevalence of behavioural dysfunction in ALS populations has been investigated by several large-scale studies in recent years. In a cohort of 225 ALS patients, Witgert et al. (2010) reported that 40% of patients had impairment in at least one of the FrSBe scores of apathy, executive dysfunction, or disinhibition (apathy most common at 31%). In a subset of patients (n = 141), the authors also demonstrated that although half of those with behavioural impairment had cognitive deficits, a significant proportion (16%) of cognitively intact patients also presented with behavioural dysfunction, suggesting that although associated, cognitive and behavioural impairments can occur independently. Similar results were reported by Lillo et al. (2011) who reported that 41% of ALS patients had moderate to severe apathy as assessed by the Cambridge Behavioural Inventory, with 20% also displaying evidence of further abnormal and stereotypic behaviours, although it should be noted that 11% of the cohort met criteria for ALS-FTD. Raaphorst et al. (2012) reported a lower prevalence of behavioural impairment in non-demented ALS; 33% had behavioural disturbances as measured by the FrSBe and Frontal Behaviour Inventory, whereas only 18% had behavioural impairments as assessed by the ALS-FTD-Q, a specifically designed behavioural screen for ALS patients. Some studies have also investigated the presence of neuropsychiatric symptoms in ALS (Lillo et al., 2011, 2012), although prevalence was reported to be low at only 5%.

The studies investigating social cognition and behaviour discussed above lend support to the existence of a spectrum between ALS and FTD. Indeed, Witgert et al. (2010) showed that cluster analysis could differentiate between ALS patients with mild, moderate, or severe cognitive and behavioural impairments, but that all three groups were similar qualitatively. This relationship was replicated is a smaller study by Lillo et al. (2012) who showed that ALS, ALS-FTD, and bvFTD patients have overlapping cognitive, behavioural, and neuropsychiatric syndromes. Finally, these studies also serve to highlight the heterogeneity of presentations in this disorder as patients may exhibit impairments in neuropsychological assessment, social cognition, or behaviour, either in isolation or as a constellation of deficits.

1.8 Neuroimaging and cognition in non-demented ALS

Neuroimaging has been used in the investigation of ALS pathology for the last 30 years (Turner, 2011); staring out with CT images revealing hyperintensities in the corticospinal tract (Goodin, Rowley & Olney, 1988), advances in radioisotopes facilitated the measurement of cerebral blood flow and glucose metabolism. With improvements in magnetic resonance imaging (MRI) and computer processing power, non-invasive and more spatially refined techniques have been developed and applied to ALS research. These techniques have not only increased our understanding of pathology in the motor system, but have contributed significantly to the recognition of extra-motor abnormalities that are now a recognised component of the ALS syndrome (Turner, 2011). Moreover, neuroimaging techniques have been employed to investigate the relationship between cognitive impairment in ALS and cerebral functioning, either directly (via activation paradigms) or indirectly (via correlations with structural abnormalities). Studies investigating the relationship between cognition and cerebral change are summarised in Table 2.

Table 2. Neuroimaging correlates of cognition in ALS

Study	ALS Cohort	Method/Technique	Findings
Ludolph et al., 1992	18 ALS	PET resting state	Verbal fluency scores correlated with reduced glucose uptake in frontal cortex and thalamus
Kew et al., 1993	10 sporadic ALS (5 ALSi, 5 ALSu; verbal fluency)	PET activation. Stereotyped vs. free joystick movements	All ALS patients showed reduced rCBF in anterior cingulate at rest. During freely selected joystick task ALSu showed reduced activation in left medial prefrontal cortex. ALSi showed reduced activation in the medial prefrontal cortex, right anterior cingulate cortex, right parahippocampal gyrus and the anterior thalamic nuclear complex. ALSi showed reduced activation in comparison with ALSu in the right parahippocampal gyrus, the anterior thalamic nuclear complex and the rostral anterior cingulate cortex. Fluency score correlated with right parahippocampal activation and anterior thalamic complex, picture recall correlated with anterior thalamic complex.
Abrahams et al., 1995	12 sporadic ALS (6 ALSi, 6 ALSu; verbal fluency)	PET activation. Verbal fluency; generation vs. repetition conditions	ALSi patients showed bilateral reduced activation in the prefrontal cortex (dorsolateral, lateral and medial), the premotor areas, insula, and the anterior thalamus. ALSu showed reduced activation in the right DLPFC and the left middle and superior temporal gyrus.
Yamauchi et al., 1995	25 sporadic ALS (5 ALSi; MMSE, verbal memory)	SPECT + Structural MRI; corpus callosum ROI ratios	ALSi showed reduced SPECT uptake in prefrontal regions (dorsolateral, medial and inferior). Corpus callosum ratio reduced, predominantly anterior quarter. ALSu showed reduced corpus callosum ratio in anterior half. Corpus callosum ratio correlated with cognitive impairment.
Abrahams et al., 1996	12 sporadic ALS (6 ALSi, 6	PET activation; Verbal fluency.	ALSi group showed reduced activation in the DLPFC, lateral premotor cortex, medial prefrontal and premotor cortices, insular cortex bilaterally and the anterior

	ALSu; verbal fluency)	Neuropsychological testing	thalamic nuclear complex. ALSu showed minor reduction of activation in DLPFC and bilateral inferior parietal lobule. Executive and memory dysfunction in the ALSi group only.
Frank et al., 1997	74 sporadic ALS	Structural MRI; cluster analysis with cognition	ALS patients had lower parenchymal and higher ventricular volume compared to controls. Cluster analysis indicated a subgroup (n = 45) with ALSi in short-term memory, attention and WAIS. The subgroup did not differ from ALSu (n = 15) in clinical characteristics but did have greater ventricular enlargement.
Strong et al., 1999	13 ALS; 8 longitudinal	Spectroscopy N-acetylaspartatecreatine (NAA/Cr) ratio	Bulbar patients (more cognitively impaired) showed neuronal loss in anterior cingulate and motor strip at initial testing. Limb onset patients showed no changes at initial testing but showed neuronal loss in both areas at follow-up (6 months).
Abrahams et al. 2004	28 Sporadic ALS	fMRI; Letter fluency, confrontation naming. Neuropsych testing	ALS patients showed reduced activation in the middle and inferior frontal gyri and anterior cingulate gyrus, in addition to regions of the parietal and temporal lobes during the letter fluency task. Reduced activation in the inferior frontal gyrus and regions of the temporal, parietal and occipital lobes during the confrontation naming task. Neuropsych assessment consistent with executive and short-term memory dysfunction.
Abrahams et al., 2005	23 sporadic ALS; (11 ALSi, 12 ALSu; verbal fluency)	Structural MRI; VBM. Correlations with neuropsych testing.	ALSi patients had reduced white matter volume in extensive prefrontal regions, including superior, medial, and anterior cingulate association fibres as well in regions through which run the occipitofrontal fasciculus, cingulum, and superior longitudinal fasciculus, inferior longitudinal fasciculus, and anterior commisure. These patients demonstrated a corresponding cognitive profile of executive and memory dysfunction. ALSu patients had less extensive white matter reductions corresponding to corpus callosum, anterior and posterior cingulum, occipitofrontal fasciculus, and precuneus. White matter volumes correlated with performance on memory tests (letter span and VPAL). No significant reductions in grey matter volumes.

Mezzapesa et al., 2007	16 sporadic ALS	Structural MRI; Whole brain and VBM	ALS patients had lower brain parenchymal fraction than controls. VBM revealed reduced grey matter density in right superior, middle, and parahippocampal temporal gyri as well as inferior and superior frontal gyri. Left hemispheric changes were found in middle temporal gyri as well as inferior frontal gyrus and insula. No white matter changes. 8/16 patients were ALSi; 2SD below normative data on 2 tests.
Lule et al., 2007	13 sporadic ALS	fMRI; response to picture with emotional valence	ALS had similar BOLD response characteristics to controls. However ALS patients had a different base response to emotional stimuli with increase activation in right supramarginal/inferior parietal lobe and inferior frontal operculum as well as left cerebellum and primary visual areas. Lower BOLD response in higher visual areas. At 6 month follow up, further reduced activation was found in parahippocampal, lingual and precentral gyri as well as anterior insula.
Murphy et al., 2007	22 ALS (3 familial)	Structural MRI; automated volumetric. Neuropsych classification	From 22: 5 met FTLD criteria, 2 had executive impairment and 4 had behavioural impairment (neuropsychiatric inventory). Patients with FTLD or evidence of cognitive or behavioural impairment had reduced volumes in right frontal, parietal and limbic areas compared to ALSu patients.
Bartels et al., 2008	13 ALS	Structural MRI; DTI of corpus callosum. Neuropsych testing.	No FA differences between patients and controls in frontal, corticospinal or occipital portions of the corpus callosum. However, ALS patients did show within group differences with reduced FA in corticospinal corpus callosum relative to frontal and occipital portions. No correlations with neuropsychological tests.
Wicks et al., 2008	12 ALS	PET binding; correlations with neuropsych testing	Higher fluency indices (worse performance) correlated with reduced flumazenil binding in right inferior frontal gyrus, superior temporal gyrus and anterior insula. Poorer scores in confrontation naming (GNT) correlated with reduced binding in left inferior and middle frontal gyri as well as left cuneus.
Grossman et al.,	34 ALS (14 of	Structural MRI; VBM	More patients were impaired in action knowledge (73%); performance correlated

2008	cohort ALSi or ALS-FTD)	correlated with action and object knowledge.	with reduced volumes in premotor areas as well as bilateral dorsolateral prefrontal cortex and inferior frontal cortex. Performance in object knowledge only correlated with dorsolateral prefrontal and inferior frontal cortex. Action knowledge correlated with executive functioning (verbal fluency and reverse digit span).
Rusina et al., 2010	42 ALS	SPECT and neuropsych testing	Neuropsych battery included; trail making test (A+B), Stroop test, Wisconsin card sort test, tower of London, digit and letter span. 17/42 patients were ALSi (below 1.5SD in at least 2 tests). However, there were no correlations with SPECT imaging and any cognitive measure.
Palmieri et al., 2010	9 sporadic ALS	fMRI: emotional attribution and recognition	ALS patients exhibited abnormal lateralisation of the emotional processing and recognition, predominantly of negative words, with increased BOLD activation in left inferior frontal gyrus and reduced activation in right parietal and precentral areas. Control participants displayed the typical pattern of right lateralised activation.
Goldstein et al., 2011	14 sporadic ALS	fMRI; Stroop inhibition and negative priming	No difference in Stroop effect or negative priming effect between ALS and controls (behavioural data). However, ALS group showed *increased* activation during Stroop effect of several left hemisphere areas; middle and superior temporal gyri, anterior cingulate gyrus, as well as hippocampus, caudate, insula and cerebellum. In addition, ALS group showed *reduced* activation during the negative priming effect in left hemispheric areas; cingulate gyrus, precentral gyrus, and medial frontal gyrus.
Sarro et al., 2011	16 sporadic ALS	Structural MRI; DTI tractography and neuropsych testing	69% of ALS patients were impaired in one cognitive test, and 13% were ALSci (impaired on at least 2 tests). ALS had reduced white matter integrity in bilateral corticospinal tracts, corpus callosum, superior longitudinal fasciculus, uncinate fasciculus, as well right cingulum. ALS patients without cognitive deficits only had reduced integrity in corticospinal tract and left uncinate fasciculus. Correlations between white matter parameters and cognitive tests revealed relationships between with Trail Making Task (corpus callosum, corticospinal

			tract, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, bilaterally, and right uncinate fasciculus), letter fluency (left cingulum), verbal memory (fornix) and visuospatial abilities (unicinate). Only trail making test correlations remained significant after multiple comparisons correction.
Tsujimoto et al., 2011	21 sporadic ALS	Structural MRI; DTI and VBM. Behavioural testing; Frontal systems behaviour scale (FrSBe)	Patients were impaired relative to controls on MMSE and Frontal Assessment Battery. In addition, apathy scores increased from pre to post ALS diagnosis. ALS group had volumetric reductions in occipital, limbic, insula, and frontal lobes as well as midbrain. DTI abnormalities were present in bilateral corticospinal tracts as well as subcortical frontal white matter. Reduced FrSBe apathy scores correlated with reduced grey matter volume in bilateral orbitofrontal cortex and frontal pole as well as right dorsolateral prefrontal cortex. Apathy scores also correlated with white matter integrity in right medial frontal gyrus (FA) and left superior frontal gyrus ⟨D⟩.
Libon et al., 2012	16 ALS	Structural MRI; cortical thickness. Neuropsych testing; Delis-Kaplan executive function system (D-KEFS)	Cortical thickness was reduced in ALS patients in frontal (anterior, dorsolateral, inferior, ventral), motor and premotor, as well as anterior temporal and parietal regions. D-KEFS card sort (free recall) was not associated with any cortical region. However, D-KEFS card sort (recognition) scores were associated with cortical thinning in left dorsolateral prefrontal cortex and left parietal cortex.
Yabe et al., 2012	10 sporadic ALS	PET; binding. Neuropsych testing	Writing errors correlated with PET binding potential in frontotemporal areas but were most strongly associated with reduced binding potential in bilateral anterior cingulate
Agosta et al., 2013	16 sporadic ALS	fMRI; resting state networks. Neuropsych testing	Relative to controls, resting state networks in ALS patients showed altered connectivity in the default mode network, the right frontoparietal network, and the left frontoparietal network. No group differences in salience or executive resting state networks. 7 patients were ALSi, (below 5th percentile on 1 executive test); performance in the WCST was negatively correlated with connectivity between left precuneus and angular gyrus in the default mode network, and right angular gyrus and left posterior cingulate in the right frontoparietal network.

Mioshi et al., 2013	22 ALS, 17 ALS-FTD	Structural MRI; VBM. Neuropsych testing	ALS patients (whole group) showed volume reductions in motor areas as well as frontal and temporal regions. 14 ALSu patients vs 8 ALSi patients(either cognitive or behavioural according to Strong 2009 criteria); ALSi patients had more atrophy across motor and somatosensory regions as well as superior frontal gyrus, superior parietal gyrus, and left planum temporal. ALS-FTD vs ALSi; more atrophy in orbitofrontal cortex, frontal pole, temporal pole and cingulate gyrus.

CT = computed tomography. PET = positron emission tomography. MRI = magnetic resonance imaging. fMRI = functional magnetic resonance imaging. rCBF = regional cerebral blood flow. BOLD = blood-oxygen level dependent. SPECT = single photon emission computed tomography. ERP = event related potential. VBM = voxel based morphometry. DTI = diffusion tensor magnetic resonance imaging. FA = fractional anisotrophy. ⟨D⟩ = mean diffusivity. ROI = regions of interest. ALSi = ALS with cognitive impairment. ALSu = ALS without cognitive impairment. FTD = frontotemporal dementia.

1.8.1 Resting state and ligand studies

Some of the earliest studies employing neuroimaging techniques to investigate cerebral changes in ALS used single positron emission computed tomography (SPECT). Several studies have employed the SPECT tracer hexamethylpropylene amine oxime (HMPAO) to indirectly measure brain glucose uptake and regional cerebral blood flow (rCBF) during rest. An initial study by Neary et al. (1990) demonstrated that 4 ALS patients with dementia had reduced tracer uptake in the frontal lobes and exhibited cognitive and behavioural impairments. A subsequent study in ALS patients without dementia revealed reduced uptake relative to controls in bilateral orbitofrontal cortex, anterior and medial prefrontal cortex, as well as bilateral anterior temporal regions (Talbot et al., 1995). In addition, the authors reported that these ALS patients showed deficits in picture sequencing and trends toward impairment in executive measures providing tentative evidence that prefrontal and anterior temporal abnormalities may underpin cognitive dysfunction.

Following on from these findings, Abe et al. (1997) demonstrated that low tracer uptake in frontal regions was associated with a subgroup of ALS patients who performed poorly in verbal fluency, digit span and the WCST. Concordantly, case analyses by Yamauchi et al. (1995) revealed reduced tracer uptake in prefrontal regions (see Table 2) in ALS patients with cognitive and psychiatric symptoms who also exhibited atrophy of anterior portions of the corpus callosum. Moreover, SPECT abnormalities indicative of reduced rCBF in frontal, temporal, and limbic regions have been associated with cognitive impairment in tests including verbal fluency, confrontation naming, and logical memory (Mantovan et al., 2003). A more recent study employing SPECT in combination with three-dimensional statistical imaging has demonstrated that prefrontal hypoperfusion can be detected in non-demented ALS patients, albeit to a lesser extent than ALS-FTD cases, suggesting that this

methodology can be applied to improve the resolution and objectivity of SPECT data (Ishikawa et al., 2007). However, Rusina et al. (2010) reported that although approximately 40% of a cohort of 42 ALS patients exhibited cognitive impairment in tests of attention and executive functioning (see Table 2), regional glucose uptake in prefrontal, anterior temporal, and parietal regions were not associated with performance in any cognitive measure.

Resting state characteristics in ALS have also been investigated using positron emission tomography (PET) which provides higher spatial resolution than SPECT imaging – furthermore, the availability of a variety of binding ligands enables the investigation of different cerebral properties (Turner & Leigh, 2000). Several early PET studies employed the ligand *2-[^{18}F]-2-deoxy-D-glucose* (FDG) to investigate regional cerebral metabolic rates for glucose, and reported reduced glucose uptake in the multiple cerebral areas including the brainstem and basal ganglia (Dalakas, Hatazawa, Brooks & Di Chiro, 1987), sensorimotor cortex and putamen (Hatazawa, Brooks, Dalakas, Mansi & Di Chiro, 1988), as well as the entire cortex (Dalakas et al., 1987; Ludolph et al., 1992), suggesting the presence of widespread functional abnormalities in ALS patients. Moreover, the latter study also reported that a proportion of the cohort of 18 patients exhibited impairments in tests of verbal and non-verbal fluency which correlated with reduced glucose utilisation in the cortex, thalamus, and caudate nucleus. A series of studies by Kew and colleagues (1993a, 1993b) investigated resting state rCBF in ALS; the first reported reduced uptake of the water-binding PET tracer (H_2O^{15}) in motor, parietal, and insular areas, whilst a subsequent study employing a carbon-dioxide-binding tracer ($C^{15}O_2$) demonstrated reduced perfusion in anterior cingulate, and further rCBF reductions in inferior and superior parietal areas as well as left medial temporal lobe and hippocampus in patients exhibiting impaired verbal fluency.

Other PET investigations have employed Flumazenil, a ligand which binds to cerebral GABA receptors, which may be more representative of neuronal loss and degeneration than indirect measures such as glucose uptake and rCBF. Lloyd et al. (2000) reported reduced flumazenil uptake in multiple prefrontal regions including Brocas's area, left dorsolateral and ventral areas, as well as posterior reductions in parietal and visual association areas. Although this study did not include neuropsychological assessment, a later study by Wicks et al. (2008) reported that reduced flumanzenil binding in right frontotemporal regions (see Table 2) at rest correlated with poor ALS performance in written verbal fluency indices. Moreover, poor patient performance in confrontation naming was associated with reduced uptake in left middle frontal gyrus (Broca's area) and left cuneus suggesting that different functional networks underpinned poor performance in these tasks. Further associations between flumanzenil binding reductions and cognition have been reported by Yabe et al. (2012) who reported that writing errors in ALS patients correlated with reduced uptake in bilateral anterior cingulate gyri. Serotonin receptor-binding ligands have also been used in ALS investigations with reports of reduced uptake over the entire cortex with pronounced reductions in cingulate and frontotemporal regions, especially in patients with bulbar symptoms (Turner et al., 2005). Neuropsychological assessment was not performed in this study, however, similar results have been reported in FTD patients (Lanctôt et al., 2007) suggesting that serotonin binding tracer reductions may be particularly sensitive to cognitive impairment.

A recent development in neuroimaging research has been the implementation of functional connectivity analyses, a functional MRI technique which allows the extraction of data describing connections between disparate brain areas to visualise various purported

functional networks (Van den Heuvel, Mandl, Kahn, Pol & Hilleke, 2009). Various resting state networks have been investigated in ALS cohorts. Mohammadi et al. (2009) reported significant differences in activation between patients and controls in the so called "default mode network" in anterior and posterior cingulate as well as bilateral inferior parietal cortex. Further reduced activation was exhibited in the sensorimotor network although in anterior premotor regions as opposed to primary motor and somatosensory areas. By contrast, others have reported intact functional motor networks in ALS (Verstaete et al., 2010), whilst another study has reported *increased* functional connectivity in a network comprising of sensorimotor, premotor, prefrontal, and thalamic areas (Douand, Filippini, Knight, Talbot & Turner, 2011) suggesting the neural changes underpinning functional connectivity analyses are not yet fully understood. A recent study by Agosta and others (2013) reported "alteration" of functional connectivity in ALS patients; decreased connectivity was observed in right orbitofrontal cortex in the default network, and left inferior frontal cortex of the fronto-parietal network, together with increased connectivity in left parietal cortex in the fronto-parietal network. Moreover, enhanced parietal connectivity correlated with poor performance in the WCST which the authors theorized may reflect compensatory attentive processing in response to diminished frontotemporal functioning.

1.8.2 Activation studies

A more direct approach to the relationship between cognitive performance and the associated neural correlates can be made with activation studies in which cortical responses to "on-line" cognitive tasks can be elucidated. Activation studies were initially achieved by way of PET employing the water-binding (H_2O^{15}) and carbon dioxide-binding ($C^{15}O_2$) tracers to provide an index of rCBF. Kew and colleagues (1993a, 1993b) investigated rCBF

during a joy-stick moving task which had two conditions; a stereotyped condition in which movements were predefined, and a random condition requiring intrinsic generation and monitoring to produce novel sequences. During the executively demanding random condition, relative to controls ALS patients exhibited rCBF reductions in medial prefrontal and parahippocampal gyri compared to controls. A follow up study revealed that patients with verbal fluency deficits had additional rCBF reductions in anterior cingulate and the anterior thalamic complex during the same task (Kew et al., 1993b), supporting the earlier findings of Ludolph et al. (1992) who reported an association between verbal fluency performance and reduced glucose uptake in cortico-thalamic pathways.

Using a similar approach to that of Kew et al. (1993b), a series of studies (Abrahams et al., 1995, 1996) investigated online spoken letter fluency performance in ALS patients who were divided into impaired or normal groups based on performance in a written letter fluency task. Changes in rCBF were investigated in two conditions; a generation condition in which participants produced as many words as possible, and a repetition condition in which participants read out their previously generated responses. A contrast between the generation and repetition conditions thus revealed areas of rCBF (i.e. activation) associated with the executively demanding intrinsic generation component of the task. Compared to controls, ALS patients with impaired written fluency exhibited reduced activation in bilateral prefrontal, motor, temporal, and thalamic regions (see Table 2). By contrast, ALS patients who performed normally in the written fluency task also exhibited relatively normal activation in the scanning task, with only small areas of reduced activation observed. The findings suggested that verbal fluency deficits in ALS patients reflected cerebral dysfunction in predominantly prefrontal and thalamic networks. Moreover, (Abrahams et al., 1996) demonstrated that patients with verbal fluency deficits were also impaired in other

tests of executive functioning and memory (WCST, Random movement generation, Paired Associates, and object recall), suggesting that the observed reductions in cerebral activation may also underpin impaired performance in other cognitive domains.

In more recent investigations activation studies have employed functional MRI (fMRI) instead of PET methodology; fMRI has the benefit of being entirely non-invasive as well as offering greater flexibility and availability as radioisotopes are not required. fMRI provides a measure of rCBF by utilising the paramagnetic properties of oxygenated haemoglobin to produce the blood-oxygen-level-dependent (BOLD) response which is tightly coupled with cellular glucose demand (Huettel, Song & McCarthy, 2009). In addition fMRI allows more refined spatial resolution that PET, although it is unable to provide information reflecting the functioning of discrete receptors (Logothetis, 2008).

A study by Abrahams and others (2004) employed fMRI to investigate verbal fluency performance and confrontation naming in ALS in an effort to determine whether cerebral abnormalities were specific to executively demanding fluency tasks. Group comparisons in the modified letter fluency task revealed that ALS patients had significantly reduced BOLD responses (i.e. activation) in the middle and inferior frontal gyri as well as the anterior cingulate which may have been a reflection of the executive and attentional demands of the task (Frith, Friston, Liddle & Frackowiak, 1991). In addition, reduced activation was observed in parietal and temporal regions proposed to be involved in phonological processing and storage (Paulesu, Frith & Frackowiak, 1993). BOLD responses during the confrontation naming task revealed reduced activation in patients in inferior frontal gyrus (including Broca's area) and regions corresponding to the ventral pathway involved in

object recognition (Mishkin & Ungerleider, 1983). Patient and control performance during scanning conditions was matched excluding the possibility that different BOLD responses were a reflection of varying ability between the groups. However, subsequent neuropsychological testing revealed group differences in letter fluency, confrontation naming, and short-term memory span suggesting that the observed pattern of cerebral dysfunction may underpin impaired performance in these tasks. Taken together, the findings of Abrahams et al. (2004) replicated previous investigations (e.g. Ludolph et al., 1992; Abrahams et al., 1996) into verbal fluency by implicating dysfunction in dorsolateral prefrontal cortex and anterior cingulate, although abnormalities also extended to parietal and temporal regions. In addition, the results indicated that cerebral abnormalities were also evident in confrontation naming implicating regions involved in language networks and further extending the heterogeneity of dysfunction in ALS.

Functional MRI has also been used to investigate other cognitive domains in ALS. For example emotional processing and recognition has been investigated by Lulé et al (2007), and Palmieri et al., (2010), with both investigations revealing abnormal cortical activation patterns in tasks requiring emotional processing (see Table 2 for details). In contrast to studies reporting reduced activation during motor task performance, *increased* activation has been shown during a random hand movement task in a network of areas comprising sensorimotor cortex, inferior parietal lobule, and superior temporal gyrus (Stanton et al., 2007). The increased activation observed in sensorimotor networks may represent processes of cortical plasticity in an attempt to compensate for dysfunction in primary motor regions (Schoenfeld et al., 2005). However, consistent with the results of earlier PET studies (Kew et al., 1993a, 1993b), ALS patients exhibited reduced activation in several prefrontal regions, potentially reflecting the executive demands of random generation. Cerebral

responses to executive and attentional processing have also been investigated by way of Stroop task paradigms (Goldstein et al., 2011). Inhibition of prepotent responses was investigated during Stroop colour-word interference and negative priming scanning conditions. Compared to controls, ALS patients displayed *increased* activation in several areas including left middle and superior temporal gyri, as well as left anterior cingulate during the interference condition. By contrast, *reduced* activation was evident in left precentral, cingulate, and medial frontal gyri during the negative priming condition. The authors proposed that the findings were indicative of altered inhibitory processing; although not significant, behavioural data revealed that patients had a tendency to find the Stroop interference more difficult than controls, and the authors concluded that increased activation in the observed areas may reflect additional processing required by ALS patients to maintain task performance. Alternatively the findings may suggest that cerebral abnormalities can occur before cognitive impairments are evident, and that the observed pattern of activation may reflect compensatory processing in the ALS group.

Thus activation studies have provided neural correlates for observed cognitive deficits in ALS, with robust findings implicating dorsolateral and anterior cingulate dysfunction in verbal fluency impairements. However, PET and fMRI findings have suggested that cerebral dysfunction also encompasses more diffuse brain areas with functional changes particularly evident in thalamic, insular and parietal regions, as well as those involved in linguistic processing. These findings serve to show ALS as a multi-system disorder and demonstrate the heterogeneity that is present with patient groups. Although fMRI paradigms have proved useful in identifying changes in rCBF in response to cognitive tasks, caution must be applied when interpreting the results of such studies; rCBF measures do not provide

an explanation of underlying neural functioning which may be excitatory, inhibitory, or compensatory in nature (Logothetis et al., 2008).

1.8.3 Structural studies

1.8.3.1 Volumetric studies

The first investigations of structural abnormalities in ALS patients were facilitated by computerised tomography (CT). Although compared to modern techniques CT provided fairly coarse information, some investigators were able to detect frontotemporal atrophy and significantly enlarged ventricles in patients with co-occurring ALS and dementia (Mitsuyama & Takayama, 1979). Subsequent studies in primarily non-demented ALS cohorts produced conflicting results; David and Gillham (1986) reported that over 50% of patients showed cortical atrophy (although measures were not quantified or correlated with neuropsychological impairments), whilst another study reported that CT abnormalities were rare and uncorrelated with cognitive performance (Poloni, Capitani, Mazzini & Ceroni, 1986). Moreover, a study of 35 ALS patients (Gallassi et al., 1989) reported that although cognitive deficits were evident in a proportion of patients, there was no difference relative to controls in volumetric CT analyses. However, a longitudinal investigation revealed that atrophy developed in frontal and anterior temporal regions in the 20 out of 22 patients over the duration of the disease course (Kato, Hayashi & Yagishita, 1993). Interestingly, extra-motor atrophy was observed before the development of atrophy in precentral and postcentral gyri, as well as further changes in the anterior cingulate and corpus callosum in over half of the patients. However, neuropsychological assessment was not conducted by this study, and the cohort did include 3 patients who developed dementia.

In more recent years, the refinement of MRI technology and analysis techniques has facilitated the development of more sensitive imaging protocols which enable subtle cerebral changes to be detected. Some studies have applied MRI to investigate changes in specific regions of interest (ROI) as well as global cerebral abnormalities. Kiernan & Hudson (1994) used manual tracing to determine the surface areas of the precentral gyri and anterior frontal lobes in ALS and reported that although there were no significant differences compared to controls in grey matter (cortical) measurements, the surface area of the white matter (subcortical) underlying the frontal lobes was significantly reduced in the ALS group. A subsequent study employed similar techniques to investigate regional volumetric changes within the corpus callosum and reported that ALS patients had significant atrophy of the anterior portion of the frontal lobes (Yamauchi et al., 1995). Moreover, severe atrophy of the anterior fourth of the corpus callosum was evident in a subgroup of patients with behavioural abnormalities and those exhibiting cognitive impairment in the Mini Mental State Exam and verbal memory. In a large study, Frank et al. (1997) also obtained volumetric data from 74 ALS patients who were divided into subgroups by cluster analysis based on their cognitive performance in tests of letter fluency, WCST, visual attention (D2 test), and visual and verbal memory (recurring figures/words test). As a group, ALS patients had larger ventricles and lower parenchymal volumes than the control group, and furthermore those patients with cognitive impairment had significantly worse MRI parameters than those without, suggesting that cognitive dysfunction was a reflection of underlying cerebral atrophy.

Rather than looking for atrophy and other cerebral changes on a case-by-case basis using manual tracing methods, statistical imaging packages have been developed to quantify and segment grey and white matter volumes into spatially normalised templates which can be

analysed to investigate group differences across the whole brain. Such techniques known as voxel based morphometry (VBM; Ashburner & Friston, 2000) have the advantage of being automated, and therefore can be performed relatively quickly and without human biases or errors. Each participant's imaging data is normalised into three dimensional space and each point (voxel) within a template can be directly compared. However, accuracy is highly dependent upon the extent to which individual brains can be mapped onto standardised stereotactic templates – a process that is being continually refined but still remains contentious (Ashburner, 2007).

VBM has been applied to the investigation of cerebral changes in ALS; the first study of 16 patients (Ellis et al., 2001) revealed reduced grey matter volumes in superior, medial, and mid frontal gyri relative to controls. White matter changes were also reported but only in regions corresponding to the corticospinal tract (internal capsule and brainstem), and only in those patients with bulbar disease onset. By contrast, a subsequent study of 22 non-demented ALS patients by Kassubek and others (2005) showed regional white matter reductions in corticospinal tract, corpus callosum, and frontal and occipital association fibres, accompanied by reduced grey matter density in primary motor areas and left medial frontal gyrus. Grosskreutz et al. (2006) revealed reduced grey matter volumes in motor regions (precentral gyrus and superior frontal gyrus), somatosensory regions (postcentral gyrus), as well as extra-motor regions (middle frontal gyrus and inferior parietal gyrus) in ALS patients compared to controls. Consistent with the Ellis et al. (2001), white matter changes were not found in this investigation. In a cohort of 25 mildly disabled ALS patients, Agosta and colleagues (2007) found that relative to controls, patients showed locally reduced grey matter density in right premotor cortex, left inferior frontal gyrus, and bilateral superior temporal gyri. Similar results have been reported by recent VBM studies, extending

findings to right inferior frontal gyrus and insula (Mezzapesa et al., 2007; Senda et al., 2011), anterior cingulate (Filippini et al., 2010), and parahippocampal gyrus (Mezzapesa et al., 2007), further demonstrating multi-system involvement in the ALS disease process.

Although VBM has proved useful in revealing extra-motor structural changes in ALS, few of the studies discussed above related their findings to cognitive performance, especially in non-demented patients. However, a study by Abrahams and colleagues (2005) demonstrated that patients with impaired fluency indices showed greater volumetric reductions than those with intact fluency performance. VBM volumetric data from 11 fluency impaired ALS patients and 12 cognitively intact ALS patients were independently compared to the data of matched control participants. In contrast to others in the field (Ellis et al., 2001; Kassubek et al., 2005; Grosskreutz et al., 2006), the authors reported no significant differences between either ALS group and controls in grey matter volumes. However, fluency impaired ALS patients showed extensively reduced white matter volumes in regions corresponding to the corticospinal tract, as well as encompassing extensive frontotemporal association fibres and regions through which run several major white matter tracts – see Table 2 for details. Cognitively intact ALS patients also exhibited volumetric white matter reductions relative to controls but in a less extensive pattern suggesting that white matter changes may precede cognitive impairment. Neuropsychological assessment revealed that the fluency impaired patients also exhibited deficits in tests of executive functioning (category fluency) and memory (letter span and paired associates), the latter of which correlated with white matter clusters encompassing predominantly prefrontal and temporal association fibres, but also implicating occipital association fibres and the major white matter tracts connecting frontal regions to occipital and temporal regions. Thus, Abrahams et al. (2005) demonstrated extensive white matter involvement in ALS pathogenesis, particularly in patients with

cognitive impairment. Moreover, the pattern of widespread white matter atrophy in conjunction with preserved grey matter suggests that white matter degeneration may underpin the observed cognitive deficits in ALS.

Other studies have also made direct correlations between structural change and cognitive impairment using VBM. Grossman et al. (2008) reported that 34 ALS patients (35% with cognitive impairments in fluency, trail making test and reverse digit span) showed diffuse cortical atrophy in dorsolateral and inferior prefrontal cortex, anterior temporal cortex, anterior cingulate, and occipital regions relative to controls. Performance in tests of object knowledge and action knowledge correlated with cortical volumes in bilateral dorsolateral and inferior frontal gyri suggesting that these regions may be crucial in implementing executive retrieval processes from semantic memory. Of note, greater impairments were observed in tests of action knowledge which correlated with cortical atrophy in motor and premotor areas indicating that conceptual information concerning verbs and actions may be specifically linked to motor networks. Behavioural change was investigated in a study by Tsujimoto et al. (2011) who compared scores in the FrSBe before and after the diagnosis of ALS. The authors reported that ALS patients had significantly increased apathy scores in the FrSBe post-diagnosis, and that severity of apathy was correlated with multiple prefrontal regions (see Table 2). The authors proposed that their findings complemented those reported in studies of apathy in FTD (Zamboni, Huey, Krueger, Nichelli & Grafman, 2008), and may reflect "cognitive" apathy thought to be dependent on executive processing within dorsolateral prefrontal cortex and "affective" apathy thought to be dependent on orbitofrontal regions (Levy & Dubios, 2006).

Other studies have used VBM to investigate the proposed overlap between ALS and FTD. Chang et al. (2005) investigated grey and white matter changes in ALS patients compared to controls and those with ALS-FTD. Relative to controls, ALS patients had reduced grey matter volumes in motor regions, superior, middle, and inferior frontal gyri, in addition to superior temporal regions and posterior thalamus, however, no group differences in white matter volumes were observed. ALS-FTD patients exhibiting impairments in WCST, fluency and confrontation naming shared the same pattern of localised volume reductions as ALS patients, although atrophy was generally more extensive. An investigation by Murphy et al. (2007) investigated group differences between 11 cognitively and behaviourally intact patients and 11 patients who met criteria for FTLD or had evidence of cognitive or behavioural impairment. Concordant with Chang et al. (2005) significant group differences were reported between impaired ALS patients and controls in frontal and limbic structures, with findings extended to the parietal lobes (all lateralised to the right hemisphere), whilst intact ALS patients showed reduced temporal lobe volumes compared to controls. More recent studies have revealed a more detailed picture of the overlap between patients with ALS and those with FTD. Lillo and colleagues (2012) employed VBM to investigate grey matter atrophy in demographically matched ALS, ALS-FTD and bvFTD patients; the authors reported that relative to controls, ALS patients displayed volumetric reductions in motor regions and anterior cingulate, whilst ALS-FTD could be distinguished by additional temporal lobe involvement, and bvFTD patients could be identified by more extensive reductions in prefrontal regions. The findings demonstrated that atrophy in motor regions and anterior cingulate were shared by all three groups, providing support for the existence of a spectrum between the disorders. A subsequent study extended the findings of Lillo et al. (2012) by showing that only ALS patients with cognitive and behavioural impairments had cerebral atrophy beyond the brainstem (Mioshi et al., 2013). The authors reported that ALS patients' with cognitive impairments in letter fluency, the Trail Making Test, or Hayling

test, or behavioural abnormalities as assessed by the Cambridge Behavioural Inventory, but who did not meet criteria for ALS-FTD, showed volumetric reductions in motor and somatosensory regions as well as superior frontal gyrus and superior parietal gyrus. These findings are largely in support of previous investigations showing that cognitively impaired patients exhibit greater volumetric reductions than cognitively intact patients (e.g. Abrahams et al., 2005), although the findings of Mioshi et al. (2013) highlight the possibility that damage to grey matter structures may also be a factor.

1.8.3.2 Cortical thickness studies

Although VBM studies have dominated the investigation of cortical changes in ALS, recently developed neuroimaging packages have allowed the same T1-weighted MRI data used in VBM to produce cortical thickness maps. Cortical thickness procedures also rely on the segmentation of white and grey matter followed by the subsequent computation of thickness by measuring the distance between white matter and grey matter surfaces (vertexes); additional parameters of cortical surface area and volume may also be derived (Fischl & Dale, 2000). Group differences in cortical thickness between ALS and controls participants have been observed in primary motor areas of the precentral gyrus and postcentral gyrus, with the suggestion that cortical thickness parameters may be more sensitive to changes in the sensorimotor regions than surface area or volumetric data (Verstraete et al., 2012; Agosta et al., 2012). Moreover, the latter study detected reductions in cortical thickness in extensive cortical regions including prefrontal and ventral frontal cortices, cingulate gyrus, insula, superior and inferior temporal and parietal regions, and medial and lateral occipital areas, suggesting that this method may also be sensitive to subtle extra-motor changes in ALS. The association between cortical thickness and executive functioning was investigated in a recent study by Libon et al. (2012). The authors reported

that a proportion of ALS patients (9/41) exhibited impaired performance in the D-KEFS card sorting test, performance in which was correlated with letter fluency performance. Moreover, in a subgroup of patients (n = 20), age-corrected recognition performance in the card sorting test was correlated with cortical thinning in the left dorsolateral prefrontal cortex and left parietal cortex, suggesting that a left lateralised frontoparietal network underpinned impairment in this task.

1.8.3.3 Diffusion tensor imaging (DTI)

Studies employing volumetric techniques to investigate structural changes in ALS appeared to suggest that white matter pathology was by and large restricted to the corticospinal tract (e.g. Ellis et al., 2001; Grosskreutz et al., 2006). However, the findings of Abrahams et al. (2005) indicated that white matter changes were evident in extensive extra-motor areas, especially in patients with cognitive impairment. Moreover, subsequent histological studies have indicated a high degree of correspondence between TDP43 pathology in extra motor grey matter structures and the underlying local white matter further implicating the role of white matter in ALS pathogenesis (Geser et al., 2009). In contrast to the volumetric estimations provided by techniques such as VBM, diffusion tensor magnetic resonance imaging (DTI) allows the integrity and organisation of white matter structures to be investigated. DTI relies upon the diffusion properties of water molecules within neuronal axons; diffusion of water in white matter tracts is anisotropic, i.e. it moves more freely along the principal orientation of the axons, but not perpendicularly to them (Chenevert, Brunberg & Pipe, 1990). This allows 2 measures of axonal integrity to be derived: Mean diffusivity ($\langle D \rangle$) corresponds to magnitude of water molecule diffusion in any direction - low $\langle D \rangle$ indicates good axon integrity as the myelin sheath restricts diffusion; fractional

anisotropy (FA) indicates the directional coherence of water molecule diffusion - high FA indicates good axon integrity as water movement is generally in the same direction.

DTI data is typically processed and visualised in two ways; voxel by voxel analysis of whole brain white matter, or, the evaluation of specific white matter tracts. The first method has similarities to the methods employed by VBM analysis in that it relies upon the co-registration of individual brain scans to a standardised template so that comparisons can be made across every point (voxel) in standard space. Such methods are useful for exploratory investigations as white matter changes can be visualised throughout the brain without the need for prior hypotheses. Tract Based Spatial Statistics (TBSS; Smith et al., 2006), for example, performs voxel by voxel comparisons within white matter skeletons created for each subject. However, as with all methods requiring co-registration to standard space, the quality of the data is dependent upon the accuracy of the spatial deformation and smoothing algorithms used in the registration process (Jones et al., 2005); TBSS, however, does not use spatial smoothing. By contrast, individual tracts can be segmented for each subject using tractography since large white matter fibre bundles are well defined anatomically and generally have a similar topology across cohorts. Such approaches are similar to region of interest (ROI) methods in that the specific structures under investigation are determined *a priori*, and thus promote hypothesis driven research. Tractography methods rely upon the delineation of "seed points", i.e. the origin of the white matter tract of interest; algorithms then trace the white matter structure and provide average DTI parameters for the *entire* tract (Vilanova, Zhang, Kindlmann & Laidlaw, 2006). In addition, ROI approaches can be adopted which investigate predefined regions *within* major tracts or subcortical white matter areas. Such approaches have been demonstrated to be sensitive to white matter degeneration

and cognitive change in healthy older adults (Shenkin et al., 2005), but have yet to be applied in ALS.

It has long been recognised that degeneration of the corticospinal tract is a key component of ALS pathology (Smith, 1960; Turner, 2011), and DTI allows *in vivo* investigation of this structure. The majority of studies employing tractography and voxel based DTI analyses in ALS have confirmed presence of structural change in the corticospinal tract as indexed by reduced FA (e.g. Ellis et al., 1999; Abe et al., 2004; Sage, Peeters, Görner, Robberecht & Sunaert, 2007; Ciccarelli et al., 2006, 2009). Changes have been reported in various regions of the corticospinal tract including the cerebral peduncle, internal capsule and corona radiata, and a recent meta-analysis encompassing 143 patients (Li et al., 2012) revealed that the posterior limb of the internal capsule (PLIC) was the most sensitive region of the corticospinal tract for detecting white matter damage in ALS. Indeed, another recent study has suggested that integrity of the PLIC may have prognostic value (Menke et al., 2012). Although some studies have failed to show an association between corticospinal tract integrity as measured by DTI and clinical measures (e.g. Agosta et al., 2007), other studies have demonstrated correlations with disease severity (Ellis et al., 1999; Sage et al., 2007), rate of disease progression (Ciccarelli et al., 2006; Bastin et al., 2013) and electrophysiological measures of upper motor neuron degeneration (Sach et al., 2004). In addition, reduced structural integrity in the corpus callosum, and particularly the portion linking the motor cortices, has also been reported by many investigators (e.g. Sach et al., 2004; Sage et al., 2007; Agosta et al., 2007 Filippini et al., 2010; Verstraete et al., 2010; Zhang et al., 2011). Reduced FA in the splenium of the corpus callosum has been shown to correlate with clinical signs of upper motor neuron degeneration (Stanton et al., 2009). However, changes in this area are not consistently associated with disease severity or

duration (Bartels et al., 2008; Filippini et al., 2010) suggesting that the corpus callosum may be affected before the onset of clinical symptoms. The consistency of above findings and the correlation between corticospinal tract integrity and clinical and functional measures suggests that DTI techniques have the potential to be used as biomarkers of disease severity, although novel neuroimaging techniques such as whole-brain magnetic resonance spectroscopy (Stagg et al., 2013) and myelin imaging (Kolind et al., 2013) are also showing promise for this application. Such non-invasive clinical markers of ALS are crucial for differential diagnosis and also for monitoring disease progression and response to potential drug interventions (Turner, 2011).

DTI investigations have also revealed reductions in structural integrity in extra-motor regions in ALS patients. Studies employing voxel-wise whole-brain analyses have reported significant differences between ALS patients and controls in multiple subcortical regions. For example, in group of 15 patients, Sach and colleagues (2004) reported reduced FA in the corpus callosum and right thalamus as well as in white matter adjacent to left inferior frontal and medial frontal gyri. Agosta et al. (2007) also reported reduced FA in the corpus callosum, however, ⟨D⟩ was more sensitive to extra-motor changes with local increases reported in white matter adjacent to right inferior frontal gyrus and superior temporal gyrus, bilateral middle temporal gyrus, as well as left lingual gyrus. In a study of 28 ALS patients Sage et al. (2007), reported reduced FA in multiple prefrontal regions including fibres adjacent to inferior and dorsolateral prefrontal cortex as well as orbitofrontal cortex. In addition, FA reductions were found in bilateral inferior parietal white matter, insula white matter and hippocampal formations, the latter two of which also had increased ⟨D⟩. Such findings supported those of an earlier study which revealed extensive, predominantly frontotemporal, white matter abnormalities using VBM (Abrahams et al., 2005). The same

group (Sage et al., 2009) re-analysed their data using novel methods of voxel-wise analysis which overcome the limitations of co-registration and spatial smoothing incurred by traditional VBM-style techniques. In-house analysis software as well as TBSS produced by-and-large the same findings as the original study with lower overall variance in the parameters, suggesting that imaging packages such as TBSS are more reliable in the detection of subtle white matter dysfunction. Support for these findings were provided by Ciccarelli et al. (2009) who showed extra-motor FA reductions in corpus callosum, right superior frontal gyrus, bilateral inferior and medial frontal gyrus and the bilateral post-central gyrus (primary sensory cortex). Furthermore, a recent study which employed TBSS in conjunction with ROI analysis of diffusion data reported that both analyses revealed reduced structural integrity in corticospinal tract and corpus callosum in ALS patients (Prudlo et al., 2012). Moreover, the TBSS analysis revealed further FA reductions in inferior longitudinal fasciculus, superior longitudinal fasciculus, and cingulum, and integrity in these regions as well as motor regions correlated with ALSFRS-R scores.

Another investigation employing TBSS by Canu et al. (2011) which controlled for volumetric changes in a cohort of 23 ALS patients reported reduced white matter integrity in several frontotemporal regions compared to controls. Concordant with the findings of Agosta et al. (2007), the authors reported more changes in ⟨D⟩ with increases observed in left inferior frontal gyrus, insula, middle temporal gyrus, and supramarginal gyrus, as well as right temporal pole, putamen, angular gyrus, genu, and bilateral orbitofrontal white matter. By contrast, reduced FA was only reported in left inferior frontal white matter. Of note, Canu et al. (2011) did not report extra-motor white matter changes in VBM analyses indicating that diffusivity metrics are more sensitive to white matter pathology than volumetric data and suggesting that diffusivity abnormalities may precede atrophy.

Moreover, orbitofrontal ⟨D⟩ correlated with disease duration suggesting that white matter pathology may spread in an anterior direction as the disease progresses. Concordantly, a longitudinal study by Senda and colleagues (2011) reported that although white matter abnormalities were restricted to areas in close proximity to the corticospinal tract at baseline, at six month follow-up, FA reductions were also apparent in bilateral prefrontal regions. ALS patients in this study were also found to be impaired in the Frontal Assessment Battery although performance did not correlate with diffusivity metrics. However, Tsujimoto et al. (2011) did report correlations between white matter diffusivity metrics and behavioural changes: in a cohort of 21 patients, post-illness apathy scores (as assessed by the FrSBe) were correlated with reduced FA in white matter underlying predominantly right medial frontal gyrus, and increased ⟨D⟩ in white matter underlying predominantly anterior regions of the left superior frontal gyrus. These findings were concordant with grey matter atrophy observed in similar regions in the same patients suggesting that apathy in ALS was associated with the disruption of frontal lobe pathways.

Other investigations employing voxel-wise analyses have provided evidence of white matter changes that support the proposed continuum between ALS and FTD. Lillo et al. (2012) performed TBSS analyses in patients with ALS, ALS-FTD, and bvFTD which revealed white matter commonalties and differences between the three groups. In comparison to the bvFTD group, ALS and ALS-FTD patients showed more damage in corticospinal tract and the temporal poles, whereas the bvFTD group showed more damage in anterior corpus callosum, forceps minor, and inferior longitudinal fasciculus. The same pattern was revealed in comparisons between ALS and ALS-FTD patients. However, analyses of regions common to all groups revealed white matter changes in portions of the corticospinal tract, inferior longitudinal fasciculus, and anterior corpus callosum indicative of shared pathology

in frontotemporal white matter. Other studies have shown white matter disruption in posterior and sensory areas – for example Stanton et al. (2009) reported that sporadic ALS patients had reduced FA compared to familial patients with SOD1 mutations in occipitotemporal association fibers and occipitopatietal white matter as well as corpus callosum and corona radiata. A subsequent study by Lule et al. (2010) demonstrated reduced white matter integrity in fibres projecting to extra-striate visual areas and primary and secondary auditory cortices (accompanied by abnormal visual and auditory processing during sensory fMRI tasks). However, ALS patients did not exhibit impairments at the behavioural level in either the visual or auditory sensory target detection tasks.

Extra-motor changes have also been revealed in ALS patients by the application of tractography analyses to DTI data. In a large study of 46 non-demented ALS patients, Senda et al. (2009) reported reduced FA in frontal white matter, genu and splenium of the corpus callosum, as well as parietal and temporal lobe white matter, and posterior cingulum. Sato and others (2010) reported that a group of 15 ALS patients had significantly lower FA than controls in uncinate fasciculus, although group differences were not found in the apparent diffusivity coefficient. Concordantly, in a group of 20 mildly disabled ALS patients, Agosta et al. (2010) reported that in addition to corticospinal tract abnormalities, patients had increased axial diffusivity in right uncinate fasciculus relative to controls. The uncinate fasciculus connects the anterior portions of the temporal lobes to orbital and inferior gyri of the frontal lobes and lesions to this structure can result in naming deficits and impairment in the retrieval of memories (Lu et al., 2002; Diehl et al., 2008; Harvey, Wei, Ellmore, Hamilton & Schnur, 2013), problems that are often reported in ALS patients (Raaphorst et al., 2010). However, neither of the above studies administered neuropsychological assessment so structural changes in the uncinate fasciculus could not be related to cognitive

impairment. A recent study applied automated probabilistic neighbourhood tractography to the diffusivity data, which in addition to integrity parameters of FA and ⟨D⟩, also allows tract topology or shape to be compared between individuals (Bastin et al., 2013). The authors reported reduced integrity (FA and ⟨D⟩) in bilateral corticispinal tracts and cingulum (⟨D⟩) in 30 ALS patients compared to matched controls. In addition, tract topology was found to be significantly more altered in patients than controls in bilateral corticospinal tracts and the right uncinate fasciculus, providing further evidence of uncinate fasciculus abnormalities in ALS patients.

The only study to report correlations between tractography and cognitive tests was an investigation of 16 ALS patients by Sarro et al. (2011). The authors administered neuropsychological tests of verbal and spatial memory (Rey's word and figure tests), as well as attention and executive functioning (Trail Making Test, WCST, Stroop tests and letter and category fluency tests). Behavioural change was assessed by the Neuropsychiatric Inventory. Eleven patients (69%) were found to be impaired in at least one cognitive test although no group differences between patients and controls were reported. Two patients had evidence of executive impairment (ALS*ci*) according to consensus criteria (Strong et al., 2009), and a further patient met criteria for ALS with behavioural impairment (ALS*bi*). Tractography analyses revealed that compared with healthy controls, patients with ALS showed increased ⟨D⟩ and reduced FA of the corticospinal tract bilaterally as well as increased ⟨D⟩ of the corpus callosum, right cingulum, and bilateral superior longitudinal fasciculus and uncinate fasciculus. Correlations between diffusivity parameters and cognitive tests revealed several significant associations – see Table 2 for details. However, after correction for multiple comparisons were taken into account, only correlations between the Trail Making Test and FA in the corpus callosum, corticospinal tract, inferior fronto-

occipital fasciculus, inferior longitudinal fasciculus, and right uncinate fasciculus remained significant. Moreover, the majority of the correlations were with Part A of the Trail Making Tests which is primarily a measure of psychomotor speed rather than high order cognitive functioning. The only region which correlated with Part B-A (assessing executive process of switching independent of motor speed) was left inferior fronto-occipital fasciculus (FA). Nevertheless, the findings of Sarro et al. (2011) suggest that motor independent executive functioning in ALS is related to the integrity of major white matter tracts connecting frontal regions to occipital and parietal regions. As such, they are consistent with lesion studies and functional imaging studies which suggest that executive functioning is dependent upon distributed regions throughout the frontal, parietal and temporal lobes (Alvarez & Emory, 2006; Zakzanis, Mraz & Graham, 2005). Indeed, abnormalities in frontal, parietal, and temporal regions have also been reported in ALS studies employing volumetric structural imaging (Grosskreutz et al., 2006; Agosta et al., 2007), and functional imaging (Abrahams et al., 2004). Moreover, although the correlation between letter fluency and cingulum integrity did not survive correction for multiple comparisons, the relationship is consistent with other functional studies reporting reduced activation in anterior cingulate during fluency tasks (Kew et al., 1993b; Abrahams et al., 2004). However, it should be noted that motor slowing was not controlled for in the fluency task. In addition, a trend was present between immediate verbal recall performance and reduced FA in the fornix, a relationship that has been demonstrated in other neurodegenerative disorders such as Alzheimer's disease (Sexton et al., 2010).

1.8.4 Neuroimaging in ALS summary

Neuroimaging studies in ALS have consistently implicated dysfunction of prefrontal and temporal regions in ALS. In addition activation studies, and to a lesser extent structural

studies, have demonstrated that disruption to frontotemporal regions is associated with cognitive impairment in a range of tests, predominantly those assessing executive functioning. However, cerebral dysfunction in posterior and parietal regions, as well as the white matter structures which connect them has also been reported. Such findings suggest that extra-motor changes in ALS may not be restricted to frontotemporal regions, but may also reflect more diffuse TDP-43 pathology which has been shown to affect brain structures globally in ALS (Geser et al., 2008, 2009). Although the findings of the neuroimaging studies discussed above suggest that extra-motor changes in ALS are not restricted to frontotemporal areas, the observed pattern of involvement may still be consistent with executive dysfunction as recent research has demonstrated the importance of distributed cortical networks, particularly frontoparietal, in the performance of executive tasks (Alvarez & Emory, 2006). More correlations between imaging parameters and appropriate neuropsychological testing are necessary to understand the link between cognitive impairment and disease pathogenesis in ALS.

1.9 Multiple Sclerosis

In addition to healthy control participants, a cohort of patients with Multiple Sclerosis (MS) was recruited as a comparative group for the main ALS investigation. MS is primarily a disease of cerebral and spinal white matter caused by pathological mechanisms of inflammation, demyelination, and axon degeneration (Compston & Coles, 2008). The most widely accepted theory proposes that MS begins as an inflammatory autoimmune disorder mediated by autoreactive inflammatory T-cells (Weiner, 2004), before progressing into a neurodegenerative disorder characterised by microglial activation (Compston & Coles, 2008). Initial inflammatory lymphocytic pathology is focal and temporary resulting in clinical characteristics of acute dysfunction followed by periods of recovery (remission).

However, overtime microglial activation becomes chronic and widespread resulting in accumulative disabilities in coordination and balance, vision, bladder and bowel control, dysarthria and dysphasia, depression, and cognitive impairment (Noseworthy, Lucchinetti, Rodriguez & Weinshenker, 2000). Disease course is highly heterogeneous and MS patients can be grouped into 4 broad categories based on the progression of their clinical symptoms (Goldenberg, 2012):

1. Relapsing-remitting (RR): The most common form of the disorder affecting approximately 85% of MS patients is characterised by acute flare-ups (relapses) followed by periods of recovery (remission) in which symptoms improve or diminish.

2. Secondary progressive (SP): A progressive form of the disorder which affects a significant proportion of RR patients, although disease modifying treatments may delay development. Characterised by worsening symptoms in the absence of remission periods – in some MS patients symptom severity may reach a plateau.

3. Primary progressive (PP): Less common affecting approximately 10% of patients and characterised by progressive worsening of symptoms from disease onset. Patients do not experience relapses or remissions although periods of symptomatic plateau are possible.

4. Progressive-relapsing (PR): A rare form of the disorder affecting less than 5% of patients. Disease course is characterised by progressive worsening of symptoms from onset with additional intermittent flare-ups and without periods of remission.

MS is far more common than ALS; indeed it is the most common neurological disease in young and middle-aged adults in Europe and the United States (Johnson, 2007). The incidence and prevalence of MS varies geographically with risk increasing with distance from the equator – high risk areas such as Europe, the northern United States, Canada,

south-east Australia and New Zealand typically report prevalence rates of over 100 per 100,000, whilst the highest reported rate of 300 per 100,000 is in the Orkney Islands (Ebers, 2008; Simpson, Blizzard, Otahal, Van der Mei & Taylor, 2011). MS affects more women than men, with an estimated female to male ratio of 2.3:1 (Alonso & Hernán, 2008) and peak onset age of 30 (although onset in women is approximately 5 years earlier). The aetiology of MS remains unknown however several genetic and environmental risk factors have been identified. Environmental factors include vaccinations and viral infections, latitude, UV exposure and vitamin D deficiency (Ascherio & Munger, 2007a, 2007b). Genetic risk factors include the presence of certain alleles of major histocompatability complex (MHC), interleukin-7 receptor (IL-7R), and apolipoprotein-E (APO-E), and it is likely that environmental and genetic risk factors play an additive role in disease susceptibility (Lincoln et al., 2005; Compston & Coles, 2008; Bahlo et al., 2009).

Although ALS and MS are entirely separable entities, they do share some pathological and clinical similarities; both diseases commonly manifest with disruption to the motor symptoms although cognitive changes are common and can precede or occur in conjunction with movement problems (Feinstein, Kartsounis, Miller, Youl & Ron, 1992; Zipoli et al., 2010; Abrahams et al., 2005a). The aetiology of the diseases is unknown but both appear to be multifactorial in nature and implicate dysfunction of cerebral white matter (Kuzelnigg et al., 2005; Geser, 2009). In addition, MS and ALS share pathogenic processes of inflammation, oxidative stress and mitochondrial dysfunction, with the suggestion that autoimmune dysfunction of vasoacive neuropeptides may be a common pathological pathway (Staines, 2008). Moreover, both diseases present with considerable clinical and phenotypic heterogeneity. Thus it is of interest to compare the cognitive profile of MS and ALS patients to investigate whether commonalities between also exist in this domain.

1.10 Cognition in MS

A full review of cognitive impairment in MS is beyond the scope of this study, but the following section will provide a summary of the most prevalent findings. As is true for sensory and physical symptoms in MS, the presence of cognitive impairment is highly variable from patient to patient. Depending on the type of study (clinic-based or population-based) and clinical characteristics of the patient cohorts (age, disease duration, MS subtype), the frequency of cognitive dysfunction in MS ranges between 40% and 65% (Rao, Leo, Bernardin & Unverzagt, 1991; Amato, Zipoli & Portaccio, 2006), with impairments observed in all subtypes of the disease (Foong et al., 2000; Rovaris et al., 2002). Cognitive impairments in MS can affect capacity to follow treatment and rehabilitation regimes, and impinge upon social interactions and activities of daily living, independently of physical disabilities (Amato et al., 1995).

Some of the most commonly reported cognitive impairments in MS are in the domain of memory. Explicit and particularly episodic memory deficits appear to be most prevalent with a propensity towards impairments in delayed free recall and delayed recognition of verbal information (Grafman, Rao & Litvan, 1990; Grigsby, Ayarbe, Kravcisin & Busenbark, 1994; Staffen et al., 2002). However, deficits have been consistently reported in immediate and delayed conditions of spatial and figural memory paradigms, as well as story recall, and paired associate learning (see Thornton & Raz, 1997 for a quantitative review). Early research postulated that retrieval deficits underpin poor memory performance in MS (Rao, Leo & Aubin-Faubert, 1989). However more recent studies have shown that MS patients take more trials to encode verbal information than controls, while subsequent recall

and recognition is unimpaired suggesting that poor memory performance may be a reflection of poor learning, encoding, and maintenance processes, rather than retrieval difficulties (DeLuca, Barbieri-Berger & Johnson, 1994). On the other hand, recognition deficits have also been demonstrated in MS (Beatty et al., 1996) leading to the suggestion that memory impairment can be heterogeneous in MS and reflect disruption to different neural pathways (Benedict, Ramasamy, Munschauer, Weinstock-Guttman & Zivadinov, 2009). By contrast, studies investigating implicit memory and priming have reported normal performance in MS patients (Grafman, Rao, Bernardin & Leo, 1991; Rao et al., 1993). Everyday memory deficits such as that for names, faces, and routes are more evident in patients with chronic progressive disease course than relapse-remitting patients (Calabrese et al., 2000), although deficits in prospective memory have been shown a mixed cohort of MS patients (Rendell, Jensen & Henry, 2007).

Short-term and working memory can also be impaired in MS patients; Rao et al. (1993) reported the an exaggerated word-length effect in a group of MS patients that was independent of disease severity or duration suggesting specific deficit in phonological loop functioning. A subsequent quantitative review concluded that MS patients were impaired in verbal and spatial span measures, but higher effect sizes were found in working memory tasks with additional manipulation demands, namely the Brown-Peterson task and the PASAT (Thornton & Raz, 1997). MS patients with progressive forms of MS have exhibited deficits in forward and backward digit span although performance correlated with processing speed measures leading the authors to conclude that slowed central processing was the underlying problem (Grigsby, Ayarbe, Kravcisin & Busenbark, 1994). The relationship between working memory and processing speed has been further explored in a study by Lengenfelder et al. (2006). The authors demonstrated that MS patients could

perform a modified version of the PASAT with a 1-back manipulation to the same level as controls if they were allowed slower stimulus presentations suggesting that processing speed interacts with working memory ability. However, some patients were unable to perform the 2-back manipulation regardless of the time limit imposed, suggesting that core working memory functioning was also compromised in a proportion of patients.

One of the most well documented impairments in MS is that of slowed information-processing speed, with some investigators proposing that slowed processing speed constitutes the most common deficit in MS (DeLuca, Chelune, Tulsky, Lengenfelder & Chiaravalloti, 2004). Processing speed has been shown to decline longitudinally in MS and be a predictor of overall cognitive decline (Bergendal, Fredrikson & Almkvist, 2007), with large scale studies demonstrating that secondary-progressive patients have a significantly higher prevalence of impairments than other subtypes (Fischer, 2001). Typically processing speed is assessed by the PASAT which is the cognitive component of the multiple sclerosis functional composite, a specifically designed outcome measure for assessing MS severity (Fischer, Rudick, Cutter & Reingold, 1999). Although the PASAT places demands on processing speed and has shown reasonable sensitivity (74%) and specificity (64%) to multiple sclerosis (Rosti, Hämäläinen, Koivisto & Hokkanen, 2007), as has been previously mentioned in relation to ALS research, the test also has a substantial working memory component and therefore deficits in this task do not necessarily represent a pure processing speed deficit. Other investigators have reported significant impairments in MS patients in tasks such as digit-symbol coding and symbol search (components the Wechsler Adult Intelligence Scales III processing speed index; Wechsler, 1997), as well as the Symbol Digit Modalities Test and choice reaction time paradigms (DeLuca et al., 2004; Hughes, Denney & Lynch, 2011). Although these tasks impose less demand on working memory and

therefore are better measures of processing speed, they typically rely on timed responses and thus results can be confounded by physical dysfunction and slowing.

Further evidence for a processing speed deficit has been provided by studies investigating attentional processes. A detailed study by De Sonneville et al. (2002) employed multiple computer based reaction time tasks to investigate different attentional processing stages including target detection, divided attention, inhibition, focussed attention, sustained attention, flexibility, and motor pursuit. Compared to controls MS patients exhibited slower reaction times in all the tasks indicative of slowed processing in automatic and controlled processing stages. The authors also reported that MS patients exhibited a dramatic increase in reaction times in the more complex tasks of divided attention, sustained attention, and flexibility, indicative of impairment in controlled (i.e. cognitively demanding) processing speed. De Sonneville et al. (2002) showed that on average, MS patients were 40% slower than controls suggesting that reaction time paradigms were sensitive to MS and that slowed attentionally-demanding processing speed underpins cognitive dysfunction. However, accuracy was also impaired in the complex tasks but not in simple tasks such as target detection suggesting that MS patients experienced deficits in complex attentional tasks independent of slowed processing speed. Moreover, a subsequent study showed that while MS patients exhibited slowed reaction times in a test of basic tonic alertness, they did not show slowed reaction times in a divided attention task but did make significantly more errors than controls (Tinnefeld et al., 2005). These finding suggest that deficits in attentionally demanding tasks are independent of basic processing speed impairments. Of note, both of the above studies reported that patients with progressive disease course and more severe physical symptoms exhibited more marked deficits, particularly in complex attentional tasks.

Many of the studies discussed above investigating working memory, processing speed and attention in MS have employed methodology that incorporates a "speed versus accuracy confound". The basis of this confound is that accuracy in performance generally decreases as the speed needed to process information increases (Pike, McFarland & Dalgleish, 1974). This confound makes it extremely difficult to attribute whether individuals with MS have specific problems in attention, working memory, or processing speed, or whether there is an interaction between these functions (Lengenfelder et al. 2006). Thus, there is a need to delineate the processes and design tasks that can investigate these processes independently.

The reported deficits in divided and sustained attentive processing measures are consistent with disruption to proposed systems of executive and frontal lobe functioning (Baddeley, Logie, Bressi, Della Sala & Spinnler, 1986; Stuss et al., 1995 – see Chapter 3 Section 3.3 for model summaries). Indeed, a significant proportion of MS patients present with impairments in tests of executive functioning, albeit less frequently than those in memory and processing speed. Population-based studies have shown that between 15 – 20% of MS patients exhibit impairments in executive functioning (Roa et al., 1991; Fischer, 2001), with a recent population-based study of 95 patients (including all disease subtypes) reporting that 17% exhibited impairments in the D-KEFS battery (Drew, Tippett, Starkey & Isler, 2008). Deficits have been reported in a wide range of tests including letter fluency (Foong et al, 1997; Henry & Beatty, 2006), category fluency (Foong et al., 1997; Henry & Beatty, 2006), Stroop interference (Foong et al., 1997; Drew et al., 2008), dual tasking (D'Esposito et al., 1996), Wisconsin Card Sort Test (Parmenter et al., 2007), D-KEFS sorting test (Parmenter et al., 2007; Drew et al., 2008), and Tower of London-based paradigms (Foong et al., 1997). Some studies have suggested that some executive tasks are more sensitive to impairments in

MS patients; for example Henry and Beatty (2006) showed in a quantitative review that letter and category fluency tests were significantly more sensitive to executive dysfunction than the WCST. Concordantly Drew et al. (2008) demonstrated that fluency measures, and particularly switching fluency, along with Stroop interference were the most sensitive executive tests in MS. However, when the same authors attributed each test from their battery (D-KEFS) to one of the following executive domains; planning, inhibition, shifting, reasoning, and fluency, they reported that MS patients did not exhibit a higher proportion of impairment in any single executive domain. The interpretation of executive dysfunction in MS patients must be made with some caution as executive tests are particularly sensitive to the effects of depression (Arnett, Higginson & Randolph, 2001), the rates of which are elevated in MS (Arnett, Barwick & Beeney, 2008). Indeed, Parmenter et al. (2007) showed that group differences between patients and controls in the WCST were attenuated by depression scores, although differences in the D-KEFS sorting test remained significant. Moreover, some studies have reported that executive dysfunction is independent of physical disability (Foong et al., 1997), however others have reported correlations between executive impairments, although regression analyses demonstrated that the variance explained by physical disability was low (Drew et al., 2008). Some investigators have shown that executive deficits are worse in patients with a chronic progressive disease course (Henry & Beatty, 2006), whilst others have demonstrated that relapse-remitting patients perform as poorly as progressive subtypes in tests of executive functioning (Huijbregts et al., 2004).

Thus, the cognitive profile of MS is characterised by heterogeneity – a significant proportion of patients will present with cognitive dysfunction with deficits most likely in tasks assessing delayed memory, attention, and working memory and speed of processing. Although executive impairments are a feature of MS, they are not as common as

impairments in other domains and are less likely to occur in isolation (Drew et al., 2008). However, as with neuropsychological assessment in ALS patients, verbal fluency tests appear to be particularly sensitive to cognitive impairment in MS which may reflect the demands imposed by fluency tasks on multiple cognitive processes (Henry & Beatty, 2006). Studies comparing the cognitive profile of MS to subcortical disorders such as Parkinson's disease and Huntington's disease, and cortical disorders such as Alzheimer's disease have demonstrated that MS patients do not resemble any of these dementia syndromes (Beatty, Goodkin, Monson & Beatty, 1990). Indeed, cognitive impairments in MS have been associated with both white matter pathology and grey matter atrophy (Filippi et al., 2010), leading some investigators to postulate that MS is best described in terms of a "multiple disconnection syndrome" in which more than one cognitive domain can be interrupted (Calabrese & Penner, 2007; Dineen et al., 2009).

1.11 Aims

1.11.1 Aim 1

The current study sought to investigate whether cognitive impairments in ALS and MS patients are characterised by slowed processing speed or deficits in executive functioning.

1.11.2 Design – neuropsychological and experimental assessment

A cross-sectional design was employed in which ALS patients, MS patients, and age and education matched healthy controls were recruited for cognitive assessment. Participants were administered several experimental tests that were specifically developed to be sensitive to executive dysfunction and processing speed in motor degenerative disorders:

Executive functioning

- Dual Task: Participants were required to complete two cognitive tasks, first independently, and then at the same time.

Processing speed

- Visual Inspection Time (VIT): Participants were required to make a forced-choice decision about an abstract visual stimulus – the duration of the stimulus was manipulated to investigate processing speed.

- Rapid Serial Letter Identification (RSLI): Participants were required to identify a target letter from a stream of distracter letters. The durations of the letter stimuli were manipulated to investigate processing speed.

In addition to the experimental tasks, neuropsychological tests that have been shown to be sensitive to ALS cognitive impairment were included to assess the domains of executive functioning, language, working memory, and verbal memory.

1.11.3 Justification of design, part 1

Dual Task: Executive functioning was investigated by way of a dual task which required participants to perform two tasks concurrently. The only previous study of dual tasking in ALS patients utilised reaction time as the outcome measure (Schreiber et al., 2005) and previous investigations of dual tasking in MS have typically included a motor task as one of the component tasks (D'Esposito et al., 1996; Stoquart-Elsankari et al., 2010). Such studies have suggested that there is a correlation between dual task performance and processing speed measures, however the effect of processing speed (independent of motor functioning) on dual tasking has not been directly investigated. The current study employed a dual task

which utilized a processing speed task and a working memory task as its sub-components, and had minimal demands on the motor system. Similar paradigms have been used to investigate dual task abilities across the lifespan (Cocchini, Logie, Della Sala, MacPherson & Baddeley, 2002; Anderson, Bucks, Bayliss & Della Sala, 2011), and allow processing speed and working memory to be investigated independently and under dual task conditions.

VIT task: Processing speed is inherently difficult to measure in populations with motor dysfunction due to the reliance of most tasks on timed motor responses, or reaction times (e.g. Digit-Symbol Substitution Test, Wechsler, 1981; Digit-Digit task, Salthouse, 1994). Thus, the current investigation employed tasks that do not utilize reaction time as their output measure, and place minimal demands on the motor system. Inspection Time paradigms have been used previously to investigate processing speed for abstract visual stimuli in cognitive ageing and Parkinson's disease (Edmonds et al., 2008; Johnson et al.,2004), and can be measured in terms of accuracy instead of reaction time, making them appropriate for use in ALS and MS patients.

RSLI task: Rapid Serial Visual Presentation (RSVP) paradigms have been consistently used as a measure of perceptual speed and to understand the temporal resolution of human vision under a variety of conditions (Schneider & Shiffrin, 1977; Broadbent & Broadbent, 1987). Processing speed for meaningful stimuli such as letter characters is well characterized and known to be faster than that of other stimuli such as faces (Nasanen, Ojanpaa, Tanskanen & Paallysaho, 2006). The current study adapted an RSVP paradigm to make the outcome measure accuracy rather than reaction time to investigate whether letter identification was slowed in ALS and MS patients.

Background Neuropsychological Testing: Impairments in tests of executive functioning are the most commonly reported cognitive deficit in ALS (Ringholz et al., 2005), therefore the current study employed two standardised tests of executive functioning (verbal fluency and card sorting) that have been shown by previous studies to be sensitive in this disorder (e.g. Abrahams et al., 2000; Abrahams et al., 1997). Language impairment in ALS (e.g. Taylor et al., 2012) may affect performance in the tests of executive functioning as both tasks have a linguistic component, especially verbal fluency. As such a confrontation naming task, sensitive to ALS (Abrahams et al., 2004), was employed to assess language by the current study. Working memory was assessed with Digit and Spatial span procedures; impairments in ALS have been demonstrated with Reverse Digit Span (Rakowicz & Hodges, 1998) as well as other tests (Serial Digit Learning Test - Hanagasi et al., 2002). Memory impairment is being increasingly recognised in ALS (Raaphorst et al., 2010), although it is still unclear whether it is secondary to an executive deficit. The current study employed the Logical Memory subtest of Wechsler Memory Scale III which has been shown by others to be sensitive to verbal memory deficits in ALS (e.g. Phukan et al., 2012) and allows distinctions to be made between encoding, retrieval, and recognition processes.

1.11.4 Aim 2

The current study also sought to elucidate the neural correlates of any observed cognitive impairments in ALS patients, and more specifically, to determine whether white matter integrity in specific pathways underpins specific cognitive deficits.

1.11.5 Design – structural imaging

The primary focus of the current investigation was white matter integrity as measured by diffusion tensor imaging (DTI). A hierarchical approach was adopted with regard to the complexity of the DTI techniques employed; a semi-automated Regions of Interest (ROI) protocol was employed initially which required minimal pre-processing and derived values from each subject's native images. The second technique employed was Tract Based Spatial Statistics (TBSS) from the Oxford centre for Functional MRI of the Brain Software Library (FSL). TBSS is a fully automated whole-brain protocol which registers all subjects onto a standard template and makes group comparisons and correlations on the derived "average" image. In addition to the DTI parameters, T1 data was used to perform volumetric whole-brain analyses of grey matter. Each imaging parameter was correlated with scores on cognitive tasks in an effort to determine whether relationships exist between regional white matter integrity and performance in different cognitive tests.

1.11.6 Justification of design, part 2

Previous studies have highlighted several non-motor white matter regions which may underpin impairment in verbal fluency (Abrahams et al., 2005) and other cognitive functions (Sarro et al., 2011), suggesting that pathology in different white matter structures may affect different cognitive processes. However, correlations between structural imaging measures and cognitive data have rarely been undertaken in ALS, and have never been investigated in respect to processing speed and dual task paradigms. The current study aimed to address this issue by correlating cognitive performance in the ALS group with the parameters expressed by several brain imaging techniques. DTI allows inferences to be

made regarding the structural integrity of white matter by way of parameters which are functions of the flow of water within axons; fractional anisotrophy (FA) - the coherence of water molecule movement, and mean diffusivity (⟨D⟩) - the degree of water diffusion across axons. This methodology has been shown to be effective in identifying structural changes in motor and non-motor areas in ALS (Ciccarelli et al., 2009; Agosta et al., 2010; Canu et al., 2011; Prudlo et al., 2012). The aim of the hierarchical approach was to deduce whether any of the methods had increased sensitivity to white matter pathology in ALS, as well as investigates the degree of consistency – and therefore robustness – within the different methodologies. Volumetric analyses of grey matter parameters were carried out to determine the extent to which grey matter changes corresponded to any observed white matter abnormalities.

1.12 Hypotheses

Different behavioural and structural predictions arise when considering whether cognitive impairments in ALS and MS are a manifestation of an underlying processing speed deficit, or executive dysfunction. As such, a strong inference approach was employed to develop the following differential hypotheses:

If a core processing speed deficit is responsible for cognitive impairment it is predicted that, relative to healthy controls:

1. Patients will exhibit impairments in the experimental processing speed measures.

2. With regard to the dual tasks, patients will exhibit worse performance than controls in the Visual Inspection Time component, under both single task and dual task conditions.

3. ALS patients will show reduced structural integrity in diffuse white matter regions and tracts.

4. Correlations will exist between processing speed tasks and *diffuse* white matter regions whereby poor performance is associated with reduced structural integrity.

If executive dysfunction is responsible for cognitive impairment it is predicted that, relative to controls:

1. Patients will exhibit impairments in background measures of executive functioning.

2. With regard to the dual task, patients will exhibit comparable performance to controls in the Visual Inspection Time component under single task conditions, but show a disproportionate performance decrement under dual task conditions.

3. ALS patients will show reduced structural integrity/volume in predominantly frontotemporal regions and tracts.

4. Correlations will exist between tests of executive functioning and *specific* white/grey matter regions whereby poor performance is associated with reduced structural integrity/volume.

Chapter 2. Participant characteristics

This chapter addresses participant recruitment and details the clinical and neuropsychological tests that were employed in the assessment of ALS, MS, and healthy control participants. In addition, comparative analyses of demographic data and standardised neuropsychological tests are presented for a) a two-way comparison between ALS patients and healthy controls, and b) a three-way comparison between a subset of ALS patients, MS patients, and healthy controls.

2.1 Ethics

The current study was reviewed by several NHS and university ethical committees. The application for the cognitive assessment of ALS and MS patients titled "Executive dysfunction or slowed-information-processing speed in motor disorders; a comparative study" gained a favourable opinion from the South East Scotland Research Ethics Committee (REC reference: 11/AL/0369). The magnetic resonance imaging of ALS patients was submitted as a substantial amendment to an on-going study with the following title; "The heterogeneity of cognitive impairment in Motor Neurone Disease" (REC reference: 08/MRE00/50) which was given a favourable opinion by the Scotland A Research Ethics Committee. In addition, the cognitive assessment of healthy controls in university premises was reviewed and given favourable opinion by the University of Edinburgh PPLS Ethics Committee (Title: "Processing speed and dual task ability in younger and older adults", reference number: 148-0910). For copies of the letters of favourable opinion and Participant Information Sheets and Consent Forms, please refer to Appendix A and B respectively.

2.2 Participant recruitment

2.2.1 ALS patients

Thirty people with Amyotrophic Lateral Sclerosis (26 sporadic, 4 familial) were recruited from regional ALS services at the following NHS sites; Western General Hospital, Edinburgh, Southern General Hospital, Glasgow, and Ninewells Hospital, Dundee. Prospective patients were identified by the site relevant consultant neurologist or ALS specialist nurse. An invitation letter was then sent which included a Participant Information Sheet – patients were then able to contact the study team directly to express an interest in participating. In an effort to exclude patients with potentially confounding conditions, and in accordance with the NHS ethics applications, prospective patients' gave consent for their medical notes to be made available to the research team. All ALS patients met the following inclusion criteria:

- Clinical and electrophysiological evidence of combined upper and lower motor neurone involvement.
- Fulfilled the revised El Escorial criteria for clinically definite or probable ALS (Brooks, Miller, Swash, & Munsat, 2000).

In addition, the following exclusion criteria were applied:

- Mental or physical incapacity to give informed consent.
- Severe disability which would prevent a participant from physically undertaking the tests.
- History of and/or current illnesses which are known to affect cognitive functioning:
    1. Significant longstanding psychiatric illness, or alcohol/substance related disorders
    2. Significant trauma, e.g. stroke, head injury

3. Coexisting neurological condition e.g. Parkinson's Disease
4. Participants with known and established ophthalmological disease (not optic neuritis)

- High cardiovascular risk factors.
- Forced Vital Capacity (FVC) of less than 70% of predicted value based on age and height (Rollings, 1984).
- Participants older than 80 years and younger than 18 years of age.

Unfortunately, one patient had to be excluded from the final analyses after cognitive assessment and evaluation of MRI data revealed that he met the inclusion criteria for probable Frontotemporal Dementia (Rascovsky et al., 2011). Of the remaining twenty-nine patients, nine patients had bulbar disease onset, eleven had upper limb onset, and nine had lower limb onset. Twenty-five of the patients had sporadic ALS whilst four patients had a familial history of probable ALS in a 1st degree relative and were thus classified as familial cases. Detailed patient demographics are described later in section 2.4.

2.2.2 MS patients

Twenty-five MS patients were recruited from the Royal Infirmary of Edinburgh. Prospective patients were identified by a consultant neurologist or MS specialist nurse. An invitation letter was then sent to these patients which included a Participant Information Sheet containing details of the study – patients were then able to contact the study team directly to express an interest in participating. As with the ALS patients, prospective MS patients gave consent for their medical notes to be accessed by the study team. All MS patients met the following inclusion criteria:

- A diagnosis of MS based on revised MacDonald's criteria (Polman et al., 2005).
- Capacity to give consent.

The same exclusion criteria as for ALS patients were applied to MS patients (listed above). No MS patients had to be excluded from the study. Of the twenty-five MS patients, 8 were diagnosed as Relapsing-Remitting, 8 as Primary Progressive, and 9 as Secondary Progressive. Detailed patient demographics are described later in section 2.4 and Table 3.

2.2.3 Healthy controls

In total, thirty-eight healthy controls (HC) were recruited for the current study. Thirty-one were recruited from the University of Edinburgh Psychology department's Volunteer Participant Panel, and a further seven were the spouses of participating patients. All control participants had normal hearing and normal or corrected to normal vision, and did not have any history of neurological problems, major medical or psychiatric illness, or learning disability. Several controls took medication to regulate blood pressure, but none were on any form of medication that could affect their cognitive performance. All control participants were tested at the university, and received 6 pounds per hour reimbursement for their time spent testing. Healthy controls were divided into two overlapping subgroups on the basis of matching age and education to the respective ALS and MS patient groups. Thus, thirty healthy controls were assigned to the ALS control group and twenty-five healthy controls were assigned to the MS control group, with an overlap of seventeen between the two groups.

2.3 Background and neuropsychological testing

2.3.1 ALS specific assessment

ALS Functional Rating Scale-Revised (ALSFRS-R; Cedarbaum et al., 1999)

The ALSFRS-R was employed to assess disease progression and severity. It is a questionnaire comprising of 12 multiple-choice questions each assessing a different domain of daily functioning such as speech, ambulation, dressing and hygiene, and breathing. The separate domains allow the clinician to identify areas of specific weakness, while the total score reflects overall disease progression and severity. A measure of disease progression rate was also derived by the following formula:

$$\frac{\text{ALSFRS-R maximum score (48)} - \text{current ALSFRS-R score}}{\text{Disease duration in months}}$$

Epworth Sleepiness Scale (ESS; Johns, 1991)

The ESS was employed to measure the degree and impact of respiratory symptoms and daytime sleepiness. It is a simple multiple-choice questionnaire that assesses the likelihood of falling asleep under various everyday situations. All patients had scores within the normal range (9 or less) on the ESS.

2.3.2 MS specific assessment

Expanded Disability Status Scale (EDSS; Kurtzke, 1983) and the *Multiple Sclerosis Impact Scale 29* (MSIS29; Hobart, Lamping, Fitzpatrick, Riazi & Thompson, 2001) were employed to assess disease progression, severity and impact.

2.3.3 Premorbid functioning

Wechsler Test of Adult Reading (WTAR; Wechsler, 2001)

The WTAR was employed as a measure of pre-morbid intelligence. It correlates very highly with standard intelligence measures such as the Wechsler Adult Intelligence Scale – Revised (WAIS-R), and is comprised of a list of 50 irregularly pronounced words of increasing difficulty. Participants are instructed to read the words aloud, and the number of errors is recorded and converted into an Intelligence Quotient (IQ) score.

2.3.4 Mood

Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983)

The HADS was employed to screen for anxiety and depression. It is a self-report assessment of mood and emotional state comprising of questions with multiple choice answers that are designed to be differentially sensitive to anxiety (HADS A score) and depression (HADS D score). However, in line with the procedure described in Abrahams et al. (1997, 2000), the question "I feel as if I am slowed down" has exaggerated salience to ALS patients who experience motor difficulties, and was therefore not included in the score.

2.3.5 Neuropsychological assessment

Graded Naming Test (GNT; McKenna & Warrington, 1983)

The GNT was employed as a test of confrontation naming and was included in the battery to assess word finding abilities which could potentially contribute to verbal fluency performance. The test has been shown to be sensitive to language impairment in ALS (Abrahams et al., 2004; Wicks et al., 2008), and comprises of 30 line drawings of uncommon words that increase in difficulty. Participants are asked to name the drawings, and the number of errors was recorded.

Digit Span (adapted from the Wechsler Memory Scale III; Wechsler, 1997)

An adapted version of The Digit Span subtest of the WMS III was employed to assess verbal working memory. Similar tasks have revealed impairments in ALS patients (Bartels et al., 2008; Hammer et al., 2011; Lillo et al., 2012).

Forward Digit Span: Participants are read a sequence of digits and asked to immediately recall them.

Reverse Digit Span: In this condition participants are again read a sequence of digits, however, they are required to recall the sequence in reverse order. This condition requires more manipulation of the to-be-recalled sequence and is therefore thought to be a better reflection of working memory ability.

In both conditions the number of digits in each sequence is increased systematically until the participant can no longer recall the sequence accurately in 2 out of 3 attempts. All digit sequences were recorded previously and played back to participant via laptop speakers. In all sequences, digits were presented at a rate of 1 per second.

Spatial Span (adapted from the WMS III, Wechsler, 1997)

An adapted version of the Spatial Span subtest of the WMS III was employed to assess spatial working memory.

Forward Spatial Span: Participants are shown a random sequence of spatial locations on a board containing 10 raised blocks – they are asked to immediately recall the sequence by touching the blocks in the same order in which they were presented.

Reverse Spatial Span: In this condition, participants are again shown a random sequence of spatial locations on the board, however, they are required to recall the sequence in reverse order. This condition requires more manipulation of the to-be-recalled sequence and is therefore thought to be a better reflection of working memory ability.

In both conditions the number of spatial locations in each sequence is increased systematically until the participant can no longer recall the sequence accurately in 2 out of 3 attempts. All spatial locations were presented at a rate of approx. 1 per second.

Logical Memory (Wechsler Memory Scale III, Wechsler, 1999)

The Logical Memory subtest of the WMS III was employed to assess immediate and delayed recall of verbal information and has been shown to be sensitive to memory impairment in ALS (Mantovan et al., 2003; Christidi et al., 2012), and was comprised of four components:

Immediate recall condition: Participants are read a short story and instructed to retain as much information as possible for immediate recall. This stage is then repeated with a different short story. The number of correctly recalled items for both stories is recorded.

Delayed recall condition: After a delay of approximately 25 minutes participants are asked to recall both stories again (they are made aware of this delayed condition). Again, the number of correctly recalled items for both stories is recorded.

Delayed recognition condition: After the delayed condition, participants are asked a series of forced choice (yes or no) questions about each story and the number of correct answers is recorded. Correct responses in each condition for the two stories are combined and converted into scaled immediate, delayed, and recognition score.

Retention: In addition to the standardised parameter of the logical memory task, the current study reported the proportion of information retained in delayed recall condition compared to the immediate recall condition. The proportion was expressed as a percentage using the following formula:

$$\text{Retention} = \frac{\text{Delayed Recall Score}}{\text{Immediate Recall Score}} \times 100$$

Brixton Spatial Anticipation Test (Burgess & Shallice, 1997)

The Brixton test was employed as a measure of executive functioning and assesses inductive reasoning, set-shifting ability and working memory. It has shown to be sensitive to left-lateral frontal dysfunction (Reverberi et al., 2005), and a recent study has demonstrated that ALS patients can also show impairments in this measure (Taylor et al., 2012). The Brixton spatial anticipation test comprises a booklet in which each page shows an array of ten

circles, split into two rows of five. One circle in each page is coloured blue, and as the pages progress, the blue circle moves location in a logical pattern. The participant is shown a page and asked to predict where the blue circle will be on the subsequent page. Patterns are always evident in the test, however, the patterns change without warning, requiring participants to learn the new pattern quickly and adapt their predictions accordingly. Errors in predictions were tallied and converted into a scaled score.

Sorting Test (Delis-Kaplan executive functions system; Delis, Kaplan & Kramer, 2001)

The Sorting Test subtest of the D-KEFS was employed as a measure of concept-formation, modality-specific problem-solving (verbal/nonverbal), and the ability to explain sorting concepts abstractly. The Sorting Test has been shown to be sensitive to left frontal lesions (Fine et al., 2009), and has been shown to be sensitive to executive dysfunction in ALS and MS (Taylor et al., 2012; Parmenter et al., 2007). Participants are presented with 6 practice cards and instructed that the cards can be sorted into 2 groups of 3 based on a rule that will link the cards in each group. Rules can be based on verbal cues such as the meanings of the words written on the cards, or non-verbal cues such as the size and shape of the cards. An example of each is shown. Participants are then presented with 2 sets of different cards and asked to sort them in as many ways as possible. Each time a sort is made, participants are required to explain the rule. The number of correct sorts and rule explanations made is tallied for each set of cards and converted into a scaled score. In addition, participants are subsequently presented with cards already arranged into categories and asked to recognise the sorting rule – those which they previously produced themselves and any others they may have missed. Three scores were recorded for the purpose of the current investigation; the total number of correct sorts, the recognition score, and the scaled score.

Verbal Fluency (Abrahams et al., 1996; Abrahams et al., 2000)

Spoken and written phonemic fluency tests were employed to assess intrinsic response generation, strategy formation and monitoring. Phonemic fluency tests have been shown to be highly sensitive to patients with frontal lobe damage (Baldo, Schwartz, Wilkins & Dronkers, 2006), and are the most sensitive test of cognitive dysfunction in ALS (Phukan et al., 2012).

Spoken Letter Fluency Test: The spoken fluency task was adapted from Benton and de Hamsher's (1983) Controlled Word Association Test (COWAT). Participants are instructed to generate as many words as possible beginning with a specified letter in a 60 second time period. Three conditions are employed with the letters "P", "R", and "W" used respectively. Words beginning with the given letters occur in different frequencies in the English language; words beginning with "P" have the highest frequency, those beginning with "R" have a lower frequency, and those with "W" have the lowest frequency. Thus, the respective letter conditions require increasing cognitive demand as the word frequencies decrease. In addition, a measure of total "PRW" output was calculated by adding the individual letter conditions together.

Written Letter Fluency Test: The written fluency task was adapted from Thurstone and Thurstone's (1962) written fluency test. Two conditions were employed in the written fluency test; in the first participants are instructed to write down as many words as possible beginning with the letter "S" in 5 minutes. In the second condition, participants are instructed to write down as many words as possible beginning with "C" in 4 minutes, however, the words produced had to contain only 4 letters. The "C4" condition is more

executively demanding as it requires highly constrained search conditions and imposes greater demands on inhibition.

Fluency Procedure: In all fluency tasks, participants are instructed to avoid using people's names, place names, or plurals of a previously generated word (e.g. "peach, peaches"), and to avoid producing different endings of the same root word (e.g. "pot, potted, potter, potting"). As such, any examples of these were marked as errors. Perseverations (using the same word twice) were also considered errors. The fluency tasks were scored in terms of the number of correct words generated for each condition.

Fluency Index: Fluency tasks are essentially time based and involve a motor response (either spoken or written), and as such they will be affected by slowed motor functioning evident in ALS and MS. To control for this issue, the current study employed a Fluency Index (*fi*), as devised by Abrahams et al. (2000). Each fluency task employed a generation condition (as described above), and a motor control condition in which participants read aloud or copied the words they generated previously. This procedure provided a measure of the same motor responses required in the generation conditions, but without the cognitive requirements of each task. Thus, indices of the *average* time to think of a word could be calculated that were independent of motor functioning; *fi's* were calculated as follows;

$$\text{Fluency Index } (fi) = \frac{\text{Total Generation Time} - \text{Control Copy/Read Time}}{\text{Number of Items Generated}}$$

Errors (perseverations and any words which broke the fluency rules) were excluded from the *fi* calculations. Separate *fi's* were calculated for each fluency condition as well as an average for all the letters combined.

2.3.6 Statistical analyses

The data were explored for normal distribution using histograms, boxplots and the Shapiro-Wilk's test of normality. In addition, all variables were checked for homogeneity of variance. Not all ALS and MS patients completed all of the tasks (see Tables 1 – 4 for exact participant numbers); some patients were unable to complete some tests due the inability to speak or to write, and others did not complete all tests due to fatigue or time pressures. One healthy control was unable to complete all the background neuropsychological tests due to time constraints. In addition, the DKEFS Sorting Test was added to the assessment battery midway through data collection and therefore data is only available in a subset of the ALS and Healthy control groups (see Table 3 for exact participant numbers).

In the two-way analysis between ALS patients and healthy controls, comparative group analyses of demographic and cognitive data were performed using t-tests in normally distributed data and Mann-Whitney U tests in populations that were not normally distributed. Chi-Square tests were employed for categorical variables. In the ALS group, case analyses were also employed in which standardised scores (Z-scores) for individual ALS patients were derived from the mean and standard deviation of the healthy control group. In cases where statistical significance was marginally missed, measures of effect size are provided by Cohen's *d*.

In the three-way analysis between ALS patients, MS patients, and healthy controls, comparative group analyses were performed using one-way ANOVAs in normally distributed data and Kruskal-Wallis tests in populations that were not normally distributed. In parametric data planned post-hoc group comparisons with Tukey's HSD or Games-Howell corrections (for unequal variances) are reported for any variables in which there were significant group differences. In non-parametric data, Kruskal-Wallis post-hoc comparisons corrected for family wise errors are reported for any variables in which there was a significant group effect. Chi Square tests were employed for categorical variables. In cases where statistical significance was marginally missed, measures of effect size are provided by Cohen's *d*. Associations between performance in neuropsychological tests and age were performed in the ALS group. Associations between performance in neuropsychological tests and mood were investigated in the MS patients. Spearman's *rho* correlations were employed to investigate all associations as age and mood data were found to be non-parametric and covariate analyses were performed using Quade's Rank ANCOVA (Quade, 1967). Quade's Rank ANCOVA is a procedure where by the dependent variable and covariate of interest are first transformed by rank and then entered into a regression analysis. The unstandardized residual values of the regression are subsequently used in a standard one-way ANOVA.

2.4 ALS patients versus healthy controls

2.4.1 Demographic and mood data

Participant's demographic data are detailed in Table 3. There were no significant differences between groups in terms of age, gender, or premorbid IQ as assessed by the WTAR,

indicating that ALS patients and healthy controls were well matched. In addition, there was no difference between groups in self-reported levels of anxiety and depression. The ALS cohort was relatively heterogeneous in terms of disease duration, severity, and onset site, suggesting that the sample was not skewed toward a certain phenotype of ALS.

Table 3. Demographic data for ALS patients and healthy controls

	n **(ALS:HC)**	**ALS**	**HC**	***t or U or X^2***	***P value***
Age (years)	29:30	58.3 (28 – 79)	59.1 (34 – 79)	-0.264	0.793
Gender (M:F)	29:30	16:13	17:13	0.013 (X^2)	0.908
WTAR IQ	27:30	104.0 (81 – 123)	108.4 (87 – 124)	-1.524	0.133
HADS A	29:30	7 (0 – 19)	5.4 (0 – 14)	-1.112 (U)	0.266
HADS D	29:30	3 (0 – 9)	3.1 (0 – 10)	0.016 (U)	0.988
Disease Dur. (months)	28	24 (5 – 88)	----------	----------	---------
ALSFRS	28	38.6 (21 – 47)	----------	----------	---------
FVC (% Pred)	29	103.9 (70.2 – 175.6)	----------	----------	---------

Mean values with ranges in parentheses are presented. Ratios are presented for number of patients versus controls in each task and for group gender breakdown. WTAR = Wechsler Test of Adult Reading, HADS A = Hospital Anxiety and Depression Scale - Anxiety, HADS D = Hospital Anxiety and Depression Scale – Depression, ALSFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale, FVC = Forced Vital Capacity, M = male, F = female, Dur. = duration, Pred = predicted.

2.4.2 Neuropsychological data

Group comparisons in the background neuropsychological tests are detailed in Table 4. ALS patients and controls performed comparably in terms of confrontation naming as assessed by the GNT. In terms of short-term memory and working memory, no significant differences were observed in the Spatial Span measures, however, ALS patients were impaired relative to healthy controls in both the forward and reverse measures of Digit Span. Moreover, ALS patients were impaired relative to controls in the Immediate, Delayed, Delayed Recognition, and Retention conditions of the Logical Memory task. In terms of executive functioning, ALS patient and controls performed comparably in the Brixton Spatial Anticipation Test, however, patients were impaired relative to controls in all conditions of the D-KEFS Sorting Test as well as the Spoken Letter Fluency Test (*fi*). ALS patients also appeared to perform worse than controls in the Written Letter Fluency Test (*fi*). However, despite a medium effect size, there was only a trend towards significance in these data. Therefore a breakdown of performance in each condition is provided in Table 5; although patients had longer fluency indices in both letter conditions, neither difference was statistically significant.

Table 4. Background neuropsychological test data for ALS patients and healthy controls*

	n (ALS:HC)	**ALS**	**HC**	***t or U***	***P value***
Graded Naming Test	26:29	23.8 [4.1]	25.0 [3.4]	1.077 (U)	0.282
Forward Spatial Span	27:30	5.7 [1.1]	5.5 [0.9]	-0.615 (U)	0.539
Reverse Spatial Span	27:30	4.9 [1.2]	4.7 [1.1]	-0.391 (U)	0.696
Forward Digit Span	27:29	6.8 [1.2]	7.4 [1.0]	2.078 (U)	**0.038**
Reverse Digit Span	27:29	5.0 [1.0]	5.6 [1.2]	2.084 (U)	**0.037**
Log. Memory Imm.	28:30	23.8 [6.7]	27.8 [7.9]	-2.122	**0.038**
Log. Memory Del.	28:30	18.9 [6.7]	24.7 [8.1]	-2.964	**0.004**
Log. Memory Rec.	29:30	24.8 [2.6]	26.3 [2.8]	2.181 (U)	**0.029**
Log. Memory Ret.	28:30	78.7 [18.1]	87.2 [11.1]	2.172 (U)	**0.030**
Brixton (Errors)	27:30	16.8 [7.8]	14.5 [7.4]	-1.355 (U)	0.175
Brixton (scaled)	27:30	5.7 [2.4]	6.5 [2.3]	-1.309 (U)	0.190
Sorting Test (no. of sorts)	15:17	9.8 [1.7]	11.4 [1.8]	-2.591	**0.015**
Sorting Test (Recog)	15:17	42.2 [9.6]	50.6 [7.9]	-2.715	**0.011**
Sorting Test (scaled score)	15:17	12.1 [2.2]	13.8 [1.5]	-2.671	**0.012**
Spoken Letter Fluency Test (*fi*)	28:30	4.5 [2.0]	3.2 [1.0]	-2.894 (U)	**0.004**

Written Letter Fluency Test (*fi*)	16:30	9.5 [4.6]	7.4 [3.8]	-1.730 (U)	0.084 (*d*= 0.50)

Mean values with standard deviations in parentheses are presented. * Significant results are highlighted in bold. Ratios are presented for number of patients versus controls in each task. GNT = Graded Naming Test, Fwd = Forward, Rev. = Reverse, Log. = Logical, Imm. = Immediate recall, Del. = Delayed recall, Rec. = Recognition, Ret. = Retention, *fi* = fluency index, No. of sorts = number of correctly identified sorts in the DKEFS Sorting test, Recog = score in the recognition condition of the DKEFS Sorting test.

Table 5. Letter condition performance in the Written Letter Fluency Test for ALS patients and healthy controls

	n (ALS:HC)	**ALS**	**HC**	***t or U***	***P value***
"S" condition (*fi*)	16:30	4.7 [1.6]	4.0 [1.9]	1.397	0.169
"C4" condition (*fi*)	16:30	14.3 [8.4]	10.9 [6.0]	-1.626 (U)	0.104

"S" = generation condition of words beginning with S, "C4" = generation condition with words beginning with C and containing exactly 4 letters, *fi* = fluency index.

2.5 ALS case analyses

Z-scores describing each ALS patients' performance relative to the healthy control group mean were derived for each cognitive measure. According to the consensus criteria suggested by Strong et al. (2009), patients with cognitive impairment (ALS*ci*) were classified as those exhibiting performance at or below the 5th percentile of the control group mean in at least 2 tests sensitive to executive dysfunction. Tests employed by the current study meeting this criterion were the spoken and written letter fluency indices, D-KEFS sorting test, the Brixton Spatial Anticipation Test, and reverse digit span. In addition, based

on the method employed by Phukan et al. (2012), patients with cognitive impairments in non-executive domains were also identified. Patients with memory impairment were classified as those with z-scores at or below the 5th percentile ($\leq$ 1.65) of the control mean in at least 2 of the following measures; logical memory immediate recall, logical memory delayed recall, logical memory recognition, and logical memory retention. Patients with language impairment were classified as those with z-scores at or below the 5th percentile of the control mean in the GNT. Patients with non-executive impairments were identified as those with impairments in memory and/or language domains, in the absence of executive impairment. Case analyses revealed that 7 patients met the criteria for ALS*ci*, whilst 4 met the criteria for memory impairment, and 4 met criteria for language impairment. The Spoken Letter Fluency Test was the most sensitive task with 8/29 patients meeting the criteria for impairment. Of the patients with memory and language impairments, 2 did not present with co-occurring executive dysfunction and could thus be classified as having non-executive impairment. Of these patients, one presented with memory impairment, and one with language impairment.

2.6 ALS patients versus MS patients versus healthy controls

2.6.1 Participants

MS and healthy control participants are identical to those described previously in Section 2.2.2, and 2.2.3 respectively. ALS patients were also the same as those described in previously (Section 2.2.1), except that the four oldest participants were excluded from the following analyses in an effort to match the groups as well as possible in terms of age whilst maintaining equal group sizes of 25.

2.6.2 Demographic and mood data

Details of participants' age, intelligence, and mood are displayed in Table 6. Comparative analyses revealed significant group differences in age; H (2) = 13.50, p = 0.001. Post-hoc analyses showed that ALS patients were significantly older than MS patients (p =0 .001) but not healthy controls (p = 0.060, *d* = 0.59), and there was no difference between MS patients and healthy controls (p = 0.585). A Chi-Square analysis revealed that there was no difference in the gender split between the groups; X^2 (2) = 0.962, p = 0.618. No significant group differences in WTAR IQ were observed; F (2, 70) = 1.297, p = 0.280, indicating that the groups were well matched in terms of premorbid intelligence. Significant group differences were observed for the depression index of the HADS; H (2) = 6.05, p = 0.049. However post-hoc analyses corrected for multiple comparisons showed only a trend towards significance in comparisons between MS patients and healthy controls (p = 0.059, *d* = 0.70). There was no significant difference in HADS D scores between MS and ALS patients or between ALS patients and healthy controls. No significant group differences were observed in the anxiety index of the HADS; H (2) = 2.917, p = 0.233.

Table 6. Demographic data for ALS patients, MS patients, and healthy controls

	n (ALS:MS:HC)	ALS	MS	HC
Age	25:25:25	55.5 (28 – 67)	47.6 (36 – 61)	50.1 (34 – 62)
Gender (M:F)	25:25:25	14:11	11:14	14:11
WTAR IQ	23:25:25	102.7 (81 – 120)	101.8 (74 – 125)	106.8 (87 – 124)
HADS A	25:25:25	7.6 (0 – 19)	6.9 (0 – 12)	5.6 (0 – 14)
HADS D	25:25:25	3.3 (0 – 9)	5.4 (0 – 13)	3.0 (0 – 10)
ALSFRS-R	25:0:0	38.4 (21 – 46)	----------	----------
FVC (% Pred)	25:0:0	97.5 (70.2 – 152.6)	----------	----------
Disease Dur. (months)	25:25:0	23.3 (5 – 88)	124.3 (24 – 336)	----------
EDSS	0:25:0	----------	5.3 (1 – 8)	----------
MSIS-29	0:25:0	----------	87.9 (40 – 132)	----------

Mean values with ranges in parentheses are presented. M = male, F = female, WTAR = Wechsler Test of Adult Reading, HADS A = Hospital Anxiety and Depression Scale Anxiety score, HADS D = Hospital Anxiety and Depression Scale Depression score, ALSFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale, FVC = Forced Vital Capacity, EDSS = Expanded Disability Status Scale, MSIS-29 = Multiple Sclerosis Impact Scale, Dur. = duration, Pred = predicted.

2.6.3 Neuropsychological data

Group data for the background neuropsychological tests are detailed in Table 7. Comparative analyses revealed significant group differences in the GNT; H (2) = 6.500, p = 0.039. Post-hoc analyses indicated that healthy controls had significantly higher scores than MS patients (p = 0.041) but not ALS patients, suggesting that only MS patients were impaired in confrontation naming. The comparison between ALS patients and MS patients was not significant.

In terms of short-term memory and working memory, comparative analyses revealed significant group differences in Forward Digit Span; H (2) = 7.084, p = 0.029, as well as Reverse Digit Span; H (2) = 8.810, p = 0.012. Post-hoc analyses of Forward Digit Span showed only trends toward significance in comparisons between healthy controls and ALS patients (p = 0.076, *d* = 0.69) and MS patients (p = 0.056, *d* = 0.76) although effect sizes were medium-large in each case suggesting that the result may have been restricted by sample size. The comparison between ALS patients and MS patients was not significant. Post-hoc analyses of Reverse Digit Span indicated that healthy controls retained significantly more digits than ALS patients (p = 0.036) and MS patients (p = 0.028). Once again the comparison between ALS patients and MS patients was not significant. No significant group differences were found in Forward Spatial Span; H (2) = 4.417, p = 0.110, or Reverse Spatial Span; H (2) = 1.631, p = 0.442. The results suggest that both ALS and MS patients showed the same pattern of selective impairment in Reverse Digit Span, with trends towards impairment present in both patient groups in Forward Digit Span.

Impairments in both patient groups were also found in the Logical Memory Scales. Comparative analyses revealed significant group differences in the Immediate recall condition; H (2) = 9.050, p = 0.011, with post hoc analyses indicating that healthy controls recalled significantly more information than ALS patients p = (0.010) but not MS patients, suggesting that the ALS group had a selective impairment in immediate recall. The comparison between ALS patients and MS patients was not significant. Comparative analyses also revealed significant group differences in the Delayed recall condition; F (2, 72) = 8.272, p = 0.001, with post-hoc analyses indicating that healthy controls recalled significantly more information than ALS patients (p = 0.001) and MS patients (p = 0.006), suggesting that both patient groups were impaired in this measure. The comparison between ALS and MS patients was not significant. A significant group effect was revealed in the Retention condition; H (2) = 8.745, p = 0.013, with post-hoc analyses indicating that healthy controls retained significantly more information than MS patients (p = 0.016), although only a trend was present between healthy controls and ALS patients (p = 0.076, *d* = 0.57), suggesting that MS patients may have had a selective retention deficit. The comparison between ALS and MS patients was not significant. Comparative analyses in the Recognition condition also revealed significant group differences; H (2) = 6.031, p = 0.049, however post-hoc analyses indicated that only the ALS group had significantly lower recognition scores than healthy controls (p = 0.045). Again the comparison between ALS and MS patients was not significant.

In terms of executive functioning, no significant group differences were revealed in either the Brixton test scaled score; H (2) = 1.598, p = 0.450, or the number of errors made; H (2) = 1.685, p = 0.431. However, impairments in the patient groups were found in the D-KEFS sorting test. Significant group effects were revealed in terms of the number of sorts; F (2,

57) = 4.862, p = 0.011, with post-hoc comparisons indicating that healthy controls made significantly more sorts than ALS patients (p = 0.018) and MS patients (p = 0.041), although the comparison between ALS and MS patients was not significant. Similar significant group differences were found in the Recognition condition; F (2, 57) = 9.372, p = 0.000, with post-hoc comparisons revealing that healthy controls had significantly higher recognition scores than ALS patients (p = 0.001) and MS patients (p = 0.003). Again, the comparison between ALS patients and MS patients was not significant. With regard to the Sorting Test scaled scores, comparative analyses revealed a significant group effect; F (2, 57) = 4.743, p = 0.013, and post-hoc comparisons indicated that healthy controls had higher scores than MS patients (p = 0.012). Although only a trend was present between healthy controls and ALS patients (p = 0.099, *d* = 0.92), the large effect size observed suggested that this result may be due to a lack of statistical power. The comparison between ALS patients and MS patients was not significant. Finally, impairments in the patient groups were also observed in the fluency tests. Comparative analyses of the Spoken Letter Fluency Test (*fi*) revealed significant group effects; H (2) = 19.387, p = 0.000, with post-hoc comparisons indicating that healthy controls performed significantly better than ALS patients (p = 0.001) and MS patients (p = 0.000), although the comparison between ALS and MS patients was not significant. A significant group effect was also found in the Written Letter Fluency Test (*fi*); H (2) = 8.234, p = 0.016. However post-hoc comparisons indicated that only the MS group had significantly worse scores than healthy controls (p = 0.015). Again the comparison between ALS and MS patients was not significant. The results suggested that while both patient groups exhibited impaired letter fluency performance, only MS patients exhibited impairment in the Written Letter Fluency Test.

Table 7. Background neuropsychological test data for ALS patients, MS patients, and healthy controls

	n (ALS:MS:HC)	ALS	MS	HC
GNT	22:20:25	23.4 [4.2]	22.8 [3.6]	25.6 [2.5]
For. Spatial Span	24:23:25	5.8 [1.2]	5.4 [0.9]	6.0 [1.1]
Rev. Spatial Span	24:23:25	5.0 [1.2]	4.7 [0.9]	5.0 [1.1]
For. Digit Span	23:25:25	6.8 [1.3]	6.8 [1.1]	7.6 [1.0]
Rev. Digit Span	23:25:25	5.1 [1.0]	5.0 [1.3]	6.0 [1.4]
Log Memory Imm.	24:24:25	23.8 [7.1]	26.1 [6.9]	30.2 [6.7]
Log. Memory Del.	24:24:25	19.3 [7.0]	20.6 [8.0]	27.4 [7.5]
Log. Memory Rec.	25:24:25	24.9 [2.6]	25.3 [3.2]	26.5 [2.7]
Log. Memory Ret.	24:24:25	80.6 [18.7]	77.4 [20.0]	89.3 [10.9]
Brixton (Errors)	23:23:25	16.1 [7.6]	13.0 [4.8]	14.9 [6.0]
Brixton (scaled)	23:23:25	6.0 [2.4]	6.8 [1.7]	6.2 [1.9]
Sorting Test (no. of sorts)	13:25:20	9.8 [1.6]	10.2 [2.3]	11.8 [1.6]
Sorting Test (Recog)	13:25:20	41.9 [9.1]	44.8 [9.1]	53.4 [6.3]
Sorting Test (scaled score)	13:25:20	11.8 [2.0]	11.5 [2.6]	13.6 [1.9]

Spoken Letter Fluency Test (*fi*)	24:25:25	4.5 [2.1]	5.0 [2.3]	3.0 [0.9]
Written Letter Fluency Test (*fi*)	14:14:25	9.5 [4.9]	11.1 [4.8]	6.9 [3.0]

Mean values with standard deviations in parentheses are presented. Ratios are presented for number of patients versus controls in each task. GNT = Graded Naming Test, For. = forward, Rev. = reverse, Log. = Logical, Imm. = Immediate recall, Del. = Delayed recall, Rec. = Recognition, Ret. = Retention, *fi* = fluency index, No. of sorts = number of correctly identified sorts in the DKEFS Sorting test, Recog = score in the recognition condition of the DKEFS Sorting test.

2.7 Correlations with age and depression

Comparative analyses of age revealed that the average age of the ALS group was significantly higher than the MS group, although not healthy controls. Moreover, ALS patients had the largest age range of any of the participant groups indicating that any potential age effects would most likely exist within the ALS population. Thus, to further investigate the effect of age, correlational analyses were performed between age and all background variables in the ALS patient group. Only significant correlations are reported. Age correlated significantly with GNT score; rho = 0.47, p = 0.029, Logical Memory Retention; rho = -0.42, p = 0.039, and the Sorting Test scaled score; rho = 0. 64, p = 0.019. The correlations suggested that while retention in the Logical Memory scales decreases with age, GNT performance Sorting Test performance increases with age in the ALS group. Therefore, the group effects in Logical Memory Retention, GNT, and Sorting Test scaled score were subjected to covariate analyses with age.

Quade's Rank ANCOVA revealed significant group differences in Logical Memory Retention; F (2, 70) = 5.217, p = 0.008. Post-hoc comparisons indicated that MS patients had significantly lower scores than healthy controls (p = 0.006), however no significant differences were observed between ALS patients and healthy controls, or ALS and MS patients. The result suggested that the ALS group did not perform worse than the control group once age was accounted for. In terms of GNT performance, Quade's Rank ANCOVA revealed significant group differences; F (2, 64) = 5.157, p = 0.008. Post-hoc comparisons showed that ALS patients named significantly fewer items than healthy controls (p = 0.009) but only a trend towards significance was observed between MS patients and healthy controls (p = 0.069, *d* = 0.90). There was no significant difference in GNT performance between ALS and MS patients. This result suggests that once age is accounted for ALS patients are in fact impaired relative to controls in the GNT whereas MS patients are not. However, it should be noted that a large effect size was present between MS patients and healthy controls in this data suggesting that group differences would have been significant in a slightly larger sample size. Finally, Quade's Rank ANCOVA revealed significant group differences in the Sorting Test scaled scores; F (2, 55) = 3.891, p = 0.026. Post-hoc comparisons indicated that ALS patients had significantly lower scores than healthy controls (p = 0.039) whilst only a trend towards significance was present between MS patients and healthy controls (p = 0.072, *d* = 0.92) and there was no significant difference between ALS and MS patients. The results suggest that once age is accounted for ALS patients are impaired relative to controls in the terms of the Sorting Test scaled score. Although only a trend towards significance was observed between MS patients and controls, the presence of a large effect size suggested that this marginal result may be due to low statistical power.

In addition, the significant effect of depression in the MS group was investigated by performing correlational analyses between HADS D scores and all background neuropsychological measures in the MS group. No significant relationships were found (see Appendix C for details), and as such no further covariate analyses were performed.

2.8 ALS patients versus healthy controls summary

Relative to the demographically matched healthy controls, ALS patients exhibited impairments in tests of executive functioning, working memory, and verbal memory. Deficits were observed in the Spoken Letter Fluency Test (*fi*) which is concordant with the majority of previous studies investigating cognition in ALS (e.g. Abrahams et al., 1997, 2000, 2004; Ringholz et al., 2005; Taylor et al., 2012; Phukan et al., 2012), providing further evidence that fluency tests are among the most sensitive to cognitive impairment in ALS. Of note, ALS patients were unimpaired in the GNT suggesting that basic word retrieval difficulties may not have been the underlying cause of poor letter fluency performance. However, although patients had lower average scores than healthy controls in the Written Letter Fluency Test (*fi*), significant group differences were not found in this measure. This may have been due to the high proportion of ALS patients (n = 14) who were unable to complete the written task, thus lowering statistical power. Further evidence of executive dysfunction in the ALS group is provided by significant group differences in all measures of the D-KEFS Sorting Test (no. of sorts, recognition score, and scaled score). These findings are consistent with others reporting that a significant proportion of patients have impairments in this test of flexibility and concept formation (Libon et al., 2012; Taylor et al., 2012) and other similar tests such as the WCST (Abrahams et al., 1997; Lomen-Hoerth et al., 2003; Sarro et al., 2011).

Evidence of working memory impairment was also exhibited by the ALS group as patient performance was significantly lower than that of controls in both forward and reverse digit span measures. Such findings have also been reported by other studies (Bartels et al., 2008), although not all (e.g. Ludolph et al., 1992; Jelsone-Swain et al., 2012) with deficits in reverse digit span reported more often (Rakowicz & Hodges, 1998; Hanagasi et al., 2002; Lillo et al., 2012). Although forward digit span deficits may be a better reflection of a short-term memory/attentional impairment (Engle et al., 1999), the observed deficits in reverse digit span provide a more robust indication of working memory impairment in the ALS group. Of note, no impairment was exhibited in either forward or backward spatial span measures suggesting that these abilities may be dissociable in ALS patients. Spatial working memory has not been extensively investigated in ALS, but deficits in spatial span have been reported by some investigators in conjunction with abnormal ERP characteristics (Volpato et al., 2010; Hammer et al., 2011).

The ALS patients also exhibited impairments in all measures of the Logical Memory scales with significant group differences between patients and controls evident in immediate, delayed, recognition, and retention conditions. Deficits in immediate and delayed conditions of story recall tests have been reported by some previous studies (Mantovan et al., 2003; Christidi et al., 2012) whereas other have reported unimpaired performance in both conditions (Newsom-Davis et al., 2001). ALS patients also exhibited deficits in the recognition condition and in the percentage of information recalled at delayed compared to immediate conditions (retention). Such findings suggest that memory impairment in ALS is not restricted to immediate recall conditions which are assumed to be a reflection of executive dysfunction (Lezak et al., 2004) and have been more commonly reported by

previous studies (Massman et al., 1996; Robinson et al., 2006). As such, the logical memory deficits observed in the current investigation may indicate that memory impairment in ALS is not solely an encoding/retrieval problem, but may also be indicative of a failure to maintain memory traces (Christidi et al., 2012). Inconsistent findings within the literature in the domain of memory may reflect inherent heterogeneity of memory impairment in ALS as large scale studies indicate that between 11% and 14% of patients exhibit memory impairments (Taylor et al., 2012; Phukan et al., 2012).

In terms of the case analyses, z-scores revealed that 9/29 (31%) ALS patients had cognitive impairment. This proportion is concordant with a recent population based study which reported that 35% of 160 incident ALS patients presented with cognitive impairment (Phukan et al., 2012). Executive dysfunction was the most common deficit with 7/29 (24%) patients exhibiting deficits in 2 or more tests sensitive to executive dysfunction, also concordant with the proportion reported by Phukan and colleagues (2012). Furthermore, 4/29 (14%) of ALS patients exhibited evidence of either memory, or language impairment. The number of patients who exhibited memory or language impairment in the absence of executive impairment (i.e. non-executive impairment) was 2/29 (7%) which is lower than the proportion (14%) reported by Phukan et al. (2012). Thus, the ALS cohort in the current investigation appear to be a representative sample of patients as findings are largely consistent with those of previous large scale studies (e.g. Massman et al., 1996; Ringholz et al., 2005; Phukan et al., 2012; Elamin et al., 2013), with approximately 30% of patients showing evidence of cognitive impairment, predominantly in tests of executive functioning, with a smaller proportion exhibiting impairments in tests of language and memory. A recent study reported that language deficits in ALS were more common than executive dysfunction

(Taylor et al., 2012) which was not replicated by the current investigation – however, performance in this domain was not investigated as thoroughly as by Taylor and colleagues.

2.9 ALS patients versus MS patients versus healthy controls summary

In terms of ALS patient performance, the findings of the three-way analysis between ALS, MS, and healthy controls revealed largely the same pattern of impairment as the 2-way analysis between the whole ALS group and age-matched healthy controls. Although there were no significant differences between the ALS and MS groups themselves, there were a few instances in which ALS and MS performance differed relative to the control group. In measures of Forward Digit Span and Logical Memory Retention, the MS group performed worse than healthy controls but significant differences were not observed between the ALS group and healthy controls (although a trend towards significance was present in Forward Digit Span). Of these measures, Logical Memory Retention was found to correlate with age in the ALS group suggesting that the retention deficit observed in the two-way analysis may have been exacerbated by age. Nevertheless, ALS patients exhibited evidence of impairments in the same neuropsychological tests as described above suggesting that the effects are robust as they persist in analyses between younger patient and control cohorts.

With regard to the MS group, compared to their age and education matched control group, patients were impaired in a number of the neuropsychological tests, displaying a similar pattern of impairment to that exhibited by ALS patients. In agreement with other investigators (Foong et al., 1997; Henry & Beatty, 2006), MS patients exhibited impairments in letter fluency indices. Significant group differences were found in spoken and written versions of the test (despite a relatively low number of patients completing the

written version) suggesting that these tasks are particularly sensitive to cognitive impairment in MS. Further deficits in tests of executive functioning, namely the D-KEFS Sorting Test, were also observed in MS patients. There were significant group differences in terms of the number of sorts made and the recognition score consistent with the findings of other studies employing this test (Parmenter et al., 2007).

MS patients also displayed deficits in working memory as evidenced by impaired performance relative to healthy controls in Reverse Digit Span. While post-hoc comparisons in Forward Digit Span were not significant, there was a strong trend toward significance suggesting that short-term memory capacity may also be effected in MS. Working memory impairment in MS is more commonly demonstrated by way of deficits in more demanding tasks such as the PASAT (Lengenfelder et al., 2006; Rosti et al., 2007), however, deficits in forward and reverse digit span procedures have been reported by a quantitative review (Thornton & Raz, 1997) suggesting that these are robust and commonly exhibited impairments in MS cohorts. Moreover it has been suggested that span deficits appear to be particularly evident in patients with progressive forms of the disease (Grigsby et al., 1994).

In addition, there was evidence of verbal memory impairment in the MS cohort with deficits observed in the Delayed and Retention conditions of the Logical Memory scales. Deficits in delayed recall have been particularly well documented in MS (Grafman, Rao & Litvan, 1990; Staffen et al., 2002) although reports of impairment in immediate recall are also common (DeLuca et al., 1994; Thornton & Raz, 1997). The observation that the recognition component of the Logical Memory scale was not impaired is consistent with the finding of previous investigations of recognition memory in MS (Rao et al., 1993), although others

have reported recognition deficits in a proportion of patients (Beatty et al., 1996). Moreover, in contrast to other investigators (DeLuca et al., 1994) this finding suggests that retrieval/retention rather than encoding difficulties may underpin MS memory impairment in this cohort.

Finally, although there was initial evidence of a word retrieval deficit in MS patients, subsequent covariate analyses with age revealed that MS performance in the GNT was not statistically different from that of healthy controls (although a trend towards significance and a large effect size was observed). Language abilities such as simple word retrieval are regarded as generally intact in MS (Roa et al., 1991), however deficits in confrontation naming have been reported in relapsing-remitting and progressive MS patients (Friend et al., 1999). Thus the cognitive profile of the MS cohort in the current study appears to be largely consistent with the findings of large-scale studies and quantitative reviews (Rao et al., 1991; Thornton & Raz, 1997; Drew et al., 2008), characterised by deficits in free recall, short-term memory, working memory and executive dysfunction.

Although the ALS cohort was older than the healthy control participants in the 3-way analysis, the age difference between ALS and MS groups was not significant indicating that the two patients groups were relatively well matched. The analyses revealed that the cognitive profile of ALS and MS patients was very similar – relative to healthy controls deficits were exhibited in all of the same neuropsychological tests, with the exception of the GNT in which only the ALS group were impaired. However, some subtle within-test performance differences were observed. MS patients exhibited impairment in both the spoken and written fluency indices suggesting that they may be more sensitive to the written

measure than ALS patients, although previous investigations have shown ALS impairments in written letter fluency (Abrahams et al., 2000, 2004, 2005). Similarly, ALS and MS patients displayed impairments in different conditions of the Logical Memory scales; ALS patients had immediate and delayed recall as well as recognition deficits, whereas MS patients had only had delayed recall and retention deficits suggesting that while ALS memory may be a reflect difficulties in encoding, retention, or retrieval, MS deficits are more likely to reflect a problem with retention and/or retrieval.

Thus, standardized neuropsychological assessment revealed a common pattern of executive dysfunction combined with impairments in working memory and verbal memory in ALS and MS patients. Although the ALS cognitive profile is typically associated with that of FTD, the current study has shown that similarities also exist with MS, a disorder characterised by white matter pathology. Such findings may further implicate the involvement of white matter pathology in the explanation of cognitive impairment in ALS.

Chapter 3. Development of experimental tasks and dual task ageing study

This first aim of this chapter is to address the design of the experimental tasks employed by the current investigation, and the theories and models that informed them. The tasks developed for use in the current study focussed on processing speed and dual task ability, as well as the relationship between the two cognitive processes, with the aim of employing paradigms that were independent of motor impairment. Although dual tasking and processing speed have been investigated in ALS and MS (as discussed in Chapter 1, Sections 1.6.1.4 and 1.10), both abilities have been studied extensively in the cognitive ageing literature by way of a variety of techniques and paradigms, some of which are reviewed below. The second aim of this chapter was to test the functionality of a novel dual task paradigm in a pilot study, and subsequently investigate the effects of ageing in this experimental paradigm.

3.1 Processing speed

Processing speed refers to the maximum rate at which elementary cognitive operations can be achieved, assuming that faster processing is beneficial for subsequent cognitive operations (Salthouse, 1985). According to Kail and Salthouse (1994), the concept of processing speed encompasses several key characteristics:

(a) The resource is limited in nature, and can be measured in terms of quantity or effectiveness, the ability of which increases up until maturity and then decreases across the adult years.

(b) The resource facilitates cognitive operations such that performance is improved when greater amounts of the resource are available.

(c)The resource is not restricted to a small number of highly similar cognitive tasks, rather it is relevant to a broad range of cognitive operations.

According to Salthouse (1996), the effect of processing speed on higher cognitive processes has been postulated to rely on two mechanisms;

1. *Time limited effect:* asserts that if the amount of time taken to complete a low level process is too long, there will not be sufficient time to complete the next process in the hierarchy. Especially pertinent when there is a time limit to the goal-directed task.
2. *Simultaneity effect:* asserts that if processing speed for a given function is slowed, the information may no longer be available or relevant when it is needed. Especially pertinent when information may be required for storage *and* processing, such as in working memory tasks.

In addition, Salthouse (1996) asserted that any processing speed task must meet certain criteria:

a) The task should be relatively simple so that performance is attributable to how quickly the task can be carried out, and is not affected by ability in other cognitive domains.
b) However the task should not merely reflect simple sensory and motor responses or it may not represent a relevant cognitive process.

Tests that meet these criteria are those such as the DSST and perceptual speed tests, however, others such as the PASAT and Sternberg paradigm can be inferred to load too heavily on other cognitive processes such as working memory and mathematical ability. Computerised versions of perceptual speed tests are now commonly used as processing speed measures as they have the added advantage of allowing precise reaction times to be recorded for each trial, rather than a measure of the total time taken to complete the whole task, or the number of errors committed within a given time limit. For example, age effects have been reported by a study in which the DSST was modified into a computer based forced-choice reaction time task in which participants judged whether visually presented digit-symbol pairs matched those in a code table (Salthouse 1998). However, the main criticism of such tests, and one that is particularly pertinent to the current study, is their reliance on reaction times. This is not only a potential confound in ageing populations in which reaction times are known to be slowed (Zacks & Zacks, 1993; Fozard, Vercruyssen, Reynolds, Hancock & Quilter, 1994), but also a major issue in the assessment of patient populations with inherent motor impairments.

However, processing speed tests that are independent of motor functioning have been developed in the form of Inspection Time (IT) paradigms. IT paradigms are the only measures of mental speed that do not involve reaction times or high-order cognitive processes (Kranzler and Jensen, 1989). IT experiments typically involve the visual presentation of two lines of markedly different length (target), followed immediately by a backward mask to limit any additional processing from sensory traces. The participant is required to judge which line was longer (forced-choice, left or right). Inspection time is defined as the minimum target duration necessary for subjects to accurately identify the longer line. Thus, IT paradigms utilise forced-choice decision making, and the manipulation

of stimulus duration times, to allow the temporal limit at which information is available for processing to be elucidated. Indeed, IT tasks have been used to detect motor independent processing speed deficits in motor disorders such as Parkinson's disease (Shipley, Deary, Tan, Christie & Starr, 2002; Johnson et al., 2004). Moreover, IT, like other processing speed measures has been shown to correlate with general cognitive abilities, particularly Performance IQ (Deary and Stough, 1996; Nettlebeck and Rabbit, 1992). As such, IT tasks are highly suitable for use in the current study as they meet the criterion proposed by Salthouse (1996) whist remaining independent of motor impairment.

In addition to the investigation of processing speed for abstract visual stimuli via an IT paradigm, the current study sought to investigate processing speed for meaningful visual stimuli, and in particular, linguistic stimuli. Given that a proportion of ALS and MS patients have been shown to have language impairments (Bak & Hodges, 2001; Friend et al., 1999), and the reported association between verbal fluency performance and processing speed (Schaie 1989; Bryan, Lusczc & Crawford), the current study aimed to investigate whether processing speed for meaningful verbal information was differentially impaired in these patient groups. Rapid serial visual presentation (RSVP) tasks have been used in studies of perception and psychophysics to investigate the characteristics and temporal resolution of human visual processing (e.g. Schneider & Shiffrin, 1977). Processing speed for words and letters is relatively well characterised (James, James, Jobard, Wong & Gauthier, 2005), with words elucidating a more automatic and faster neural response than individual letters – the so called *word superiority effect* (Johnston & McClelland, 1974). Letter identification is a more controlled task, although processing is still significantly faster than that of more complex percepts such as faces; the temporal resolution of individual letter recognition has been reported at approx. 40ms in adults (Nasanen, Ojanpaa, Tanskanen & Paallysaho,

2006). Thus, letter identification appeared to be an appropriate method by which to investigate linguistic processing speed in ALS and MS. The current task was adapted from a standard RSVP paradigm to make accuracy the only outcome measure and allow the manipulation of stimulus duration times in an effort to make the task analogous to the VIT task.

3.2 Processing speed and ageing

It is generally accepted that processing speed becomes slower as people get older; a considerable number of studies have demonstrated age effects in different processing speed paradigms. Age effects have been reported in perceptual speed tasks which typically require participants to match or find a simple target stimulus from an array of distracter stimuli e.g. the Identical Pictures and Finding A's tests from the ETS Kit of Factor-Referenced Tests (Ekstrom, French, Harman & Derman, 1976; Schaie, 1989) and the Visual Matching and Cross-Out tests from the Woodcock-Johnston Cognitive Ability Test (Kail & Salthouse, 1994). Age effects are also reliably found in speeded tasks which require additional attentional demand and shifting between perceptual stimuli e.g. the Trail Making Test (Boll & Reitan; Kennedy, 1981) and Digit Symbol Substitution Test (DSST) from the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Salthouse, 1992). Moreover, age effects have been reported in tasks which put an additional load on working memory such as the Sternberg paradigm (Anders & Fozard, 1973) and the Paced Auditory Serial Addition Test (PASAT; Crawford et al., 1998; Diehr et al., 2003). Furthermore, reductions in processing speed have been shown to have a wider impact in older adults. For example, IT tasks have been shown to be sensitive to the effects of cognitive decline in healthy ageing whereby individuals with reduced IT ability experience more difficulties in activities of daily living (Gregory, Calaghan, Nettelbeck & Wilson, 2009). Some researchers argue that slowed

processing speed accounts for the majority of age associated cognitive decline (e.g. Salthouse, 1996). Evidence for such theories comes from studies which show that processing speed performance is a significant predictor of performance in other high-order cognitive tasks. For example, older adults have been shown to have slower rehearsal times and articulation speeds for to-be-remembered words than younger adults (Bryan & Lusczc, 1996); the authors reported that older participants were also slower than younger participants in the Digit Symbol Substitution Test (DSST), and that this relationship mediated word recall performance. Other studies have reported that processing speed mediates performance in high order tasks such as Raven's Progressive Matrices (Fry & Hale, 1996) and verbal fluency (Schaie 1989; Bryan, Lusczc & Crawford, 1997).

3.3 Models of executive functioning

A comprehensive review of models of executive functioning is beyond the scope of this study, but summarised below are models which relate best to recent findings in ALS and which have been most influential in the design of the current investigation.

Executive functions can and have been defined in numerous ways by different theorists. For example, executive functioning has been referred to as the highest order processes of human intelligence and includes the preparation and planning of actions as well as the monitoring and verification of those actions (Anderson, Jacobs, & Anderson, 2008). Others have suggested that they encompass the ability to solve novel problems, modify behaviour in light of new information, generate strategies, and sequence complex actions (Elliot, 2003). Some investigators have coined terms that encompass these wide-ranging functions such as the "Supervisory Attentional System" (Norman & Shallice, 1986), or the "Central

Executive" (Baddeley & Hitch, 1974). However, regardless of different definitions and concepts, there seems to be relative agreement that executive functions play a fundamental role in adaptive human behaviour.

3.3.1 The multi-component model of working memory

One of the most influential cognitive models of complex human behaviour was proposed by Baddeley and Hitch (1974) with the multi-component model of working memory. This model proposes that working memory, our ability to temporarily store, process, and manipulate information, is crucial to high-order human behaviour. Within the model there exists dissociable temporary storage systems for verbal (the phonological loop) and visuospatial (the visuospatial sketchpad) information, both of which are under the control of limited capacity coordinating system (the central executive). An additional component, the episodic buffer, which enables coding of information from multiple sensory domains and provides a link to episodic memory, was more recently added to the model (Baddeley, 2000). The multi-component model is based on the fundamental principle that the temporary storage of perceptual information is limited capacity in nature, and as such tasks which draw on this capacity will have a detrimental effect on the ability to complete another task simultaneously. For example, Baddeley and Hitch (1974) demonstrated that holding a string of digits in mind whilst concurrently reading a prose passage reduced performance in the recall of the digits and comprehension of the text suggesting that there was a limited capacity system for the storage and processing of verbal information. Similar results were found for the visuospatial domain in that simultaneous performance of two tasks requiring visual or spatial processing resulted in interference in the performance of both tasks (e.g. Logie et al., 1990). However, the crucial finding from this set of experiments was that when two tasks from separate domains are performed simultaneously, performance remains good

in both tasks suggesting that the verbal and visuospatial components of working memory are dissociable. However, although performance under these conditions was good, it was not as good as performance when completing the tasks in isolation, which suggested that there must be a common resource which has the ability to coordinate and control the functioning of the two sensory stores, i.e. the central executive.

A significant amount of research has led to further fractionation of the phonological loop and visuospatial sketchpad and these constructs are now relatively well characterised (see Repovs & Baddeley, 2006 for a review). By contrast, the central executive has received far less attention. The first inroads into the functions of the central executive were made with the aid of Norman and Shallice's (1986) Supervisory Attentional System which proposed that while many basic human behaviours are governed by environmental cues and occur automatically, novel situations and goal oriented behaviour requires controlled processing which is attentionally demanding. Thus, control of attention has been adopted as the main function of the central executive, and various experiments have been devised to investigate the nature of these attentional processes. Selective (or focussed) attention has been investigated by assessing the effects of random generation on other executively demanding tasks. Random generation tasks require focussed attention to ensure that number or letter sequences are not repeated and inhibit stereotyped responses (Baddeley, 1998). Such tasks when performed concurrently have been found to disrupt syllogistic reasoning (Gilhooly, Logie, Wetherick & Wynn, 1993), mental arithmetic (Logie, Gilhooly & Wynn, 1994) and chess (Robbins et al., 1996). Crucially, concurrent random generation tasks were shown to disrupt performance more than other concurrent tasks designed to disrupt the sensory storage systems (subvocal rehearsal or finger tapping), suggesting that focussed attention demands of the random generation tasks were interfering with the central executive.

The ability to switch attention between relevant tasks has also been postulated to be a function of the central executive although the evidence is less clear cut. Switching tasks such as those which require participants to switch between simple addition and subtraction have been shown to be disrupted by executively demanding tasks such as alternatively saying the days of the week and months of the year or random generation (Baddeley, Chincotta & Adlam, 2001). However, the same study also revealed that performance in an arithmetic switching task was disrupted to the same extent, and more specifically, by articulatory suppression, suggesting that the phonological loop may play a bigger role in task-switching than the central executive. These results were replicated and extended to show that concurrent tapping did not have an effect on arithmetic switching suggesting that the visuospatial sketchpad was not involved in task-switching (Saeki & Saito, 2004). Moreover, an additional finding of the above studies, as well as another investigation (Emerson & Miyake, 2003), was to demonstrate that articulatory suppression only affected task performance in the absence of external switching cues, suggesting the phonological loop may place a crucial role in *maintenance* of the switching programme by preventing decay whereas the central executive is implicated in the *execution* of task switching (Repovs & Baddeley, 2006).

Another proposed capacity of the central executive is divided attention – the ability to split attentional resources so that multiple tasks may be completed simultaneously. This process is described in more detail in the following section and so shall not be discussed here - suffice to say that neuropsychological evidence has demonstrated that patients with Alzheimer's disease present with a specific deficit in the coordination of two tasks despite normal performance when either task is performed in isolation (Baddeley, Logie, Bressi,

Della Sala & Spinnler, 1986). Thus although the multi-component model of working memory has not provided a comprehensive characterisation of executive functioning as it has for the phonological loop and visuospatial sketchpad, it has produced clear evidence for the role of attentional control, and most importantly provided a mechanism by which to assess executive functioning, namely the dual task paradigm (Della Sala, Baddeley, Papagno & Spinnler, 1995).

3.3.2 Anterior attentional functions

The previously mentioned Supervisory Attentional System (Norman & Shallice, 1986) has also provided the basis for more advanced theories of executive functioning. Drawing on data from patients with frontal lobe lesions, Stuss, Shallice, Alexander and Picton (1995) suggested that the SAS could be fractionated and that attentional processes could be differentiated as sustaining, concentrating, sharing, suppressing, switching, preparing, and setting. In addition, Stuss et al. (2005) postulated that each attentional process could be realised by multiple underlying mechanisms. For example, sustaining attention refers to the ability to remain vigilant to events that occur with relative infrequency, and thus requires mechanisms such as monitoring of the events, re-energising of the original response criteria, and inhibition of other irrelevant processes. This process is hypothesised to be a function of right prefrontal cortex as evidenced by patients with right frontal lesions who exhibited poor performance on a vigilance test at slow presentation rates but normal performance at fast presentation rate (Wilkins, Shallice & McCarthy, 1987). Moreover, patients with right anterior lesions have been shown to be impaired on simple continuous performance tests but not complex ones (Cohen et al, 1998).

By contrast, concentrating attention is postulated to be required in highly demanding tasks and instances where rapid responses are necessary. This process is dependent upon mechanisms of energising to enable multiple responses to be prepared as well as inhibition to ensure the appropriate response is activated at the right time. A potential anatomical locus for this process is cited as the anterior cingulate cortex as evidenced by functional imaging studies in which the anterior cingulate has been shown to be activated by high demand conditions such as Stroop interference as opposed to low demand conditions (Bench et al., 1993; Pardo, Pardo, Janner & Raichle, 1990).

Sharing attention in the Stuss et al. (1995) model is similar to the concept of divided attention defined by the multi-component model of working memory except that it extends to instances when two *or more* tasks are carried out simultaneously. As with concentrating attention, sharing attention requires energising mechanisms as two sets of responses must be active at once, and additionally requires monitoring mechanisms to ensure that a balance is maintained between the active response sets. Evidence for frontal lobe involvement in sharing attention has come from patients with frontal lobe lesions and behavioural dysexecutive syndrome who exhibited dual task impairments (Baddeley et al., 1997), suggesting a role for orbitofrontal cortex, and functional imaging studies which have implicated anterior cingulate cortex (Fletcher et al., 1995).

Suppressing attention is required in instances where response sets are automatically activated when they are inappropriate to the goal oriented task, an example of which would be Stroop interference. This process is reliant upon a rule detecting mechanism (so called "if-then logic") and inhibition of the inappropriate response. Stroop tasks have been shown

to be sensitive to patients with dorsolateral lesions whilst those with orbitofrontal damage perform normally (Richer, Décary, Lapierre & Rouleau, 1993; Stuss, Benson, Kaplan, Weir & Della Sala, 1981) suggesting that suppressing attention may be dissociable to specific areas in the frontal lobes. Other potential anatomical loci include the medial prefrontal regions as evidenced by patients who exhibit utilization behaviour and grasp reflex which may reflect an inability to inhibit responses (Shallice, Burgess, Schon & Baxter, 1989).

Switching attention as defined by Stuss et al. (1995) is required when a shift is required from one concept or response to another within a task. It is reliant upon an energising mechanism to activate the to-be-switched-to response as well as subtle inhibitory responses so that the initial response is still ready to be deployed if it is required. Evidence for anatomical localisation has been provided by lesion studies employing the WCST which have implicated the bilateral dorsolateral prefrontal cortex (Milner, 1963), although it is recognised that the WCST is not a "pure" test of switching, and more recent studies have shown that patients with lesions to non-frontal areas can also exhibit WCST impairment (Mukhopadhyay et al., 2008).

Preparatory attention is required when a response must be carried out at a future time point. According to Stuss et al. (1995) this process relies on mechanisms of submaximal activation so that the response can be efficiently energised when triggered by the critical stimulus. The time frame for preparatory attention is in the region of milliseconds to seconds and is most readily applicable to simple reaction time paradigms for which preparatory responses are critical. Patients with Parkinson's disease, and especially those with frontal involvement, have shown slowed reaction times in simple reaction time paradigms whereas choice

reaction times are unimpaired (Goodrich, Henderson & Kennard, 1989; Harrison, Goodrich, Kennard & Henderson, 1993) which suggests that there is a specific deficit when the response parameters are known and can be prepared for. Similar findings have been reported in patients with bilateral dorsolateral lesions (Alivisatos & Milner, 1989) implicating this area in preparatory attention.

The final component in the Stuss et al. (1995) model of anterior attentional functions is setting attention which is defined as selecting the most appropriate response-set over extended periods, and is particularly relevant when multiple response sets have been recently activated. Monitoring and evaluation mechanisms are required to ensure that the appropriate response is activated for the current demands of the task. Patients with traumatic brain injury have been shown to have highly variable performance over time which may reflect impairment in setting attention (Stuss, Pogue, Buckle & Bondar, 1994; Stuss et al., 1989), although by nature these patients have diffuse atrophy which may include frontal lobe pathology, but nevertheless makes predicting potential anatomical loci problematic.

The anterior attentional model has been influential in the investigation of executive functioning as it has fractionated an all-encompassing construct of attentional control into discrete and well defined processes that can be subjected to more stringent investigation. In addition, unlike the multi-component model of working memory, the anterior attentional model has combined cognitive theory with lesion studies and evidence from functional imaging to provide a theory of complex behaviour that has an anatomical grounding, ultimately lending itself to investigation via a variety of techniques. However, other investigators (Miyake et al., 2000; Repovs & Baddeley, 2006) have warned of the dangers

of assuming that cognitive functions map onto cortical locations in a one-to-one nature when there is a greater likelihood that networks of brain regions are responsible for executive processes. Indeed, more recent studies employing neuroimaging and lesion techniques alike have started to come to the consensus that executive functions are not solely dependent on the frontal lobe (see Jurado & Rosselli, 2007 for a review), although few theorists have doubted that the prefrontal cortex plays a fundamental role in executive control.

3.4.3 Statistical models of executive functioning

One of the main debates within the field is whether executive functioning is achieved by a single underlying ability (i.e. unitary), or whether executive functioning can only be achieved by a number of dissociable, albeit related processes (non-unitary). Unitary theories have been developed as a result of data which show that performance in many tests of executive functioning are highly correlated with a factor of general intelligence, or g (e.g. Duncan et al., 1996). However, neuropsychological studies of patients with lesions to different parts of the brain have provided evidence to suggest that different executive processes are localised to specific regions of the frontal lobes (e.g. Burgess & Shallice, 1994; Stuss et al., 1995). The question of unitary versus non-unitary was addressed by Miyake and colleagues (2000) in a study which utilised latent variable analysis in a large cohort of healthy individuals to investigate the independence of three of the most commonly postulated executive functions, namely shifting, updating, and inhibition. This was achieved by developing and employing 9 tasks; 3 of which were specifically designed to isolate switching processes, 3 were designed to isolate updating processes, and 3 were designed to isolate inhibition processes. In addition, 5 complex tasks commonly used to assess executive functioning were also administered, namely the Wisconsin Card Sort Test, the Tower of

Hanoi, Random Number Generation, Operation Span, and a Dual Task. The authors reported that the 9 tests designed to tap specific processes showed convergent and discriminant validity as significant correlations were present between tasks in the same domain (e.g. shifting), but only small correlations were revealed between tasks designed to assess different domains. Several statistical models were subsequently developed to investigate which would explain data from all the tests with the greatest accuracy. The first was a full 3 factor model of shifting, updating, and inhibition each containing 3 of the 9 tests as described above. The second was a single factor model which assumed that all 9 tests were equally related to a unitary executive construct. In addition, several 2 factor models containing combinations of shifting updating and inhibition were created to assess whether any 2 of the factors overlapped. Miyake et al. (2000) reported that the data were best explained by the 3 factor model suggesting that shifting, updating, and inhibition were independent processes. Moreover, although correlations between the 3 factors were moderate, none of the confidence intervals contained a 1.0 correlation indicating that the factors were related but dissociable. Finally, the authors also carried out Structural Equation Modelling on the 5 complex tasks of executive functioning to see which of the 3 factors contributed most to performance in these tasks. It was reported that shifting contributed to the WCST, inhibition to Tower of Hanoi, inhibition and updating to Random Number Generation, and updating to Operation span. By contrast, none of the 3 factors contributed significantly to performance on the Dual Task suggesting that this type of task may represent a different type of executive process.

The findings of Miyake et al. (2000) were replicated in a group of older adults by Fisk and Sharp (2004). They reported the same dissociations between commonly used measures of executive functioning which appeared to load on the same underlying factors of shifting,

updating and inhibition as proposed by Miyake et al. (2000). However, Fisk and Sharp (2004) also reported an additional factor which determined performance on verbal fluency tests, suggesting that these tests may tap into a separate executive function that is associated with access to long-term memory. Moreover, this factor was the only one which was shown to be independent of age-related decline in processing speed. Thus, the approach to investigating executive functioning adopted by Miyake et al., (2000) and Fisk & Sharp (2004) has demonstrated the importance of using multiple tests to assess a purported executive process. It is only by examining the combined data from multiple tests that inferences can be made regarding the underlying functions, although the validity of the findings is still dependent upon the success of the underlying tasks in tapping into the target executive processes. Moreover, these studies have highlighted the importance of testing the construct validity of commonly used tasks of executive functioning.

3.4 Dual tasking

The ability to perform two tasks concurrently is highly valuable in everyday life, humans routinely engage is dual task like behaviours whether it be driving and talking or listening while note-taking. Much of the research into dual tasking has stemmed from the model of working memory proposed by Baddeley and Hitch (1974). It has been postulated that dual tasking is a function of the "central executive", a cognitive construct which allows the coordination of visual and auditory sensory "slave" systems (Della Sala, Baddeley, Papagno & Spinnler 1995; Baddeley, 2000, Engle, 2002). However, it has also been argued that slowed processing speed can affect dual task performance because of the added processing stages required to carry out two tasks instead of one (Somberg & Salthouse, 1982; Salthouse, Fristoe, Lineweaver & Coon, 1995). A typical dual task format requires participants to perform two cognitive tasks, initially separately in the single task condition.

Participants are subsequently required to perform the same two tasks concurrently – the dual task condition. Any decrease in performance in either task between single task and dual task conditions can then be calculated and represented as dual task cost – that is the cost associated with performing two tasks concurrently.

3.5 Dual tasking, aging, and dementia

Dual tasking ability has been investigated in several patient populations, and it has been proposed that a specific dual task deficit exists in Alzheimer's disease (Logie, Cocchini, Della Sala & Baddeley, 2004), although other degenerative disorders such as Multiple Sclerosis and Parkinson's disease have shown dual task decrements when one of the concurrent tasks is a motor task (e.g. walking and talking in MS; Hamilton et al., 2009, tracking and digit span in PD; Dalrymple-Alford, Kalders, Jones & Watson, 1994). The only study investigating dual tasking in ALS also reported a deficit (Schreiber et al., 2005), however, the outcome measure in this case was reaction time and so may have been a manifestation of motor impairment rather than a dual task deficit *per se*. Indeed, methodological issues in dual task paradigms are contentious, and appear to underlie much of the debate in the literature concerning whether dual task performance decreases across the lifespan. Many studies have suggested that although there may be a small speed or accuracy cost associated with performing two tasks concurrently, in general, healthy young adults are able to perform relatively well in both tasks (Cocchini, Logie, Della Sala, & MacPherson, 2002; Della Sala, Foley, Beschin, Allerhand, & Logie, 2010), provided the constituent tasks do not involve the same sensory input. However, in terms of healthy ageing, the literature is less consistent with some authors reporting a disproportionate dual task decrement in older adults, whereas others report that older adults perform comparably with their younger counterparts (Baron & Mattila, 1989; Batsakes & Fisk, 2000; c.f. Logie

et al., 2004; MacPherson, Della Sala, Logie and Wilcock, 2007; Anderson, Bucks, Bayliss & Della Sala, 2011).

The inconsistencies in the dual tasking literature have resulted in the development of several theories to explain the observed effects (or lack thereof). For example, Task-Switching models propose that concurrent tasks may be processed in parallel, however only one task can have access to the response-selection mechanism. The prediction of such a model is that dual task conditions will delay the onset of the secondary task until the primary task is near completion (Pashler, 1994). This should be especially prevalent when tasks are performed at short Stimulus Onset Asynchronies (SOAs,) as the need for the processing resource will inherently overlap to a greater extent. Studies manipulating the delay (SOA) between the primary and secondary tasks have reported age-effects (Allen, Smith, Vires-Collins & Sperry 1998) suggesting that older adults may experience a time-sharing impairment, an effect that seems to be magnified when the response to both tasks is in the same sensory modality (Hartley & Little, 1999). In related studies, it has been suggested that older adults are more cautious and show a lack of flexibility when switching attentional resources in dual task paradigms (Korteling 1991; Batsakes and Fisk, 2000), although this was not reproduced by other studies (Salthouse, Rogan & Prill, 1984; Crosseley & Hiscock, 1992).

Capacity-Sharing models propose that there is a limited processing resource available for any given task, so that when a secondary task is concurrently presented, some of that resource must be directed away from the primary task and hence responding is slowed or hindered (e.g. Kahneman, 1973). This model predicts worse performance as task complexity increases, as each constituent task will demand more of the limited processing resource. It

has been assumed that age effects reported in dual tasking are a result of a decline in resource capacity (Hartley & Little, 1999). Indeed, several studies have shown that increasing the complexity of the constituent tasks results in a greater age effect (Wright, 1981; Lorsbach & Simpson, 1988), however, a meta-analysis reported that age-related decline in dual tasking was independent of task complexity (Verhaegen, Steitz, Sliwinski & Cerella, 2003). Moreover, Salthouse and Somberg (1982) demonstrated that controlling single task difficulty by titrating the tasks to individual ability level attenuated any age effect in dual task conditions. However, the authors argued that dual task decrements may be due to a decrease in older adults' *speed* of processing in single tasks rather than a decline in processing *capacity*. Thus, when single task ability is controlled for, dual task decrement may be substantially less than expected although a subsequent study suggested that this was not the case for more complex tasks (Salthouse et al., 1984). Furthermore, it has been asserted that the combined cost of the two component tasks under dual task conditions is a better representation of dual task cost as it controls for strategic prioritizing of one task over the other (Salthouse et al., 1995).

Single task titration has also been adopted in studies which have used dual task paradigms to investigate the models of working memory. Such studies have shown that if single tasks are titrated, healthy adults have the ability to perform simultaneous verbal and visuospatial working memory tasks (Cocchini, Logie, Della Sala, MacPherson & Baddeley, 2002), with relatively small dual task costs. The authors suggest that this is indicative of domain-specific working memory systems encompassing discrete storage and processing resources. Moreover, it has been suggested that the coordination of these independent resources is a function of the central executive, and that the modest dual task cost observed in the data may reflect the additional demand placed upon this system under dual task conditions (Duff

& Logie, 2001; Cocchini et al., 2002). Further evidence for executive control in dual task paradigms has been produced by studies into Alzheimer's disease (AD). It has been shown that AD patients have a specific deficit in dual tasking, even when both component tasks are set below individuals' titrated ability level suggesting that there is a specific problem with task coordination rather than overall load of the tasks (Logie et al., 2004). This claim was strengthened by data which showed that AD patients' dual task performance was not differentially worse than controls when demand was increased in one of the tasks suggesting that overall cognitive load was not the causal factor in the observed dual task deficit.

An interesting problem can be derived from the findings of dual task sensitivity in AD which is characterised by episodic memory impairment and medial temporal lobe atrophy in the early stages before progressing to predominant bilateral parietal, temporal and limbic atrophy (Perry & Hodges, 2010; Sebastian-Gascon & Hernandez-Gill, 2010). However, dual tasking is assumed to be a function of the central executive or SAS, disruption of which is normally associated with lesions to frontal areas (Baddeley et al., 1997). Some functional imaging studies have shown that dual task performance is associated with specific areas of the frontal lobes; for example, dorsolateral and prefrontal cortex and anterior cingulate show increased activity during dual task conditions for tasks which predominantly activate posterior regions when performed in isolation (D'Esposito et al., 1995), whereas a meta-analysis suggested that dual task manipulations are most frequently associated with right inferior prefrontal cortex (Wager & Smith, 2003). By contrast, some investigations have shown that dual tasks simply impose higher processing demands on cortical areas already involved in the component single tasks, i.e. no additional areas are recruited under dual task conditions (Adcock et al., 2000; Klingberg, 1998), and others have shown that dual tasks can be completed in the absence of any prefrontal involvement when dual task costs are low

(Smith et al., 2001). Results of this nature would suggest that dual tasking is achieved by the communication between brain networks and suggest that executive functioning may be an emergent property of this interplay between regions (Collette & Van der Linden, 2002). This theory lends itself well to the findings in Alzheimer's disease, as dual task deficits and other executive impairments can be explained in terms of a disconnection syndrome that disrupts effective communication between disparate brain regions (Delbeuck, Van der Linden & Collette, 2003).

Dual tasking has been investigated using a variety of component tasks such as; visual search and auditory detection (Broadbent & Heron, 1962), digit span and verbal reasoning (Wright, 1981), tone detection and sequential digit keying (Somberg & Salthouse, 1982), pursuit tracking and forced-choice tone identification (McDowd, 1986), rotary pursuit and choice reaction time (Ponds, Brouwer & van Wolffelaar, 1988), and dot location and tone discrimination (Allen et al., 1998). However, working memory tasks (e.g. Digit Span) are amongst the most commonly used in dual task paradigms (Baddeley & Hitch; 1976; McDowell, Whyte & D'Esposito, 1997; Baddeley, Della Sala, Papagno & Spinnler, 1997; Logie et al., 2004), along with a secondary task from a different sensory domain (e.g. Spatial Span, Cocchini et al., 2002; Macpherson, Della Sala, Logie & Wilcock, 2007) or a simple perceptuomotor task (e.g. Tracking; Baddeley et al., 1991; Della Sala et al., 1995). As such, a common dual task scenario is to test working memory and psychomotor speed concurrently. The use of secondary motor and reaction time tasks may explain some of the inconsistencies in the dual task and ageing literature; it is well documented that movement times and reaction times are affected by ageing (Brian and Luszcz, 1996; Salthouse, 1996; Salthouse, 1998), and an age effects are evident in dual task paradigms which employ concurrent motor tasks (Ponds, Brouwer & van Wolffelaar, 1988). Certainly, the use of such

paradigms would not be suitable for the current study given the motor impairments that characterise both disorders.

The current study aimed to investigate the effect of attention and processing speed on executive functioning in ALS and MS by investigating both processes within a dual task paradigm. Digit Recall was chosen as the attentional measure in the current study as it is considered a measure of short-term memory or attention and has minimal motor demands. Visual Inspection Time (VIT as described previously) was chosen as the processing speed measure as it impinges upon the visuospatial domain and thus, according to multi-component model of working memory, should not cause any interference with processing of the auditory Digit Recall task. As described previously, the VIT task has the added advantage of assessing processing speed, independently of motor speed. However, stereotypical dual task paradigms are still likely to put high demands on response selection and initiation as behavioural responses are made in parallel and thus can result in interference, especially in populations with motor difficulties. For this reason a "preload" methodology (as described in Cocchini et al, 2002) was utilised. The preload dual task procedure has three stages; first participants attend to and encode the primary memory task (in this case Digit Recall), then complete the secondary task of choice (in this case VIT), and finally recall the information from the primary task. Using a preload paradigm over comes the problem of response interference as responses are required in a serial manner. Nevertheless, *cognitive* demand must remain concurrent to allow information from the primary task to be maintained during performance of the secondary task so that is available for subsequent recall.

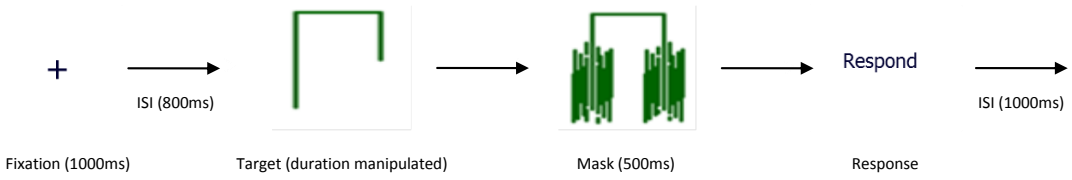
3.6 Methods

3.6.1 Experimental Task 1 – Visual Inspection Time (VIT)

In this task (adapted from Edmonds et al., 2008), participants were required to make a forced choice decision regarding an abstract visual stimulus presented briefly on a computer screen. Participants were first presented with a fixation cross on the middle of the screen (1000ms duration). An interstitial stimulus interval (ISI) of 800ms preceded the target stimulus; a simple geometric figure with a clearly elongated "tail" on either the left or right side. The target stimulus was then replaced by a mask (500ms duration) which obscured which side of the tail figure was longer. Finally participants were presented with a cue to "respond" – they were required to indicate whether they saw a longer tail on the right or left side of the stimulus figure. Responses could be made manually by using specially designed buttons applied to the keyboard, or verbally. Only response accuracy was recorded. An ISI of 1000ms preceded the start of each trial. Before the test procedure, all participants were given 9 practice trials of gradually increasing difficulty (3 x 400ms target stimuli, 3 x 150ms target stimuli, 3 x 68ms target stimuli) in which they were given feedback (with the word "correct" or "incorrect" presented for 1500ms) after each trial. During the test procedure, participants did not receive feedback, and the duration time of the stimulus was manipulated in a fixed pseudorandom order at durations of 150ms, 125ms, 102ms, 85ms, 68ms, 51ms, 34ms, and 17ms, requiring faster processing to respond accurately. A total of 80 trials were completed (10 at each stimulus duration), thus the maximum number of errors possible was 80. The target stimulus was an inverted u-shape that was 25 mm across the top, 50 mm on the long leg and 25 mm on the short leg. The mask was a similar shape, but larger than the stimulus, and included an irregular array of vertical lines in order to cover the long and short stimulus lines completely. The mask was 25 mm across the top, both legs were 55 mm long and each leg was 14 mm wide at the widest point. The VIT task was presented on a laptop

with a screen refresh rate of 17ms and participants viewed the display at 45cm from the screen. A schematic of the VIT task procedure is displayed in Figure 1.

Figure 1. Schematic of VIT task

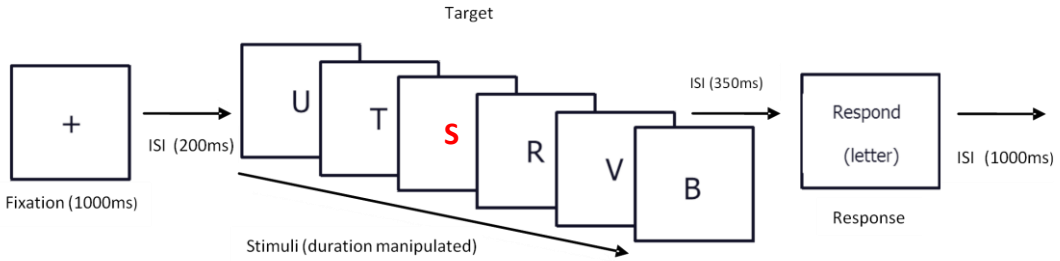


3.6.2 Experimental task 2 – Rapid Serial Letter Identification (RSLI)

In this task (adapted from Hoffman, 1978) participants were presented initially with a fixation cross (1000ms duration), followed by an ISI of 200ms and then the rapid presentation of the stimuli; a sequence of six consecutive letters. Five of the letters within the stream were black, and one, the target, was red. There were no ISI's between any of the letters in a sequence. After the letter stream, an ISI of 350ms preceded a cue to "respond" and participants were required to identify the target letter verbally. The target letter was presented randomly in positions 2, 3, 4, or 5 and could be any letter of the alphabet excluding "O" or "I". An ISI of 1000ms preceded the following trial. Before the test procedure, all participants were given 10 practice trials of gradually increasing difficulty (2 x 800msstimuli, 2 x 400ms stimuli, 2 x 200ms stimuli, 2 x 85ms stimuli, 2 x 68ms stimuli) in which they were given feedback (with the word "correct" or "incorrect", presented for 1500ms) after each trial. Processing speed was investigated by manipulating the duration of the presentation of the letter stimuli in any one sequence; duration time was manipulated in

a fixed pseudorandom order and letters could be displayed for 150ms, 125ms, 102ms, 85ms, 68ms, 51ms, 34ms, or 17ms. There were 40 trials in total (5 at each duration), thus the maximum number of errors possible was 40. All letters within any one trial had the same duration time. Letter size was approximately 10mm by 10mm (bold Arial font size 18).The RSLI task was presented on a laptop with a screen refresh rate of 17ms and participants viewed the display at approximately 45cm from the screen. A schematic of the RSLI task is displayed in Figure 2.

Figure 2. Schematic of the RSLI task



3.6.3 Dual task ageing study

Before the dual task developed by the current investigation was employed in the patient cohorts, a preliminary study was administered in healthy adults. A similar paradigm to the one employed in the current study has been used to investigate dual tasking in ageing (Anderson et al, 2011) which showed no disproportionate age-effects in dual task cost. However, the authors did not have a middle-aged group in their study. As the patients in the current investigation were likely to be aged between 25 and 80, it was anticipated that the matched control group would also encompass this age range. Therefore, an ageing study

was set up to investigate dual task performance in the newly developed paradigm in three age groups (young, middle, and older) to investigate whether there could be a disproportionate dual task cost in patients or controls of a certain age. As the dual task paradigm employed a novel procedure, a pilot study was conducted in healthy young adults, the results of which informed the final procedure described below. A full description of the pilot study is presented in Appendix D.

3.6.3.1 Participants

Participants were recruited either through the University of Edinburgh's volunteer participant panel or through friends and families of the researchers. Cognitive assessment of healthy controls in university premises was reviewed and given favourable opinion by the University of Edinburgh PPLS Ethics Committee (Title: "Processing speed and dual task ability in younger and older adults", reference number: 148-0910). Twenty-five participants were recruited for each of the following age groups: Young = 18 – 35, Middle = 36 – 64, and Older = 65 – 85.

3.6.3.2 Background measures

Wechsler Test of Adult Reading (WTAR; Wechsler, 2001)

The WTAR was employed as a measure of pre-morbid intelligence. The number of errors was recorded and converted into a predicted full scale Intelligence Quotient (IQ) score.

3.6.3.3 Experimental task 3 – dual task

Executive functioning was investigated by way of a dual task paradigm which employed VIT as one of the tasks, and delayed digit span as the other. A similar paradigm has been used to investigate dual task ability, without the confounds of reaction time based tasks, in children and older adults (Anderson et al., 2011). The dual task employed a preload paradigm (Cocchini et al., 2002) as typical concurrent dual task paradigms are likely to put high demands on response selection and initiation and thus result in interference, especially in populations with motor difficulties. All participants completed the dual task procedure in the same order as follows:

1. Baseline Delayed Digit Recall (DDR) level

An individual's baseline DDR level was determined by presenting them with increasing sequences of numbers to recall until maximum capacity was established. All participants started with trials containing a sequence of two digits, and were given three trials at each sequence length. Participants were presented with digits aurally at a rate of one per second, and asked to recall them after a fifteen second delay. If 2 out of 3 trials were completed accurately then the number of digits per sequence was increased incrementally, one digit at a time. Baseline DDR level was taken as the maximum number of digits recalled accurately in at least 2 out of 3 trials.

2. Baseline Visual Inspection Time (VIT) level

Participants completed VIT trials of decreasing stimulus duration until their own maximum level of ability was established. Before the test procedure, all participants were given 9

practice trials of gradually increasing difficulty (3 x 400ms, 3 x 150ms, 3 x 68ms) in which they were given feedback ("correct" or "incorrect") after each trial. During the titration procedure the VIT stimuli were presented at increasingly shorter durations (150ms, 125ms, 102ms, 85ms, 68ms, 51ms, 34ms, and 17ms). Six VIT trials were presented at each stimulus duration – if participants responded accurately to at least five, they moved on to the next shortest duration. The stimulus duration time at which participants failed to reach the accuracy criterion (5 out of 6 trials correct) was taken as their baseline VIT level.

3. Delayed Digit Recall single task

Participants completed the DDR single task with sequences that had one less digit than their baseline DDR level – for example if baseline level was found to be 7 digits, they would be presented with sequences of 6 digits. This procedure was adopted as the results of a pilot study in young adults indicated that performing the dual task at maximum ability was overly difficult. Digit sequences were presented, and a 15 second delay preceded a cue to recall. Each participant completed a total of 8 trials. The number of digits correctly recalled from each sequence was added up across all trials, and this was represented as a percentage of the total number of digits presented to give the DDR single task performance as follows:

$$\text{DDR \% correct} = \frac{\text{Number of digits recalled correctly}}{\text{Total number of digits presented}} \times 100$$

4. VIT single task

Participants completed the VIT single task with durations one step slower their baseline VIT level – for example if baseline level was found to be 17ms, they would be presented with trials of 35ms. This procedure was adopted as the results of a pilot study in young adults indicated that performing the dual task at the maximum ability was overly difficult. Participants were presented with 8 blocks of VIT trials, each block lasting 15 seconds and containing as many trials as would fit in that period. The number of accurate responses produced was taken as a measure of performance and represented as a percentage of the total number of trials to give the VIT single task performance as follows.

$$\text{VIT \% correct} = \frac{\text{Number of VIT trials correct}}{\text{Total VIT trials completed}} \times 100$$

5. Preload Dual Task (Delayed Digit Recall interleaved with VIT trials)

A schematic of the preload dual task procedure is presented in Figure 3. During any one trial, participants were presented with digit sequences, followed immediately by 15 seconds of VIT trials (digit sequence length and VIT durations were the same as in the single tasks). A cue was then presented to prompt recall of the digit sequence. Participants completed 8 trials so that the total number of digit items and VIT items completed was equivalent to that of the single tasks. Performance in each task was measured in the same way as described in the single task conditions above to give DDR and VIT percentage correct scores under dual task conditions. A measure of dual task cost was then produced by calculating the

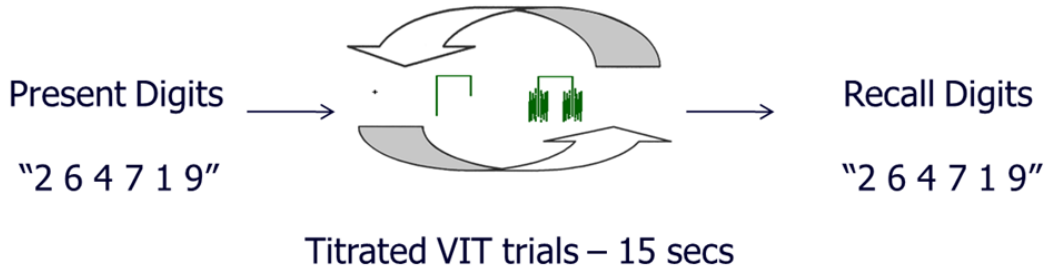
percentage change in performance between the single task conditions and dual task conditions as follows:

$$\text{Dual Task Cost (\% change)} = \frac{\text{Dual task \% correct} - \text{Single-task \% correct}}{\text{Single task \% correct}} \times 100$$

The average cost of the two component tasks under dual task conditions is a better representation of dual task cost as it controls for strategic prioritizing of one task over the other (Salthouse et al., 1995). Thus average scores were also produced for dual task cost as follows:

$$\text{Average \% change} = \frac{\text{DDR \% change} + \text{VIT \% change}}{2}$$

Figure 3. Schematic of preload dual task



3.6.3.4 Statistics

The cognitive data were explored for normal distribution using histograms, boxplots and the Shapiro-Wilk's test of normality. In addition, all variables were checked for homogeneity of variance. Group differences were explored by one-way ANOVA's. Planned post-hoc group comparisons with Tukey's HSD or Games-Howell corrections (for unequal variances) are reported for any variables in which there were significant group differences.

3.7 Dual task ageing study results

Demographic data for the participants are displayed in Table 8. A significant difference was found in the Years of Education between groups; $F(2, 72) = 5.179$, $p = 0.008$. Planned post-hoc comparisons revealed that the difference between Young and Middle participants was not significant, although Older participants had significantly fewer years of education than the Middle participants ($p = 0.025$), but not Young participants. However, there was no significant group differences in terms of the WTAR scores; $F(2, 72) = 2.003$, $p = 0.142$, suggesting that in fact the groups were well matched in terms of intelligence.

Table 8. Ageing study group demographics

	Young	**Middle**	**Older**
Year of Educ.	16.2 (1.3)	17.3 (3.0)	14.7 (3.6)
WTAR IQ	109.6 (12.1)	107.4 (10.3)	113.4 (9.7)

Mean values with standard deviations in parentheses are presented. WTAR = Wechsler Test of Adult Reading predicted full scale IQ.

Participants' baseline level of performance in the component tasks are displayed in Table 9. There were no significant group differences in the DDR level; F (2, 72) = 0.748, p = 0.477, suggesting that the ability to maintain digit sequences in mind was equal across the age groups. However, a significant group difference was revealed in the VIT level; F (2, 72) = 21.284, p = 0.000. Planned comparisons revealed that Older participants were significantly slower than Middle participants (p = 0.001) and Young participants (p = 0.000), and in addition, Middle participants were significantly slower than Young participants (p = 0.018) indicative of a linear decrease in processing speed with age.

Table 9. Ageing study baseline task performance levels

	Young	**Middle**	**Older**
DDR Level (digits)	5.8 (1.1)	5.4 (1.1)	5.6 (1.3)
VIT Level (ms)	54.4 (15.5)	70.3 (19.9)	91.3 (23.9)

Mean values with standard deviations in parentheses are presented. DDR = Delayed Digit Recall, VIT = Visual Inspection Time, ms = milliseconds.

Participant performance in the single-task and dual task conditions is displayed in Table 10. There was no significant difference between the groups in terms of DDR single task performance; F (2, 72) = 1.401, p = 0.253. However, there was a significant group difference in VIT single task performance; F (2, 72) = 5.285, p = 0.007. Planned comparisons revealed that Older participants performed significantly worse than the Middle (p = 0.013) and Young (p = 0.023) participants, although there was no difference between Middle and Young participants.

Table 10. Ageing study single task and dual task performance; percentage correct scores

	Young	**Middle**	**Older**
DDR Single	97.5 (3.9)	98.1 (4.2)	96.1 (4.7)
VIT Single	95.0 (5.3)	95.3 (3.5)	91.4 (5.4)
DDR Dual	94.4 (7.4)	93.7 (9.7)	89.0 (7.0)
VIT Dual	89.3 (9.4)	84.5 (12.6)	83.1 (7.2)

Mean values with standard deviations in parentheses are presented. DDR = Delayed Digit Recall, VIT = Visual Inspection Time

Details of the dual task costs incurred by the groups are presented in Table 11. The mean percentage change scores demonstrate that all groups experienced a modest drop in performance under dual task conditions. However, no significant group differences in dual task cost were observed in DDR; $F(2, 72) = 1.578$, $p = 0.213$, VIT; $F(2, 72) = 1.739$, $p = 0.183$, or in the Average Dual Task Cost across both tasks; $F(2, 72) = 2.066$, $p = 0.134$. This result indicated that although group differences were observed in performance in the single-task condition, the *relative* drop in performance between single and dual task conditions was not significantly affected by age.

Table 11. Ageing study dual task cost; percentage change scores

	Young	Middle	Older
DDR cost	3.2 (7.7)	4.5 (9.6)	7.3 (7.5)
VIT cost	6.1 (7.0)	11.3 (13.2)	8.9 (8.1)
Average cost	4.7 (6.3)	7.9 (7.9)	8.1 (5.7)

Mean values with standard deviations in parentheses are presented. DDR = Delayed Digit Recall, VIT = Visual Inspection Time

3.8 Dual task ageing study summary

The ageing study revealed that all participants experienced a dual task cost associated with completing the component tasks in the dual task condition compared to the single task conditions. However, there was no disproportionate drop in performance in either the middle-aged or older adults compared to the younger adults. As such, this study is consistent with the findings of others employing preload dual task methodology (Cocchini et al., 2002; MacPherson et al., 2007) and concurrent dual task methodologies (Logie et al., 2004; Anderson et al., 2011) in suggesting that there is not an age-effect in dual tasking when performance in the component single-task are titrated. This is a beneficial finding for the application of the dual task procedure in degenerative disorders as age effects are unlikely to be a factor in any observed differences between patient and control groups. In addition, the fact that participants were able to perform a processing speed task, at or close to their maximum ability, concurrently with another task without suffering from a substantial performance decrement suggests that processing speed tasks do not interfere with dual task coordination.

Chapter 4. Experimental tasks; ALS patients versus healthy controls

The following chapter investigated the performance of ALS patients compared to healthy controls in the three experimental tasks described previously in Chapter 3, namely the VIT and RSLI tasks which assessed processing speed, and the dual task which assessed executive functioning.

4.1 Participants

ALS and matched healthy control participants were the same as described in Chapter 2 (Sections 2.2.1 and 2.2.3), and group demographics are the same as reported in Section 2.4.1.

4.2 Methodology

The VIT and RSLI processing speed tasks were administered as described in Chapter 3 (Sections 3.6.1 and 3.6.2 respectively). The dual task procedure was also the same as that described in Chapter 3 (Section 3.6.3.3). The same study protocol was employed in all participants whereby the dual task was performed near the start of the testing session, followed immediately by the RSLI task and then shortly by the VIT task (see Protocol, Appendix E). Experimental tests were performed near the beginning of the testing sessions to maximise data collection in the event of participant fatigue.

4.3 Statistical analyses

The data were explored for normal distribution using histograms, boxplots and the Shapiro-Wilk's test of normality. In addition, all variables were checked for homogeneity of variance. Not all ALS patients completed the VIT and RSLI tasks (see Table 12 for exact participant numbers); some patients were unable to complete some tests due to fatigue or time pressures. Comparative group analyses were performed using t-tests in normally distributed data and Mann-Whitney U tests in populations that were not normally distributed. In the ALS group, case analyses were also employed in which standardised scores (Z-scores) for individual ALS patients were derived from the mean and standard deviation of the healthy control group – individuals with scores that fell below 2 standard deviations of the control group mean were considered to be impaired. Correlational analyses in the ALS group were performed between experimental and standardized neuropsychological tests with Pearson's *r* in parametric variables and Spearman's *rho* in non-parametric variables.

4.4 Results

4.4.1 Processing speed

Details of participant's performance in the processing speed tasks are shown in Table 12. An examination of the group means shows that ALS patients and controls performed comparably in the VIT task and the RSLI task; indeed no significant differences were observed between the groups in terms of the amount of errors made on either task. The results indicate that ALS patients did not exhibit slowed processing speed in the identification of either abstract or meaningful visual information. Calculation of Z-scores in the ALS group revealed that only 1 patient had a score that fell below 2 standard deviations

of the control group mean in the VIT, and the same result was observed in the RSLI task. Different individuals were impaired in the respective tasks.

Table 12. Processing speed data for ALS patients and healthy controls

	n (ALS:HC)	**ALS**	**HC**	***t or U***	***p value***
VIT (errors)	25:29	13.5 [8.0] (0 – 38)	12.9 [7.6] (4 – 37)	-0.565 (*U*)	0.572
RSLI (errors)	28:30	16.4 [3.9] (9 – 24)	15.8 [3.1] (9 – 24)	0.648	0.520

Mean values with [standard deviations] and (ranges) in parentheses are presented. Ratios are presented for number of patients versus controls in each task. VIT = Visual Inspection Time (max. errors = 80), RSLI = Rapid Serial Letter Identification (max. errors = 40).

4.4.2 Dual task

Details of participant performance in the baseline DDR and VIT levels are displayed in Table 13. Comparative analyses revealed that ALS patients and controls performed comparably in baseline levels in both the DDR and VIT tasks, suggesting that the ability to maintain digit sequences in mind and the speed at which visual information could be processed was equal to healthy controls. Z-scores in the ALS group revealed that no patients were impaired in the DDR baseline task, whilst only one patient met this criterion in the VIT baseline task.

Table 13. Baseline task performance levels for ALS patients and healthy controls

	n (ALS:HC)	ALS	HC	*U*	*p value*
DDR baseline (digits)	29:30	5.5 [1.1] (4 – 8)	5.8 [1.0] (4 – 7)	1.187	0.235
VIT baseline (ms)	29:30	60.9 [23.9] (34 – 150)	62.3 [18.6] (34 – 102)	0.679	0.497

Mean values with [standard deviations] and (ranges) in parentheses are presented. Ratios are presented for number of patients versus controls in each task. VIT = Visual Inspection Time, DDR = Delayed Digit Recall, ms = milliseconds.

Participant performance in the single-task and dual task conditions is displayed in Table 14. The means show that ALS patients and healthy controls performed similarly under single task conditions whereas under dual task conditions ALS patients were less accurate than controls. Indeed, comparative analyses revealed that there was no significant difference between the groups in terms of DDR single-task performance (U = -0.78, p = 0.433) or VIT single task performance (U = 0.48, p = 0.631).

Table 14. Single and dual task performance: percentage correct for ALS patients and healthy controls

	n (ALS:HC)	ALS	HC
DDR Single	29:30	97.2 [4.7]	96.4 [4.6]
		(83 - 100)	(88 – 100)
VIT Single	29:30	89.4 [10.8]	90.8 [9.3]
		(56 - 100)	(59 – 100)
DDR Dual	29:30	91.7 [10.2]	94.0 [6.7]
		(73 – 100)	(73 – 100)
VIT Dual	29:30	81.8 [13.3]	87.6 [10.3]
		(56 – 100)	(63 - 100)

Mean values with [standard deviations] and (ranges) in parentheses are presented. Ratios are presented for number of patients versus controls in each task. VIT = Visual Inspection Time, DDR = Delayed Digit Recall.

Percentage change scores are a more accurate reflection of the cost associated with performing two tasks concurrently than percentage correct scores. An examination of the mean percentage change scores (displayed in Table 15 below) indicates that ALS patients experienced greater Dual Task Costs than healthy control participants in both the DDR and VIT tasks, however, these differences did not reach statistical significance. Crucially, comparative analyses of the Average Dual Task Cost revealed significant differences between ALS patients and healthy controls suggesting that ALS patients *did* exhibit impaired dual task performance. Indeed, the mean percentage change scores show that patients exhibited a drop in performance from single to dual task that was more than twice that of controls. Z-scores in the ALS group indicated that 9 patients were impaired in terms

of DDR Dual Task Cost, with 1 further patient showing impairment in VIT Dual Task Cost. In terms of the Average Dual Task Cost, Z-scores revealed that 3 patients met the criteria for impaired performance.

Table 15. Dual Task Cost: percentage change for ALS patients and healthy controls*

	n (ALS:HC)	**ALS**	**HC**	***t or U***	***p value***
DDR Dual Task Cost	29:30	5.6 [10.5] (-21 – 25)	2.5 [5.3] (-5 – 20)	-1.007 (*U*)	0.314
VIT Dual Task Cost	29:30	8.3 [11.4] (-15 – 32)	2.6 [14.5] (-40 – 36)	1.661	0.102
Average Dual Task Cost	29:30	6.9 [7.2] (-5 – 22)	2.5 [7.7] (-20 – 17)	2.240	**0.029**

Mean values with [standard deviations] and (ranges) in parentheses are presented. * Significant results are highlighted in bold. Ratios are presented for number of patients versus controls in each task. VIT = Visual Inspection Time, DDR = Delayed Digit Recall.

4.4.3 Correlations with standardised neuropsychological tests

Associations between performance in each experimental task (VIT errors, RSLI errors, and Average Dual Task Cost) and the standardised neuropsychological tests employed in Chapter 2 were performed; no significant correlations were observed for any experimental measure. In addition, there were no significant correlations between any of the experimental tasks themselves.

4.5 Summary

ALS performance in the experimental tests showed a clear dissociation between intact performance in the processing speed tasks, and impaired performance in the executively demanding dual task. The ALS group showed no evidence of impairment in either the VIT or RSLI task, in fact performance in both tasks was almost identical to that of healthy controls, suggesting that processing speed for visually presented information was normal. Inspection time tasks have been shown to be sensitive to slowed processing speed in healthy ageing (Gregory et al., 2009) and subcortical dementias such Parkinson's disease (Johnson et al., 2004) with the suggestion that impaired inspection time ability is a reflection of slowed processing speed in early or low-level cognitive functions. The RSLI task was employed as an extension of the inspection time paradigm to investigate processing speed for meaningful verbal information. Both tests assessed processing speed by manipulating stimulus duration, and as such account for motor disability with untimed responses. The results of the current investigation suggest that reports of slowed reaction times in tasks of visuoperceptual speed such as digit cancellation and visual search tasks (Gallassi et al., 1985; Chari et al., 1996) may not be a reflection of slowed processing speed in ALS, but rather may simply reflect a compromised motor system as such paradigms place considerable demand on the motor (hand) functions. Similarly, previous reports of impairments in traditional tests of processing speed such as the SDMT (Massman et al., 1996; Messapesa et al., 2007), TMT (Hanagasi et al., 2002; Witgert et al., 2010), and PASAT (Moretti et al., 2002) are unlikely to reflect a slowing of cognitive processing in ALS. Instead, poor performance in these tasks is more likely to be a manifestation of impairments in executive processes such as working memory, and the ability to shift or divide attention, which have also been implicated in these complex tasks (Robertson et al., 1996; Bate et al., 2001; Sanchez-Cubillo et al., 2009). Thus, the current findings suggest

that studies which report deficits in psychomotor speed (see Raaphorst et al., 2010 meta-analysis) are most likely a reflection of motor impairment rather than cognitive slowing, and that ALS patients *are* able to process simple visual information at a normal rate. Processing speed, when isolated from motor functioning and other high-order processes, is not impaired in ALS patients and does not contribute to other observed cognitive impairments.

In contrast, ALS patients exhibited a selective deficit in dual task performance; the accuracy cost incurred by performing two tasks concurrently was more than twice as high in patients compared to healthy controls. The component tasks were matched to each participant's baseline level so that a dual task effect could not be the result of single task difficulty (Anderson et al., 2011). No group differences were found in terms of the baseline levels on either the DDR or VIT task indicating that ALS patients were able to perform as well as healthy controls; this was confirmed by similar accuracy scores achieved by both groups in single task conditions. Thus, the dual task decrement exhibited by patients is likely to be a reflection of a specific impairment in the ability to co-ordinate cognitive resources appropriately between the two tasks, and reflect dysfunction of the central executive. Dual task impairments are observed in Alzheimer's Disease (Logie et al., 2004; MacPherson et al., 2007) and have also been reported to a lesser extent in FTD (Perry & Hodges, 2000; Sebastian & Hernandez-Gill, 2010) and in a previous study of ALS based on reaction time measures (Schreiber et al., 2005). The current investigation employed a preload methodology to minimise motor demands (Cocchini et al., 2002), and constituent tasks for which accuracy was the outcome measure, and as such is the first demonstration of a dual task impairment in ALS that it independent of single task difficulty, processing speed, and motor functioning.

Chapter 5. Experimental tasks; ALS patients versus MS patient versus healthy controls

Chapter 5 investigates experimental task performance in a slightly smaller subgroup of ALS patients (n =25) compared to that of MS patients and healthy controls. In this way, direct comparisons can be made between the ALS and MS groups to determine whether or not they exhibit a similar cognitive profile.

5.1 Participants

MS patients and the matched healthy control participants were the same as those described in Chapter 2 (Section 2.2.2 and Section 2.2.3 respectively), and ALS patients were the same as those described in Section 2.6.1 The group demographic are identical to those described in the 3-way analysis of background neuropsychological assessment in Chapter 2 (Section 2.6.2). As a summary: significant group differences were found between age (ALS patients were significantly older than healthy controls), and HADS D score (MS patients displayed a trend towards significantly higher HADS D scores than healthy controls).

5.2 Methodology

The VIT and RSLI processing speed tasks were administered as described in Chapter 3 (Sections 3.6.1 and 3.6.2 respectively). The dual task procedure was also the same as that described in Chapter 3 (Section 3.6.3.3). The same study protocol was employed in all participants whereby the dual task was performed near the start of the testing session, followed immediately by the RSLI task and then shortly by the VIT task (see Protocol,

Appendix E). Experimental tests were performed near the beginning of the testing sessions to maximise data collection in the event of participant fatigue.

5.3 Statistical analyses

The data were explored for normal distribution using histograms, boxplots and the Shapiro-Wilk's test of normality. In addition, all variables were checked for homogeneity of variance. Not all ALS patients completed the VIT and RSLI tasks (see Table 16 for exact participant numbers); some patients were unable to complete some tests due to fatigue or time pressures. Comparative group analyses were performed using one-way ANOVAs in normally distributed data and Kruskal-Wallis tests in populations that were not normally distributed. In parametric data planned post-hoc group comparisons with Tukey's HSD or Games-Howell corrections (for unequal variances) are reported for any variables in which there were significant group differences. In non-parametric data, Kruskal-Wallis post-hoc comparisons corrected for family wise errors are reported for any variables in which there was a significant group effect. In cases where statistical significance was marginally missed, measures of effect size are provided by Cohen's *d*. In the ALS and MS groups, case analyses were also employed in which standardised scores (Z-scores) for individual ALS and MS patients were derived from the mean and standard deviation of the healthy control group – individuals with scores that fell below 2 standard deviations of the control group mean were considered to be impaired. Associations between performance in experimental tests and age were performed in the ALS group. Associations between performance in experimental tests and mood were investigated in the MS group. Spearman's *rho* correlations were employed to investigate all associations as age and mood data were found to be non-parametric and covariate analyses were performed using Quade's Rank ANCOVA (Quade, 1967). Quade's Rank ANCOVA is a procedure whereby the dependent variable and

covariate of interest are first transformed by rank and then entered into a regression analysis. The unstandardized residual values of the regression are subsequently used in a standard one-way ANOVA. In addition, correlational analyses in the ALS and MS groups were performed between experimental and standardized neuropsychological tests with Pearson's *r* in parametric variables and Spearman's *rho* in non-parametric variables.

5.4 Results

5.4.1 Processing speed

Details of the number of errors made by each group in the VIT and RSLI experimental processing speed tasks are displayed in Table 16. The mean scores show that MS patients made the most errors in both tests, and comparative analyses revealed significant group differences in the RSLI task; $F(2, 71) = 8.354$, $p = 0.001$, but not in the VIT task; $H(2) = 1.292$, $p = 0.524$. Post-hoc analyses in the RSLI task showed that MS patients made significantly more errors than healthy controls ($p = 0.007$) and ALS patients ($p = 0.016$), but there was no difference between ALS patients and healthy controls. The results suggest that MS patients exhibited slowed processing speed for meaningful visual information. Z score analyses revealed that 4 ALS patients and 4 MS patients had scores below 2 standard deviation of the control group mean in the VIT task. In the RSLI task, z-scores indicated that 1 ALS patient and 10 MS patients met the criterion for impaired performance.

Table 16. Processing speed performance: errors for ALS patients, MS patients, and healthy controls

	n (ALS:MS:HC)	ALS	MS	HC
VIT (errors)	21:23:25	12.5 [6.8] (0 – 27)	14.9 [9.5] (5 – 50)	11.6 [4.0] (5 – 21)
RSLI (errors)	25:24:25	16.2 [4.0] (9 – 24)	21.1 [7.2] (7 – 36)	16.0 [2.6] (10 – 22)

Mean values with [standard deviations] and (ranges) in parentheses are presented. Ratios are presented for number of patients versus controls in each task. VIT = Visual Inspection Time (max. errors = 80), RSLI = Rapid Serial Letter Identification (max. errors = 40).

5.4.2 Dual task

Details of participant performance in the baseline DDR and VIT levels are displayed in Table 17. Comparative analyses revealed significant group differences in baseline DDR performance; H (2) = 6.831, p = 0.033. Post-hoc analyses showed that the MS group retained significantly fewer digits than the healthy control group (p = 0.045). However no significant differences were observed between the ALS group and the MS group, or the ALS group and healthy controls. With regard to baseline VIT performance, although the mean scores show that the MS group performed more poorly than the healthy control group and the ALS group, these differences just failed to reach significance; H (2) = 5.683, p = 0.058. Unplanned post-hoc comparisons were carried out between the MS group and healthy control group and revealed a significant group effect; H (1) = 4.438, p = 0.035, however the result was no longer significant after correction for family wise error (p = 0.105, *d* = 0.63). The results replicate the findings demonstrated in Chapter 4 (section 4.4.2)

by showing that ALS patients and healthy controls performed comparably in the baseline component tasks. By contrast, MS patients showed evidence of impaired performance in DDR baseline level, and although not significant after family wise error correction, also had lower scores in the VIT baseline level. Z-scores in the patient group revealed that 5 ALS patients and 5 MS patients met the criteria for impairment in the DDR baseline level performance. In terms of the VIT baseline performance, z-scores indicated that 1 ALS patient and 3 MS patients were impaired relative to controls in this measure.

Table 17. Baseline task performance levels for ALS patients, MS patients, and healthy controls

	n (ALS:MS:HC)	**ALS**	**MS**	**HC**
DDR baseline (digits)	25:25:25	5.4 [1.1]	5.3 [1.2]	6.0 [0.9]
		(4 – 8)	(3 – 8)	(4 – 7)
VIT baseline (ms)	25:25:25	59.7 [24.6]	71.5 [26.1]	57.8 [16.3]
		(34 – 150)	(34 – 150)	(34 – 102)

Mean values with [standard deviations] and (ranges) in parentheses are presented. Ratios are presented for number of patients versus controls in each task. VIT = Visual Inspection Time, DDR = Delayed Digit Recall, ms = milliseconds.

Participants' performance under single and dual task conditions are displayed in Table 18. Comparative analyses revealed no group differences in terms of single task performance in the DDR task; $H(2) = 1.518$, $p = 0.468$, or the VIT task; $H(2) = 2.698$, $p = 0.259$. The results indicate that the patient groups were able to perform comparably to healthy controls under single task conditions.

Table 18. Single and dual task performance: percentage correct for ALS patients, MS patients, and healthy controls

	n (ALS:MS:HC)	ALS	MS	HC
DDR Single	25:25:25	97.0 [5.0]	95.3 [6.1]	96.2 [4.5]
		(83 – 100)	(83 – 100)	(88 – 100)
VIT Single	25:25:25	90.5 [10.4]	89.6 [10.1]	93.4 [6.7]
		(56 – 100)	(53 – 100)	(79 – 100)
DDR Dual	25:25:25	91.9 [10.1]	90.8 [11.1]	96.5 [4.4]
		(73 – 100)	(63 – 100)	(88 – 100)
VIT Dual	25:25:25	83.7 [12.9]	81.7 [14.7]	90.5 [8.5]
		(56 – 100)	(48 – 100)	(64 – 100)

Mean values with [standard deviations] and (ranges) in parentheses are presented. Ratios are presented for number of patients versus controls in each task. VIT = Visual Inspection Time, DDR = Delayed Digit Recall

Mean percentage change scores (Dual Task Cost) for the participant groups are displayed in Table 19 and show that the ALS and MS groups experienced substantially greater Dual Task Costs than the healthy control group in both component tasks. Comparative analyses revealed significant group differences in DDR Dual Task Cost; $H(2) = 6.914$, $p = 0.032$. Post-hoc group comparisons revealed trends towards significance suggesting that the healthy control group exhibited smaller Dual Task Costs than the ALS group ($p = 0.058$, $d = 0.69$) and the MS group ($p = 0.082$, $d = 0.74$), but there was no difference between the ALS group and MS group. Group differences in VIT Dual Task Cost scores were not statistically significant; $H(2) = 3.900$, $p = 0.142$. However, the Average Dual Task Cost was significantly different between groups; $F(2, 74) = 5.419$, $p = 0.006$. Post-hoc group

comparisons indicated that the healthy control group exhibited a significantly smaller Dual Task Cost than the ALS group ($p = 0.026$) and the MS group ($p = 0.010$) whilst there was no difference in performance between the ALS group and MS group. The results suggest that both patient groups exhibited impaired dual task performance relative to controls. In terms of individual patient performance, z-scores in the patients groups indicated that 9 ALS patients and 7 MS patients showed impaired performance in terms of DDR Dual Task Cost, whereas 2 ALS patients and 3 MS patients showed impaired performance in terms of the VIT Dual Task Cost. Z-scores for the Average Dual Task Cost revealed that 5 ALS patients and 8 MS patients exhibited impairments in the overall measure of dual task performance.

Table 19. Dual Task Cost: percentage change for ALS patients, MS patients, and healthy controls

	n (ALS:MS:HC)	**ALS**	**MS**	**HC**
DDR Dual Task Cost	25:25:25	5.2 [10.2]	4.8 [8.5]	-0.4 [5.1]
		(-21 – 22)	(-8 – 25)	(-14 – 10)
VIT Dual Task Cost	25:25:25	7.2 [11.7]	9.0 [11.5]	2.6 [11.6]
		(-15 – 32)	(-10 – 32)	(-23 – 36)
Average Dual Task Cost	25:25:25	6.2 [6.7]	6.9 [7.8]	1.1 [5.8]
		(-5 – 21)	(-7 – 21)	(-14 – 16)

Mean values with [standard deviations] and (ranges) in parentheses are presented. Ratios are presented for number of patients versus controls in each task. VIT = Visual Inspection Time, DDR = Delayed Digit Recall

5.4.3 Correlations with age and depression

The ageing study (Chapter 3, Section 3.6.3) demonstrated that the dual task paradigm employed by the current investigation was unaffected by age. However, processing speed measures have been consistently shown to be sensitive to ageing (e.g. Salthouse, 1996). Comparative analyses of age (Chapter 2, Section 2.6.2) revealed that the average age of the ALS group was significantly higher than the MS group, although not healthy controls. Moreover, ALS patients had the largest age range of any of the participant groups indicating that any potential age effects would most likely exist within the ALS population. Thus, to further investigate the effect of age, correlational analyses were performed between age and all background variables in the ALS patient group. No significant correlations were found between age and any of the experimental measures and as such no covariate analyses were performed.

The effect of depression in the MS group was investigated in all experimental variables; a significant correlation was observed between HADS D score and RSLI errors; *rho* = 0.59, p = 0.002. Thus, the investigation of group effects in this measure was subjected to covariate analyses with depression. Quade's Rank ANCOVA revealed significant group differences in the RSLI task; F (2, 71) = 4.562, p = 0.014. Post-hoc comparisons showed that MS patients made significantly more errors than healthy controls (p = 0.027) and ALS patients (p = 0.029), but there was no difference between ALS patients and healthy controls. The result indicates that the observed impairment exhibited by MS patients in the RSLI task remained once depression was accounted for.

5.4.4 Correlations with standardized neuropsychological tests

Associations between performance in each experimental task (VIT errors, RSLI errors, and Average Dual Task Cost) and the standardised neuropsychological tests employed in Chapter 2 were performed. In the ALS group no significant correlations were observed for any experimental measure. In addition, there were no correlations between any of the experimental tasks. However, in the MS group several significant correlations were revealed. Average Dual Task Cost correlated with performance in all conditions of the Logical Memory scales: Immediate recall; rho = -0.44, p = 0.031, Delayed recall; r = -0.59, p = 0.003, Retention; rho = -0.42, p = 0.041, and delayed Recognition; rho = -0.55, p = 0.006. In addition, Average Dual Task Cost correlated with performance in the RSLI task; r = 0.46, p = 0.023. There were no significant associations between the VIT task or RSLI task and any standardized neuropsychological tests.

5.5 Summary

The three-way group comparison in the experimental tasks revealed some interesting differences between ALS patients and MS patients. Relative to healthy control participants, the subgroup of 25 ALS patients exhibited the same pattern of intact processing speed and impaired dual task performance as that reported and discussed in Chapter 4. Such findings suggest that this pattern of selective dual task impairment in the absence of slowed processing speed is a robust finding in ALS, even when patients are compared to a younger control group. Moreover, correlational analyses between age and the experimental measures showed that age was not associated with Dual Task Cost or either of the processing speed tasks.

Patients with MS made more errors in the VIT task than ALS patients and healthy controls, however, the difference was not significant. The standard deviation of the MS group in the VIT task indicates that performance was more variable than that of ALS patients and healthy control participants, and further evidence for this is provided by the difference between MS patients and healthy controls in the baseline VIT level within the dual task paradigm. In terms of the RSLI task, MS patients made significantly more errors than both healthy controls and ALS patients suggesting that the MS group exhibited impaired processing speed for meaningful visual stimuli. Although scores in self-reported depression in MS correlated with performance in this task, covariate analyses demonstrated that controlling for depression did not attenuate the group differences. Processing speed deficits have been postulated by some investigators to be the most common impairment in MS (DeLuca et al., 2004; Rosti et al., 2007) and the results of the current study provide further evidence of such impairment. However, unlike commonly used tests of processing speed such as the PASAT, the RSLI task employed by the current investigation minimises demands on working memory and thus the observed impairment in this task is a more valid indication that MS patients can experience slowed processing speed independent of working memory abilities. In addition, the RSLI task utilised the manipulation of stimuli duration and was therefore independent of the motor dysfunction confounds that are inherent to other tasks such as symbol search and choice reaction time tests which previous studies have employed to demonstrate processing speed deficits in MS (DeLuca et al., 2004; Hughes, Denney & Lynch, 2011). Nevertheless, the RSLI task imposes greater attentional demands than the VIT task as it requires the identification of a specific letter as opposed to a simple choice between left and right. These additional processing demands may be the difference between normal and slowed processing speed in MS and suggest that MS patients may be particularly susceptible to slowed processing as tasks become more complex.

The MS group exhibited a dual task deficit as evidenced by significantly greater Dual Task Cost than the matched healthy control group. Although MS patients' baseline performance in the DDR and VIT task was worse than that of healthy control participants, performance in both tasks under single task conditions was comparable to that of healthy controls. This finding demonstrates the importance of matching baseline task performance to each individual's ability, and moreover suggests that the dual task deficit was specific to the demands incurred when completing two tasks concurrently. Therefore, although MS patients displayed evidence of slowed processing speed in the RSLI task, the fact that they were able to complete the VIT task under single task conditions comparably to the control group suggests that the observed dual task deficit is independent of the observed processing speed impairment. As such, the findings of the current study are consistent with others reporting greater impairments in attentionally demanding tasks that are independent of basic processing speed ability as assessed by reaction times (DeSonneville et al., 2002; Tinnefeld et al., 2005). Moreover, the current findings are concordant with others reporting dual task impairments in MS patients (D'Esposito et al., 1996; Comi et al., 1999), and extend these findings to a paradigm that is independent of motor functioning.

The comparison between ALS and MS patients in the dual task revealed essentially similar performance once single task abilities were taken into account. Both patient groups performed comparably to controls, and each other, under single tasks conditions, but showed impairment under dual task conditions as evidenced by significant differences in Average Dual Task Cost. The only clear difference in performance between ALS and MS patients in the experimental tasks was observed in the RSLI task in which MS patients showed significantly worse performance than both healthy controls and ALS patients. Such

a result indicates that although both patient groups show a pattern of intact basic processing speed (as evidenced by VIT task performance), combined with impaired executive functioning (as evidenced by dual task performance), MS patients may be more susceptible to lower levels of attentional demand required by the RSLI task which may suggest that executive dysfunction is more pervasive in MS than ALS.

Chapter 6. Structural imaging in ALS patients versus healthy controls

The following chapter primarily concerns the investigation of white matter integrity in ALS patients compared to that of matched healthy control participants by way of diffusion tensor magnetic resonance imaging (DTI). The basic principles of DTI and previous studies employing this technique in the investigation of cerebral changes in ALS have been discussed in Chapter 1 (Section 1.8.3.3). The current study employed region-of-interest (ROI) and voxel-based methods, specifically Tract-based Spatial Statistics (TBSS), to investigate diffusion data in ALS patients and healthy controls. In addition, volumetric analyses of grey matter structure obtained from high-resolution three dimensional T1-weighted scans were carried out using voxel-based morphometry (VBM) to determine the extent to which grey matter volume changes corresponded to any observed white matter abnormalities.

6.1 Participants

ALS and matched healthy control participants were the same as described in Chapter 2 (Sections 2.2.1 and 2.2.3), and group demographics are the same as reported in Section 2.4. Imaging data was collected for all 29 ALS patients and 30 healthy control participants unless otherwise stated. All MRI scans were completed within 4 weeks of the neuropsychological and experimental assessment interviews.

6.2 Methods

6.2.1 MRI acquisition

All MRI data were acquired using a GE Signa Horizon HDxt 1.5 T clinical scanner (General Electric, Milwaukee, WI, USA) equipped with a self-shielding gradient set (33 mT/m maximum gradient strength) and manufacturer supplied 8-channel phased-array head coil. The diffusion MRI protocol consisted of 7 T_2-weighted ($b \sim 0$ s/mm^2) and sets of diffusion-weighted ($b = 1000$ s/mm^2) whole brain single-shot spin-echo echo-planar imaging (EPI) volumes acquired with diffusion encoding gradients applied in 64 non-collinear directions (Jones et al., 2002). The acquisition parameters were: field-of-view 256 × 256 mm; imaging matrix 128 × 128; and 72 × 2 mm thick contiguous axial slice locations giving 2 mm isotropic voxels. The repetition and echo times for the single-shot spin-echo EPI sequence were 16.5 s and 98.3 ms respectively. The whole protocol took approximately 20 minutes.

6.2.2 *DTI preprocessing*

Diffusion MRI data were converted from DICOM (http://dicom.nema.org) to NIfTI-1 (http://nifti.nimh.nih.gov/nifti-1) format, and pre-processed with FSL tools (http://www.fmrib.ox.ac.uk/fsl) in order to extract the brain, eliminate bulk patient motion and eddy current-induced artefacts, and estimate the water diffusion tensor parameters mean diffusivity ($\langle D \rangle$) and fractional anisotropy (FA).

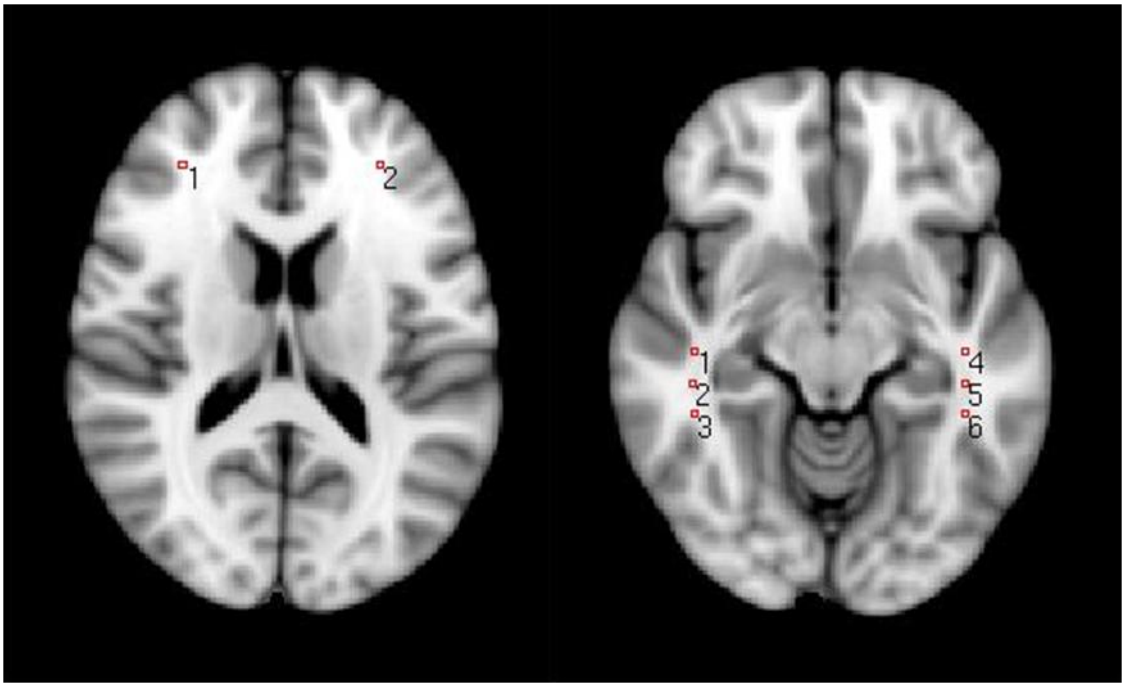
6.2.3 Regions of Interest white matter analysis

ROI analysis was performed using 'in-house' software written in MATLAB (The MathWorks, Natick, MA, USA) which allowed multiple small square ROIs to be placed on the T_2-weighted EPI volumes and then overlaid on the co-registered mean diffusivity ($\langle D \rangle$) and fractional anisotropy (FA) maps either by hand or automatically using locations defined in Montreal Neurological Institute (MNI; http://www.bic.mni.mcgill.ca) standard space. In the latter, the software allows the user to interactively move ROIs if standard to native space registration errors cause white matter ROIs to be placed over cerebrospinal fluid (CSF) or grey matter structures. Thus, the ROI analysis was semi-automated, and specifically designed to be as reproducible as possible by defining the central ROI coordinates in MNI space and transferring them to native space. This allowed the initial positioning of each ROI to be the same for every individual. This approach provides a sensible method for measuring the integrity of a range of small to medium sized white matter structures, a number of which, such as the corona radiata, white matter underlying the prefrontal gyri and temporal and occipital gyri, cannot easily be identified using tractography.

The procedure for obtaining $\langle D \rangle$ and FA values for each ROI was as follows. First, MNI coordinates were defined in standard space for each ROI using the ICBM-DTI-81 white matter atlas (Oishi et al., 2011). Typically, between 6 and 12 square ROIs were defined for each white matter structure in axial view, sizes of which were $3 \times 3 \times 1$ voxels, or 2 x 2 x 1 voxels depending on the white matter region. Several ROIs were used for each white matter region in order to reduce the effects of differences in individual ROI placement. Next, the coordinates were mapped from standard to native space using the affine transformation matrices derived by registering each subject's T_2-weighted EPI volume to MNI standard

space. The placement of the ROIs in individual images was then checked manually to ensure minimal contribution of grey matter and CSF signal to the ⟨D⟩ and FA measurements. An example of typical ROI placements is presented in Figure 4. To ensure unbiased measurements of ⟨D⟩ and FA, all ROI were defined on the T_2-weighted EPI volumes (Bozzali & Cherubini, 2007) blind to each subjects' clinical status. Values for ⟨D⟩ and FA were then obtained for each square ROI and averaged to give mean values for each white matter structure-of-interest. Finally, blinded to the original ROI selection, an assessment of intra-rater reliability of ROI placement was also performed by repeating the above analysis in 10 subjects (5 patients and 5 controls) chosen at random from the study cohort.

Figure 4. Examples of standard space white matter ROIs; association fibres in middle frontal gyrus white matter (left) and inferior longitudinal fasciculus (right)



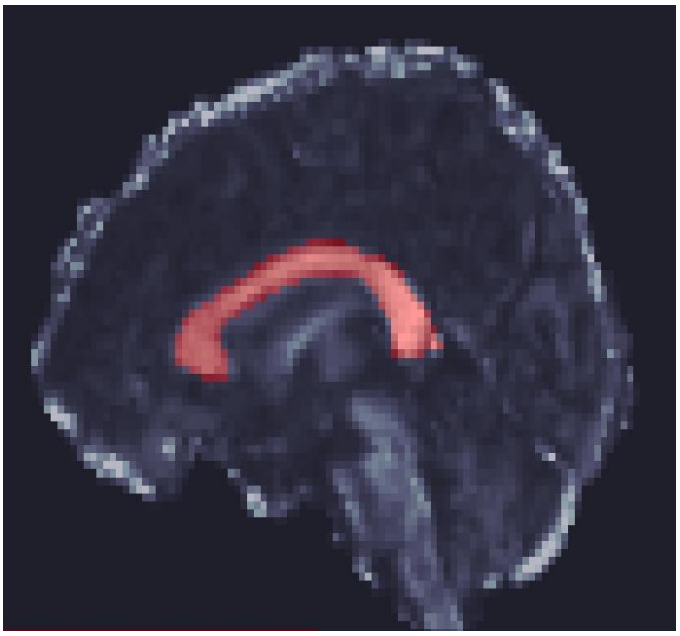
Based on previous studies, a set of white matter structures that are potentially affected in ALS were chosen for investigation (Abrahams et al., 2005; Sarro et al., 2011). These included major white matter fibre bundles of the anterior thalamic radiation, uncinate fasciculus, superior longitudinal fasciculus, inferior longitudinal fasciculus, corticospinal tract, as well as the genu and splenium of corpus callosum. Also measured were the anterior cingulum, as well as the cingulum and ventral cingulum bundle connected to the hippocampus. White matter underlying sub-regions of prefrontal cortex were investigated; a) superior frontal gyrus white matter (near cortical area BA10), b) middle frontal gyrus white matter (near cortical area BA9/46), and c) inferior frontal gyrus white matter (near cortical area BA44/45). In addition, white matter within the corona radiata (superior and posterior regions), anterior corona radiata, superior parietal lobule, and temporal gyri (superior, middle and inferior) were also measured. Finally, areas that were not expected to be implicated in ALS were included, namely the optic radiation and white matter within occipital gyri.

6.2.4 Corpus callosum segmentation

As abnormalities in corpus callosum structural integrity have been shown to be a consistent feature of cerebral pathology in ALS (Yamauchi et al., 1995; Filippini et al., 2010), the corpus callosum was extracted at midline using an automatic segmentation tool. The method takes the FA and principal eigenvector volumes and registers them to the JHU-ICBM 2 mm FA template (Johns Hopkins University, Baltimore, MD, USA; http://cmrm.med.jhmi.edu) using affine registration to ensure the midline is in the centre of the x-axis. The midline corpus callosum is then identified by applying a threshold between 0.2 and 0.4 to the FA

volume, and identifying those voxels whose principal eigenvectors have a predominantly left-right orientation (red) from the red/green/blue principal eigenvector colour map. The resulting segmentation mask (see Figure 5) is then applied to the ⟨D⟩ and FA volumes to provide average values for these water diffusion biomarkers in this structure-of-interest. Segmentation was unsuccessful in 6 ALS patients and 3 healthy controls so comparative analyses were conducted in 23 and 27 participants respectively.

Figure 5. Example of corpus callosum segmentation



6.2.5 Statistical analyses; ROI and corpus callosum segmentation

White matter ROI and corpus callosum segmentation data was explored for normality using Shapiro-Wilk tests and histograms, while comparative analyses were conducted with univariate analysis of variance with age entered as a covariate (ANCOVA; Agosta et al., 2010). Multiple comparisons were controlled for by applying a false discovery rate

algorithm to the data (Pike, 2011; Sarro et al., 2011). Associations between performance in cognitive tests and white matter ROI data was investigated in the patient group only using Pearson's *r* correlations. Correlations were only performed between regions/tracts and cognitive tests in which there were significant group differences. As such the reported p values are one-tailed.

6.2.6 Tract based spatial statistics white matter analysis

TBSS, part of the FSL image analysis platform (Smith, 2004), was used to perform a skeleton-based analysis of white matter FA and ⟨D⟩ data (Smith, 2006). Non-linear co-registration was performed using FNIRT to align the FA volumes of each individual participant to the MNI standard space of the FMRIB58_FA template (Anderson, Jenkinson & Smith, 2007a, 2007b) which uses a b-spline representation of the registration warp field (Rueckert 1999). The resulting FA volumes were then visually checked for any registration errors. After image registration, these FA maps were averaged to produce a group mean FA volume. Next, the mean FA volume was thinned to create a mean FA skeleton which represents the centres of all tracts common to the group. Each participant's aligned FA data was then projected onto this skeleton to create a 4 dimensional FA volume. The process was then repeated for ⟨D⟩ data using the same non-linear registration parameters and projection vectors used to create the original mean FA skeleton, to produce a 4 dimensional ⟨D⟩ volume.

6.2.7 Statistical analyses; TBSS

The 4 dimensional skeletonized FA and ⟨D⟩ volumes were statistically tested via a voxel-wise general linear model (GLM) design matrix. Significant clusters were formed by employing the threshold-free cluster enhancement (TFCE) method (Smith & Nichols, 2009). The TFCE method is a cluster-based thresholding method which does not require the setting of an arbitrary cluster forming threshold, instead it takes a raw statistics image and produces an output image in which the voxel-wise values represent the amount of cluster-like local spatial support. The TFCE image is then turned into voxel-wise p-values via permutation testing. Permutation testing was performed using the program Randomise, part of FSL, which uses Monte Carlo permutation testing to generate 5000 random permutations and provides a solution to the multiple testing problem (Nichols and Holmes, 2007). Group comparisons between ALS patients and healthy controls were performed for the conditions 'voxel FA/⟨D⟩ for controls > voxel FA/⟨D⟩ for ALS patients', and the converse statement 'voxel FA/⟨D⟩ for ALS patients > voxel FA/⟨D⟩ for controls'. Clusters reported have significance at $p \leq 0.05$, corrected for multiple comparisons via family-wise error correction. For the ALS patients, correlational analyses were also performed between FA/⟨D⟩ maps and neuropsychological and experimental tests in which significant group differences were exhibited. Inter-subject voxel-wise correlations were performed between skeletonised voxel FA/⟨D⟩ values and demeaned neuropsychological/experimental tests scores, while treating age as a covariate of no interest. Again, the output was thresholded using the TFCE method and corrected for multiple comparisons family-wise error ($p \leq 0.05$). Significant skeleton voxels were overlaid onto the mean FA template to allow anatomical localization by visual inspection.

6.2.8 Voxel based morphometry grey matter analysis

VBM was conducted on the three dimensional T1-weighted scans acquired during the same examination as the DTI protocol using FSL-VBM (Douaud et al., 2007, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM), an optimised VBM protocol (Good et al., 2001). These volume scans were acquired in the coronal plane with: field-of-view 256 × 256 mm; imaging matrix 192 × 192 (zero filled to 256 × 256); 160 × 1.3 mm thick contiguous slice locations giving 1 × 1 × 1.3 mm isotropic voxels; and repetition, echo and inversion times 10, 4 and 500 ms respectively. All scans were visually checked and 1 ALS patient was subsequently removed from the analysis due to motion artefacts; thus VBM group comparisons are between 28 patients and 30 healthy controls.

Preprocessing of these volumes included conversion from DICOM to NIfTI-1 format, affine registration to an axial T2*-weighted gradient echo volume (voxel resolution 1 × 1 × 2 mm) acquired during the imaging protocol, and brain extraction using a brain mask created from the T2*-weighted gradient echo volume. Grey matter volumes were then identified using FSL's Automated Segmentation Tool (FAST). Each participant's grey matter volume was registered to the MNI 152 standard space using non-linear registration (Andersson et al., 2007b). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. Subsequently, all native grey matter partial volume maps were then non-linearly registered to the study-specific template via non-linear b-spline representation of the registration warp and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 2 mm.

6.2.9 Statistical analyses; VBM

Voxel-wise general linear modelling was applied using the same TFCE method and permutation-based non-parametric testing, correcting for multiple comparisons across space, as described for the TBSS analyses above (Section 6.2.6). In addition, several ROI masks were created using Harvard-Oxford post-mortem templates available in FSL to investigate grey matter volumes in regions which corresponded to white matter changes revealed by the white matter ROI analysis. The derived ROI templates were subjected to the same TFCE and permutation based statistical testing as described previously. Correlational analyses in ALS patients were subsequently performed between VBM ROIs and cognitive data using the same methods as described previously in section 6.2.6.

6.3 Results

6.3.1 ROI reproducibility

The intra-rater reliability analysis indicated excellent reproducibility of ROI measurements with the SD of the difference between repeated measures of ⟨D⟩ and FA being 21×10^{-6} mm^2/s (mean of measurements 698×10^{-6} mm^2/s) and 0.012 (mean of measurements 0.411), respectively. This yielded coefficients of variation of 2.94 % for ⟨D⟩ (range 0.6% for cingulum to 6.1% for genu) and 2.85% for FA (range 0.5% for superior longitudinal fasciculus to 4.4% for frontal white matter), which compares well with values for other studies using ROI analysis (e.g. Shenkin et al. 2005).

6.3.2 ROI comparative between group analyses

White matter ROI analyses are displayed in Table 20. An investigation of the means shows that ALS patients had poorer structural integrity parameters (i.e. lower FA and higher ⟨D⟩) than healthy controls in almost all ROIs with the exception of posterior areas such as the occipital gyrus white matter and optic radiation. Significant group differences were found in the following frontal tracts; the anterior cingulate (FA and ⟨D⟩), anterior thalamic radiation (FA and ⟨D⟩), and uncinate fasciculus (⟨D⟩). In addition, group differences in white matter integrity were observed in the following prefrontal regions; superior frontal gyrus white matter (FA and ⟨D⟩), inferior frontal gyrus white matter (FA and ⟨D⟩), middle frontal gyrus white matter (FA), and anterior corona radiata (FA and ⟨D⟩). Large differences were observed in the corticospinal tract (FA and ⟨D⟩). Further significant differences were also found in temporal areas; the hippocampal (ventral) portion of the cingulum (⟨D⟩), temporal gyri white matter (FA), as well as in the inferior longitudinal fasciculus (FA) and corona radiata (FA). Investigation of white matter integrity in posterior brain regions (occipital gyri white matter and optic radiation) revealed no significant group differences.

Table 20. White matter ROI means and comparative analyses between ALS patients and controls*

	ALS	**HC**	***F*(1, 56)**	***p value***	***FDR adj.***
Ant. Cingulum FA	0.41 [0.056]	0.45 [0.063]	6.286	0.015	**0.016**
Ant. Cingulum ⟨D⟩†	675 [67]	632 [62]	7.278	0.009	**0.012**
Ant. Thal. Rad. FA	0.46 [0.039]	0.49 [0.037]	9.589	0.003	**0.006**
Ant. Thal. Rad. ⟨D⟩†	665 [55]	633 [37]	10.042	0.002	**0.004**
SFG white matter FA	0.28 [0.036]	0.30 [0.034]	5.007	0.029	**0.021**
SFG white matter ⟨D⟩†	773 [57]	740 [46]	6.093	0.017	**0.016**
IFG white matter FA	0.36 [0.044]	0.38 [0.030]	5.439	0.023	**0.018**
IFG white matter ⟨D⟩†	689 [47]	670 [38]	4.194	0.045	**0.028**
MFG white matter FA	0.28 [0.040]	0.31 [0.041]	6.062	0.017	**0.016**
MFG white matter ⟨D⟩†	734 [62]	713 [53]	3.421	0.070	0.056
Ant. Corona Radiata FA	0.27 [0.038]	0.30 [0.035]	11.949	0.001	**0.004**
Ant.CoronaRadiata ⟨D⟩†	805 [77]	772 [54]	4.569	0.037	**0.024**
Genu FA	0.43 [0.062]	0.45 [0.069]	1.355	0.249	0.094
Genu ⟨D⟩†	1055 [152]	1031 [164]	0.450	0.505	0.163
Uncinate Fas. FA	0.40 [0.052]	0.42 [0.054]	2.429	0.125	0.063
Uncinate Fas. ⟨D⟩†	705 [43]	680 [39]	6.179	0.016	**0.016**
Cingulum FA	0.45 [0.078]	0.47 [0.078]	0.951	0.334	0.115
Cingulum ⟨D⟩†	652 [82]	626 [72]	1.942	0.169	0.077

Ventral Cingulum FA	0.30 [0.041]	0.31 [0.036]	2.262	0.138	0.066
Ventral Cingulum ⟨D⟩†	720 [79]	678 [57]	5.777	0.020	**0.017**
CorticospinalTract FA	0.53 [0.039]	0.57 [0.036]	18.808	0.000	**0.000**
CorticospinalTract ⟨D⟩†	651 [37]	625 [29]	10.769	0.002	**0.004**
Inferior Long. Fas. FA	0.42 [0.030]	0.44 [0.029]	7.278	0.009	**0.012**
Inferior Long. Fas. ⟨D⟩†	725 [47]	713 [38]	1.896	0.174	0.077
Superior Long. Fas. FA	0.46 [0.043]	0.48 [0.044]	1.107	0.297	0.105
Superior Long. Fas ⟨D⟩†	638 [41]	628 [33]	1.145	0.234	0.092
SPL white matter FA	0.39 [0.038]	0.40 [0.037]	2.610	0.112	0.059
SPL white matter ⟨D⟩†	688 [42]	684 [41]	0.170	0.682	0.208
Splenium FA	0.57 [0.063]	0.59 [0.064]	1.730	0.194	0.082
Splenium ⟨D⟩†	757 [92]	765 [110]	0.061	0.805	0.239
TG white matter FA	0.32 [0.033]	0.34 [0.025]	11.153	0.001	**0.004**
TG white matter ⟨D⟩†	750 [53]	730 [50]	2.877	0.095	0.052
Corona Radiata FA	0.34 [0.045]	0.36 [0.035]	4.826	0.032	**0.022**
Corona Radiata ⟨D⟩†	663 [42]	650 [58]	1.270	0.265	0.097
OG white matter FA	0.39 [0.033]	0.39 [0.044]	0.305	0.583	0.183
OG white matter ⟨D⟩†	747 [75]	753 [75]	0.032	0.859	0.245
Optic Radiation FA	0.42 [0.039]	0.41 [0.039]	1.662	0.203	0.083
Optic Radiation ⟨D⟩†	741 [49]	732 [56]	0.689	0.410	0.137

Mean values with standard deviations in parentheses are presented. * Significant results are highlighted in bold. † values x 10^{-6} mm^2/s, Ant. = Anterior, SFG = Superior Frontal Gyrus, IFG = Inferior Frontal Gyrus, MFG = Middle Frontal Gyrus, Long. = Longitudinal, Fas. = Fasciculus, SPL

= Superior Parietal Lobule, TG = Temporal Gyri, OG = Occipital Gyri, FA = Fractional Anisotrophy, ⟨D⟩ = Mean Diffusivity. FDR adj = p values after adjustment for False Discovery Rate.

6.3.3 Corpus callosum segmentation

ANCOVA's revealed a significant difference in FA values between patients (Mean = 0.56, SD = 0.046) and controls (Mean = 0.59, SD = 0.043); F (1, 47) = 6.120, p = 0.017, as well as ⟨D⟩ values between patients (Mean = 780, SD = 86 × 10^{-6} mm^2/s) and controls (Mean = 743, SD = 61 × 10^{-6} mm^2/s); F (1, 47) = 4.045, p = 0.050.

6.3.4 ROI correlates

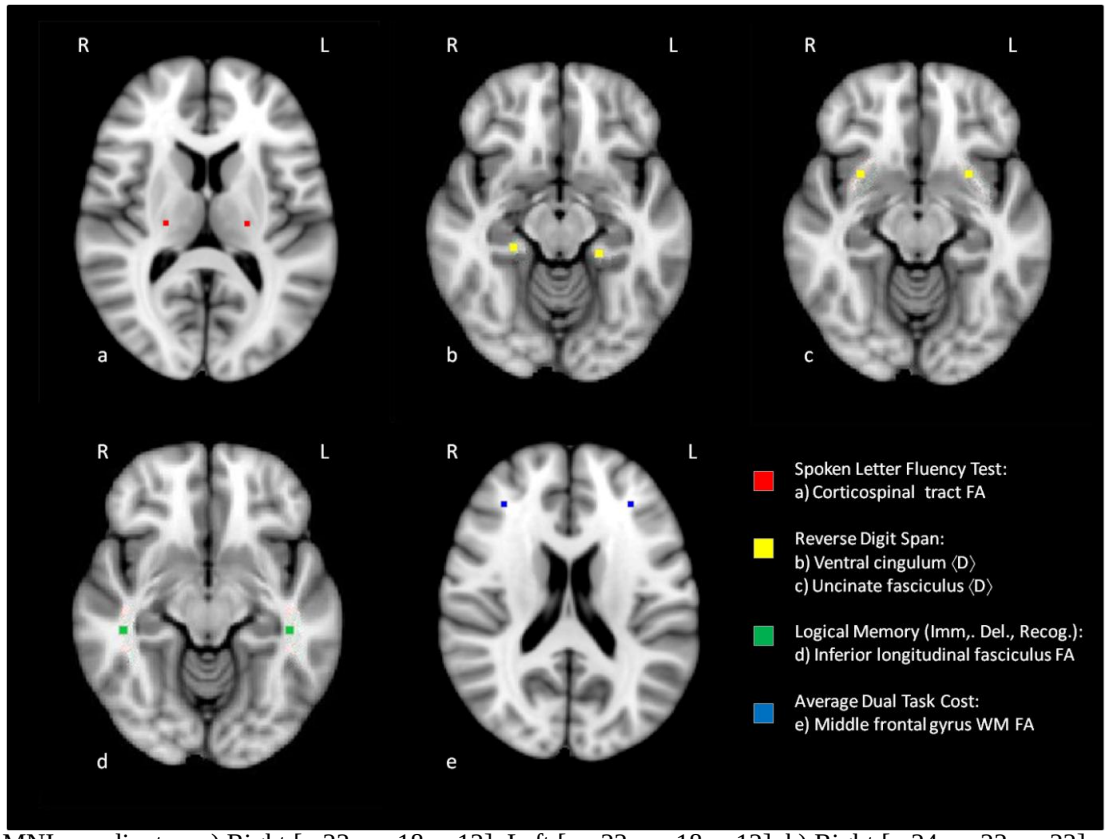
Correlational analyses were performed between cognitive measures in which ALS patients exhibited evidence of impairment (see sections 2.4 and 4.4.2) and white matter ROIs in which significant group differences were observed. Correlational analyses were also performed between corpus callosum segmentation parameters and cognitive measures. Correlations between white matter ROIs and performance in the D-KEFS Sorting Test were not performed due to the low number of ALS participants who were administered this measure. Only significant correlations are reported below. Associations between white matter ROIs and background and experimental cognitive tests are displayed in Table 21 and represented in Figure 6.

Table 21. Significant ROI correlations with background neuropsychological and experimental tests

	ROI Parameter	**Pearson's *r***	**p value (1-tailed)**
Spoken Letter	Corticospinal Tract FA	-0.41	0.016
Fluency Test (*fi*)	Corpus Callosum FA	-0.35	0.049
Reverse Digit Span	Ventral Cingulum ⟨D⟩	-0.41	0.017
	Uncinate Fas. ⟨D⟩	-0.38	0.024
Log. Memory Imm.	Inferior Longitudinal Fas. FA	0.58	0.001
Log. Memory Del.	Inferior Longitudinal Fas. FA	0.54	0.002
Log. Memory Recog.	Inferior Longitudinal Fas. FA	0.47	0.006
Average Dual Task Cost	Middle Frontal Gyrus WM FA	-0.44	0.008

ROI = Region of Interest, fi = fluency index, Log. = Logical, Imm. = immediate recall condition, Del. = delayed recall condition, Recog. = delayed recognition condition, Fas. = Fasciculus, FA = Fractional Anisotrophy, ⟨D⟩ = Mean Diffusivity.

Figure 6. Significant correlations between performance on cognitive tests and white matter ROIs in ALS patients



MNI coordinates: a) Right [x 22, y –18, z 12], Left [x –22, y –18, z 12]; b) Right [x 24, y -22, z -22], Left [x –24, y -24, z -22]; c) Right [x 30, y 9, z -11], Left [x –27, y 9, z -11]; d) Right [x 44, y -30, z -10], Left [x –43, y -30, z -10]; e) Right [x 32, y 39, z 17], Left [x –31, y 39, z 17]. MNI = Montreal Neurological Institute coordinates, FA = Fractional Anisotrophy, ⟨D⟩ = Mean Diffusivity.

With regard to the background tests, fluency indices (*fi*) in the Spoken Letter Fluency Test correlated with FA in the corticospinal tract and corpus callosum whereby longer thinking times indicative of poorer performance were associated with lower FA and hence poorer structural integrity in both regions. The relationship between fluency performance and structural integrity in the corticospinal tract and corpus callosum is presented in Figures 7 and 8 respectively.

Figure 7. Association between Spoken Letter Fluency Test performance (fluency index) and corticospinal tract integrity

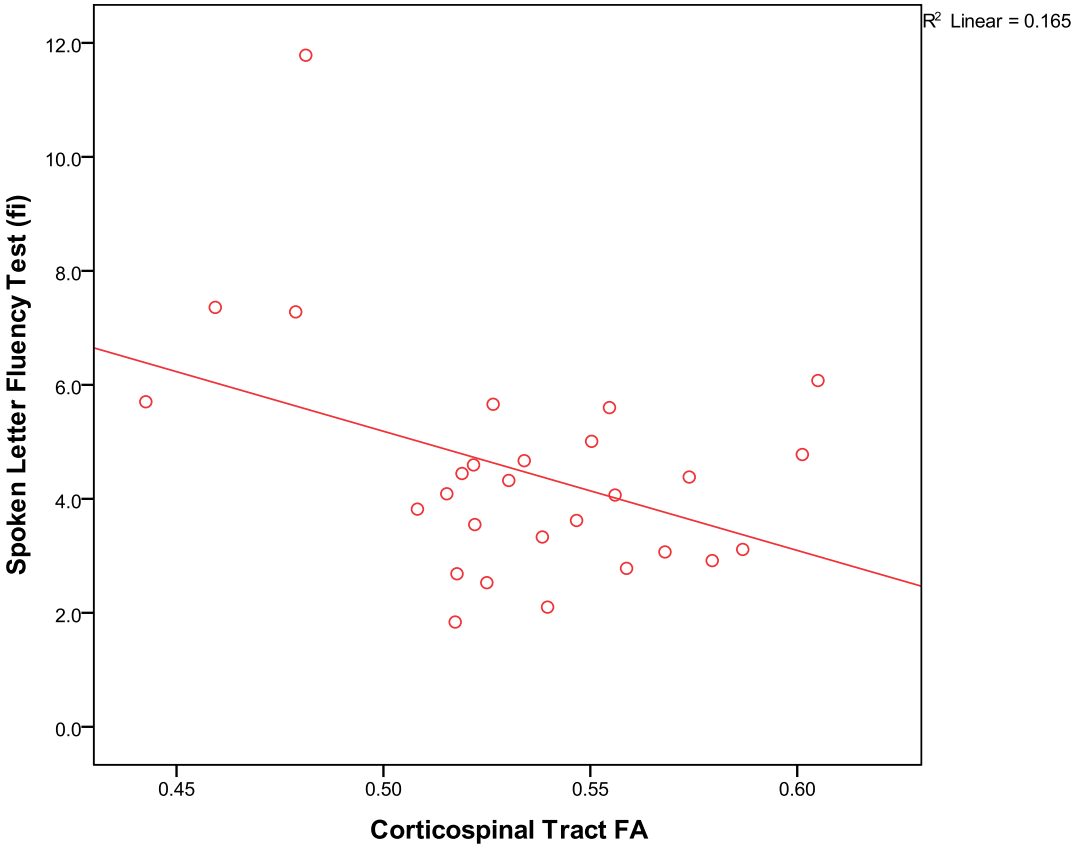
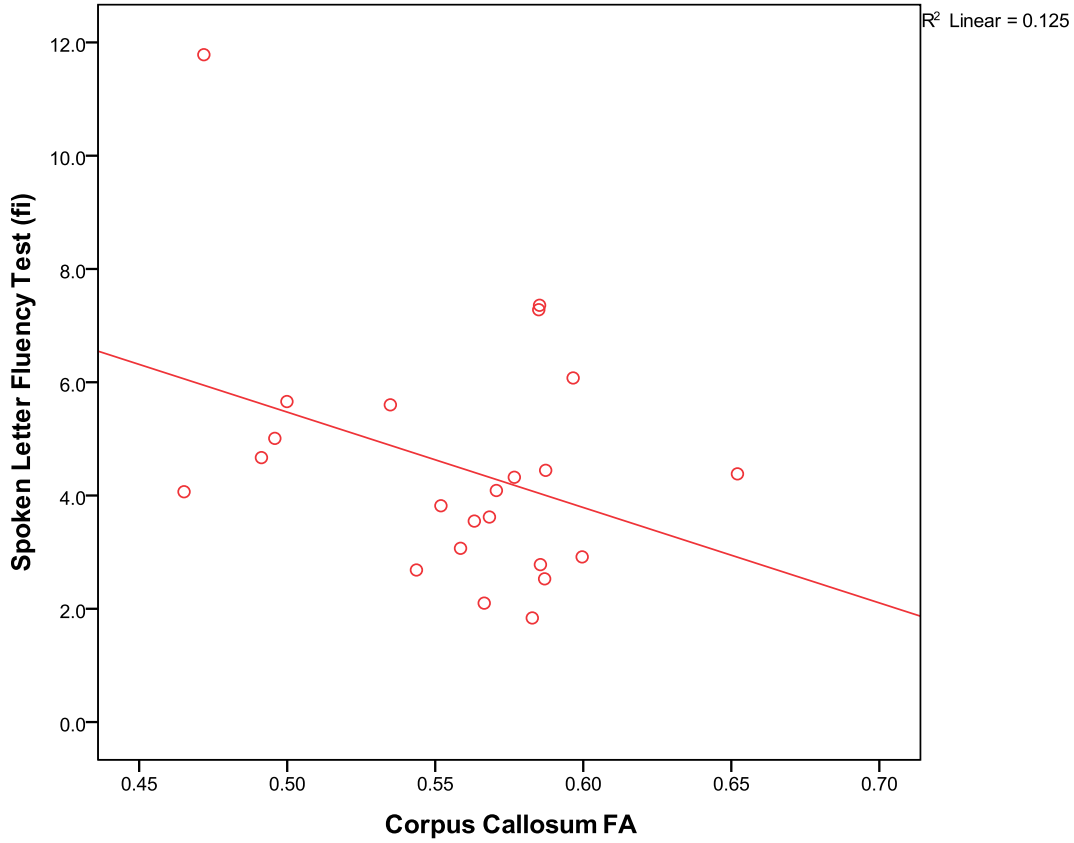


Figure 8. Association between Spoken Letter Fluency Test (*fi*) performance and corpus callosum integrity



Performance in Reverse Digit Span correlated with ⟨D⟩ in the ventral cingulum and uncinate fasciculus (see Figures 9 and 10 respectively) whereby lower span performance was associated with higher ⟨D⟩ in both regions.

Figure 9. Association between Reverse Digit Span performance and ventral cingulum integrity

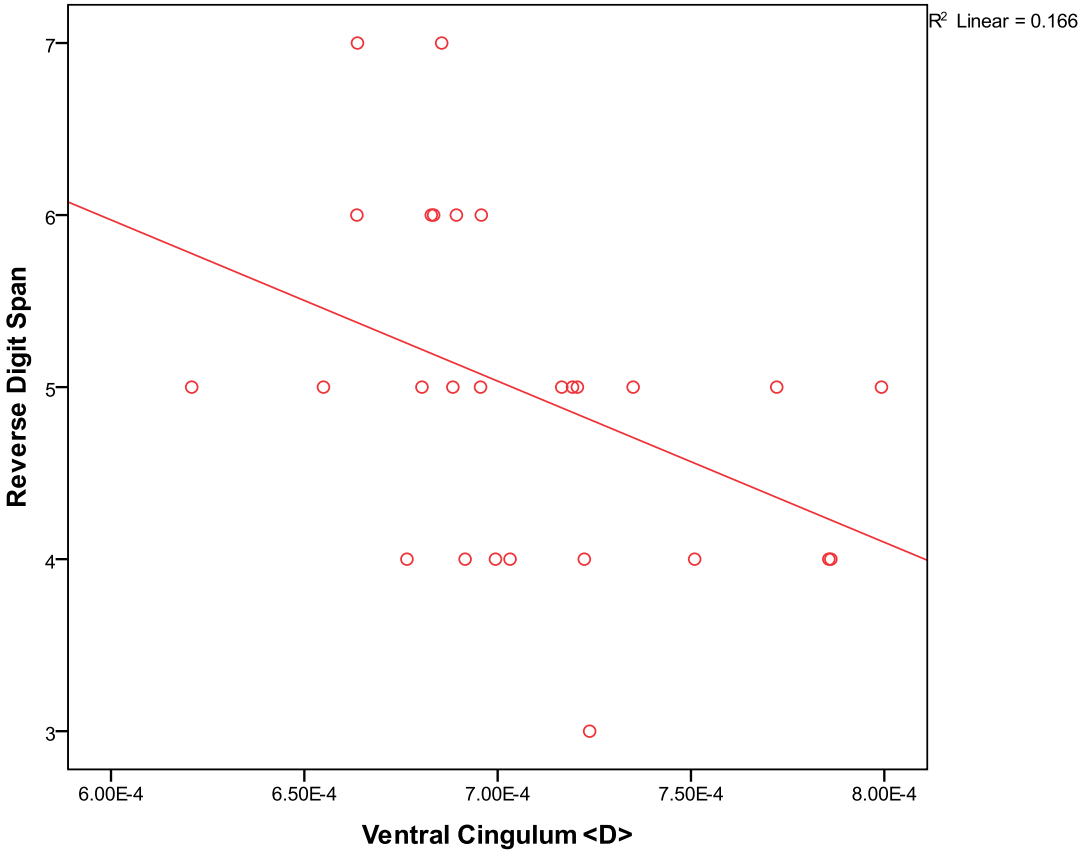
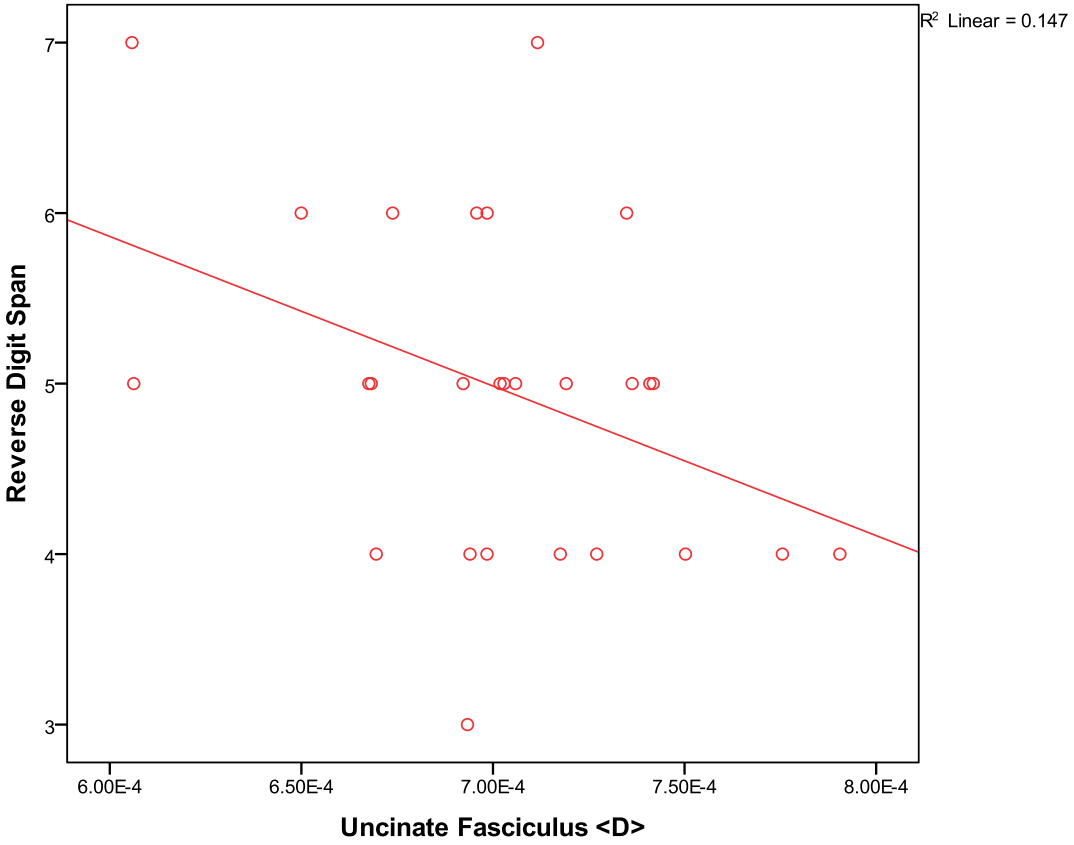


Figure 10. Association between Reverse Digit Span performance and uncinate fasciculus integrity



Performance in three measures of Logical Memory performance (Immediate Recall, Delayed Recall, and Delayed Recognition) all correlated with FA in the inferior longitudinal fasciculus whereby poorer recall and recognition scores were associated with lower FA. These relationships are depicted in Figures 11, 12, and 13 respectively.

Figure 11. Association between Logical Memory Immediate Recall performance and inferior longitudinal fasciculus integrity

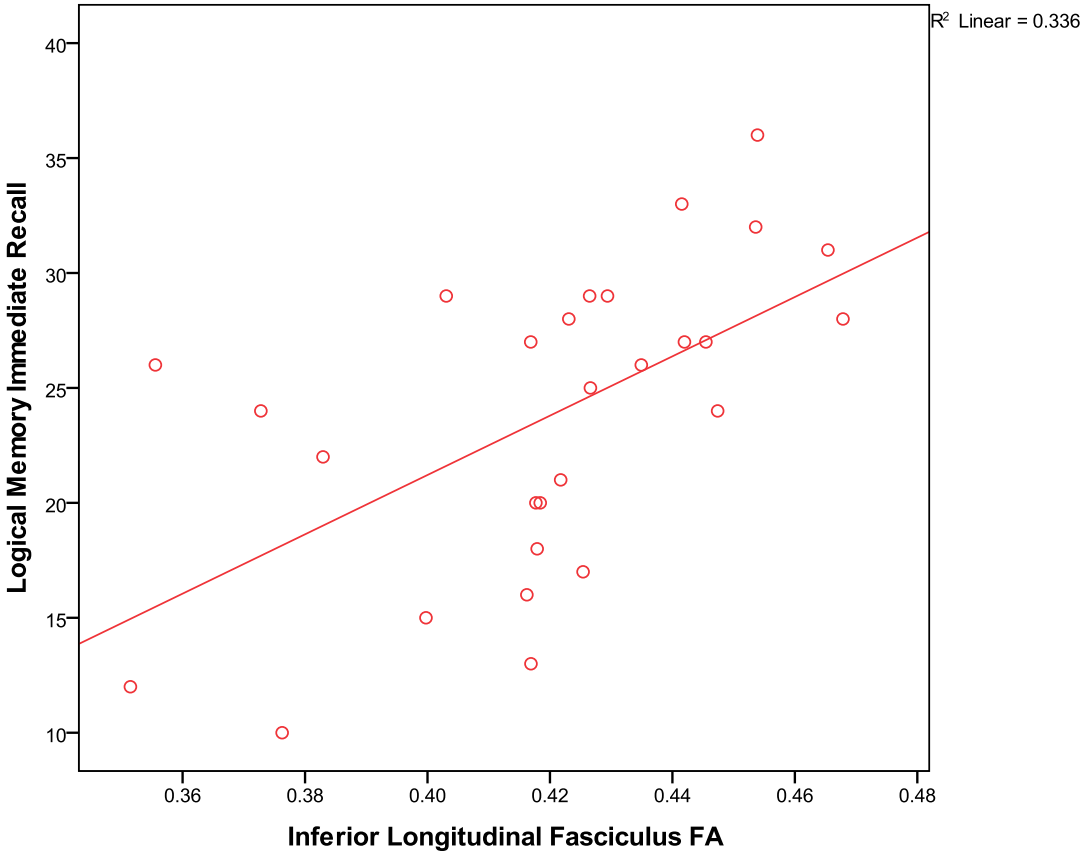


Figure 12. Association between Logical Memory Delayed Recall performance and inferior longitudinal fasciculus integrity

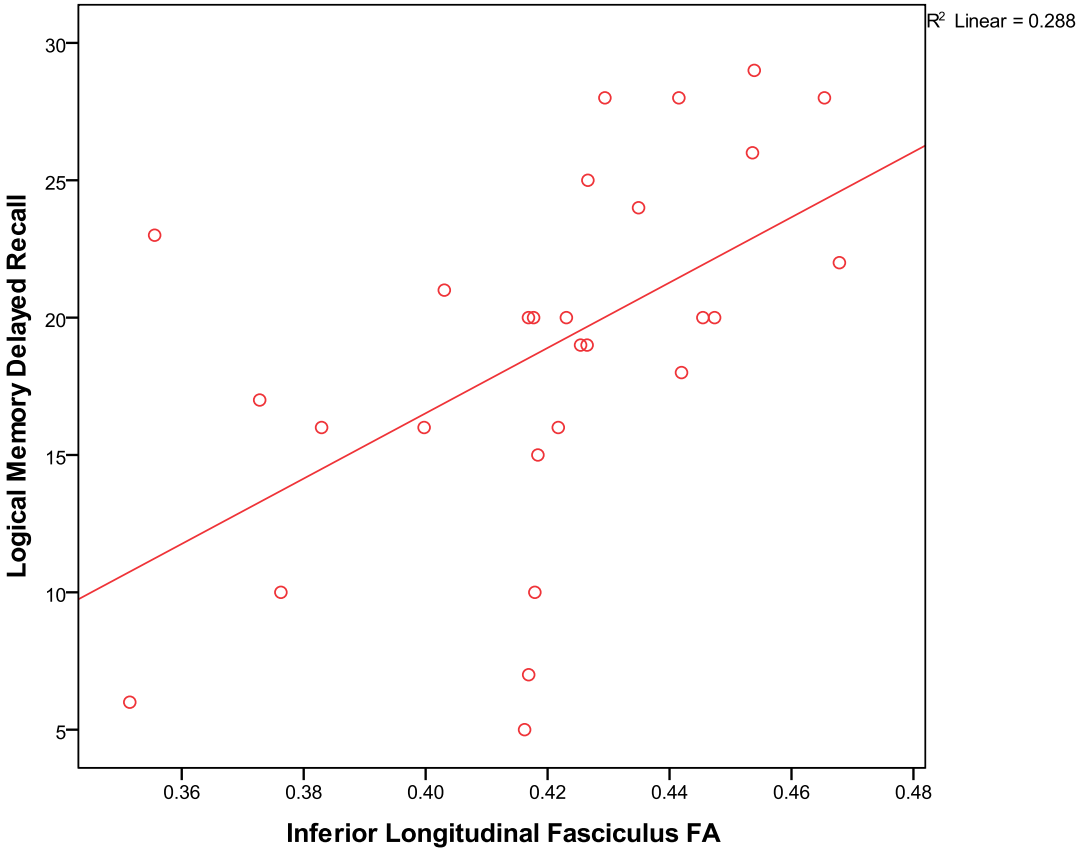
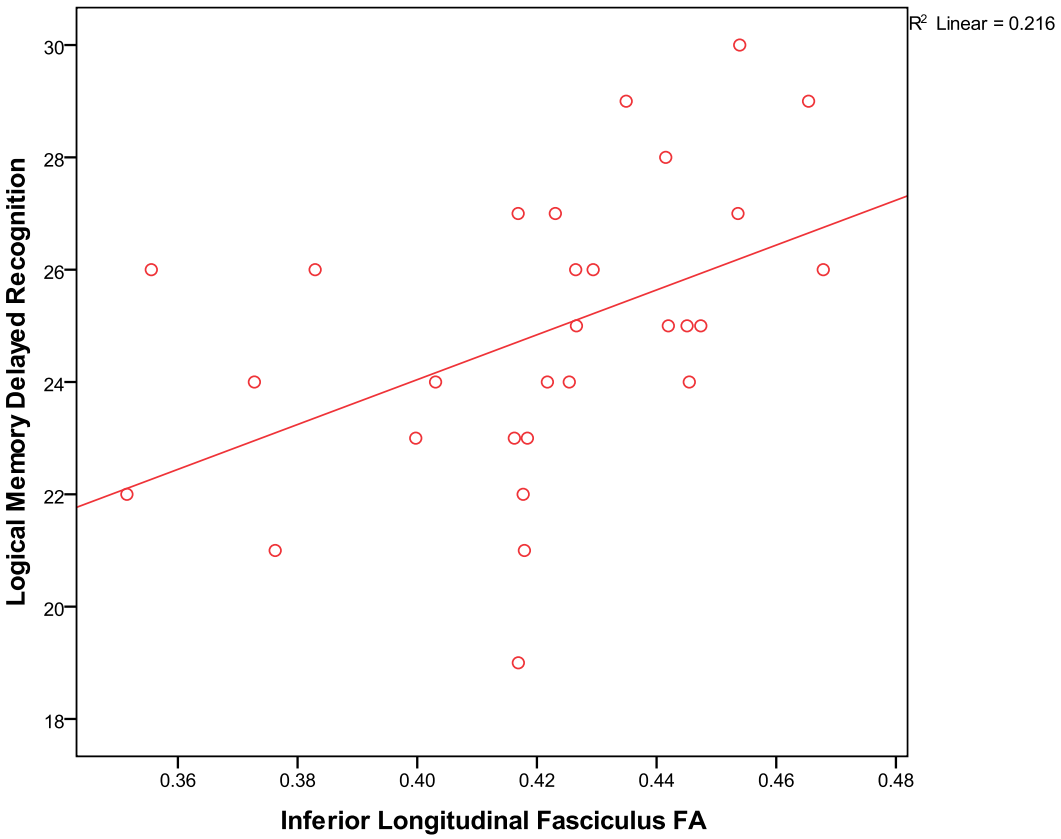
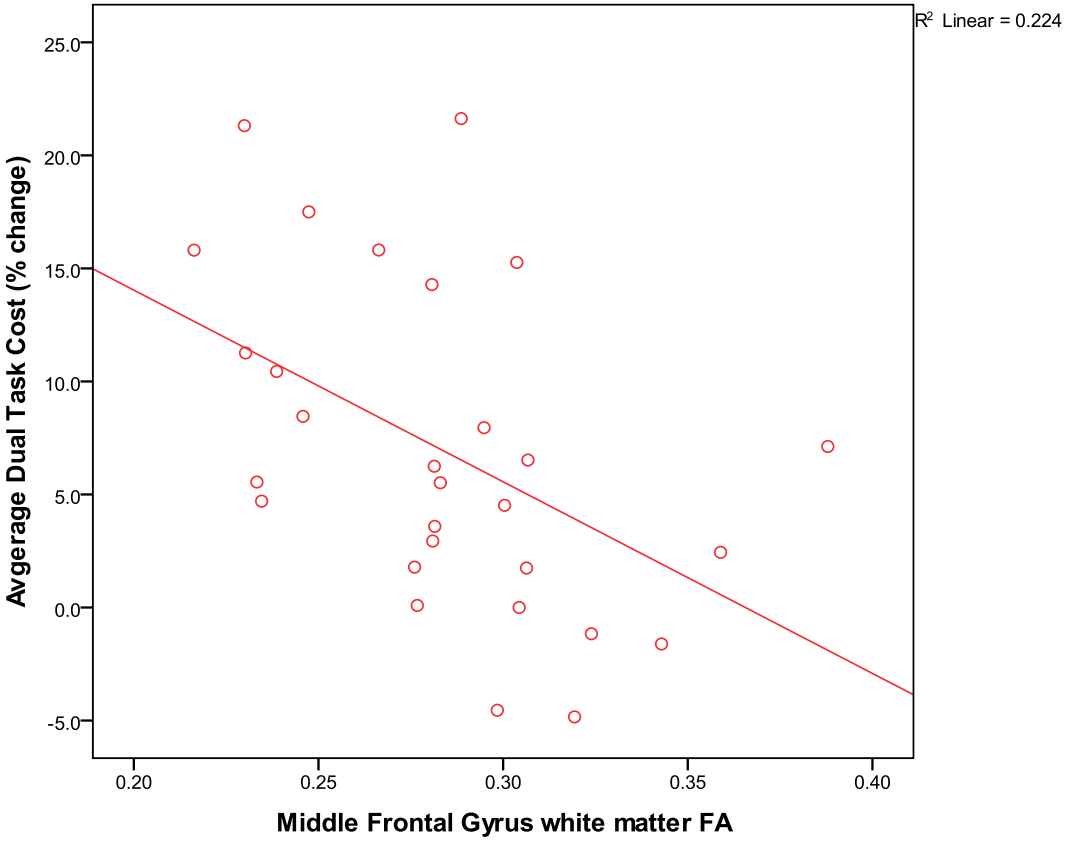


Figure 13. Association between Logical Memory Delayed Recall performance and inferior longitudinal fasciculus integrity



In terms of the experimental tasks, Average Dual Task Cost correlated with FA in white matter underlying the medial frontal gyri whereby higher percentage change between single and dual task conditions was associated with lower structural integrity. The relationship between Average Dual Task Cost and white matter integrity is presented in Figure 14.

Figure 14. Association between Average Dual Task Cost performance and middle frontal gyrus white matter integrity



6.3.5 ROI relationship with clinical variables

Comparative analyses were employed to investigate the effect of onset site (Bulbar vs. Limb) in all white matter regions/tracts; there were no significant group differences in any of the measures. Furthermore, Forced Vital Capacity predicted percentage values were not significantly associated with FA or ⟨D⟩ in any white matter regions. In addition, correlations were investigated between significantly different ROIs and disease parameters of severity (ALSFRS-R), duration and progression rate. Finally, correlational analyses were performed between corpus callosum segmentation parameters and the above disease parameters.

Significant correlations between white matter ROIs and disease parameters are displayed in Table 22. Disease duration and disease severity as measured by the ALSFRS-R did not correlate with any ROIs, however the index of disease progression rate correlated with corona radiata FA and a further strong trend was observed with FA of the corticospinal tract. Both associations indicated that faster disease progression rate was associated with lower FA and hence poorer integrity in regions implicating the major motor pathways. The relationship between progression rate and FA in the corona radiata and corticospinal tract is displayed in Figures 15 and 16 respectively.

Table 22. ROI correlations with disease parameters

	ROI	**Pearson's *r***	**p value (1-tailed)**
Progression Rate	Corona Radiata FA	-0.41	0.031
	Corticospinal Tract FA	-0.37	0.051

ROI – Region of Interest, ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised, FA = Fractional Anisotrophy, ⟨D⟩ = mean diffusivity.

Figure 15. Association between disease progression rate and corona radiata integrity

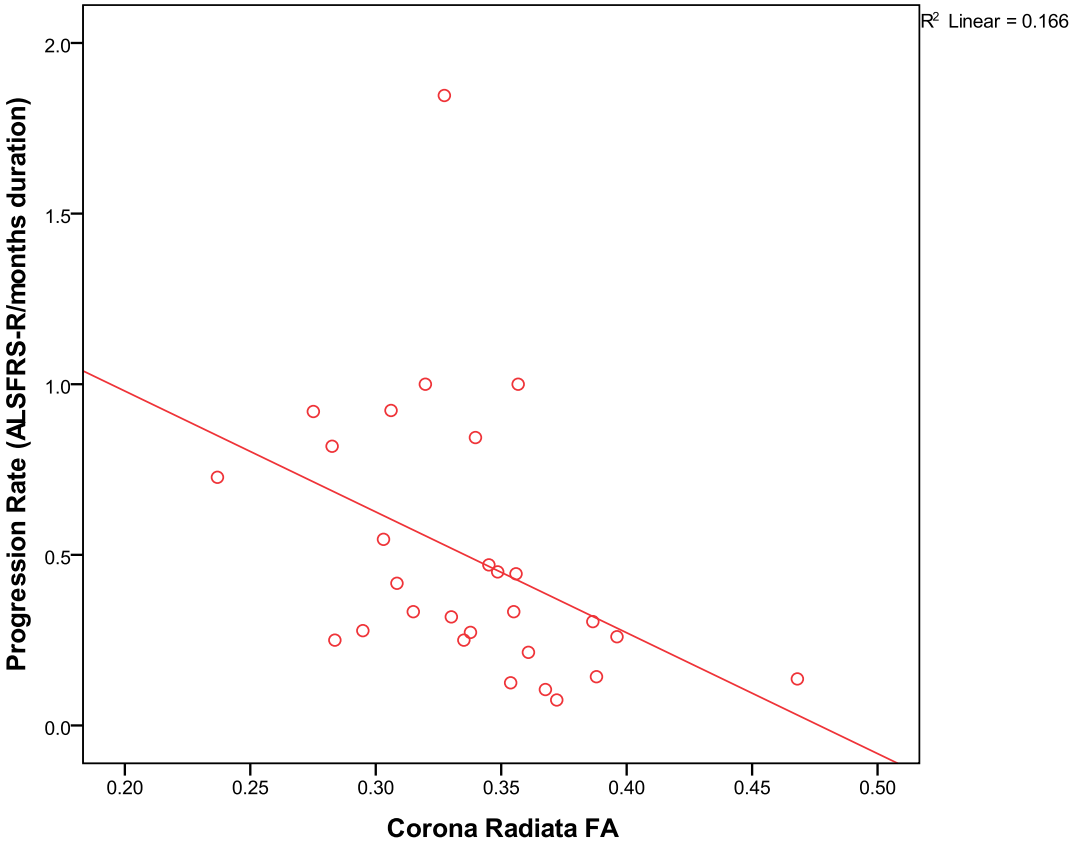
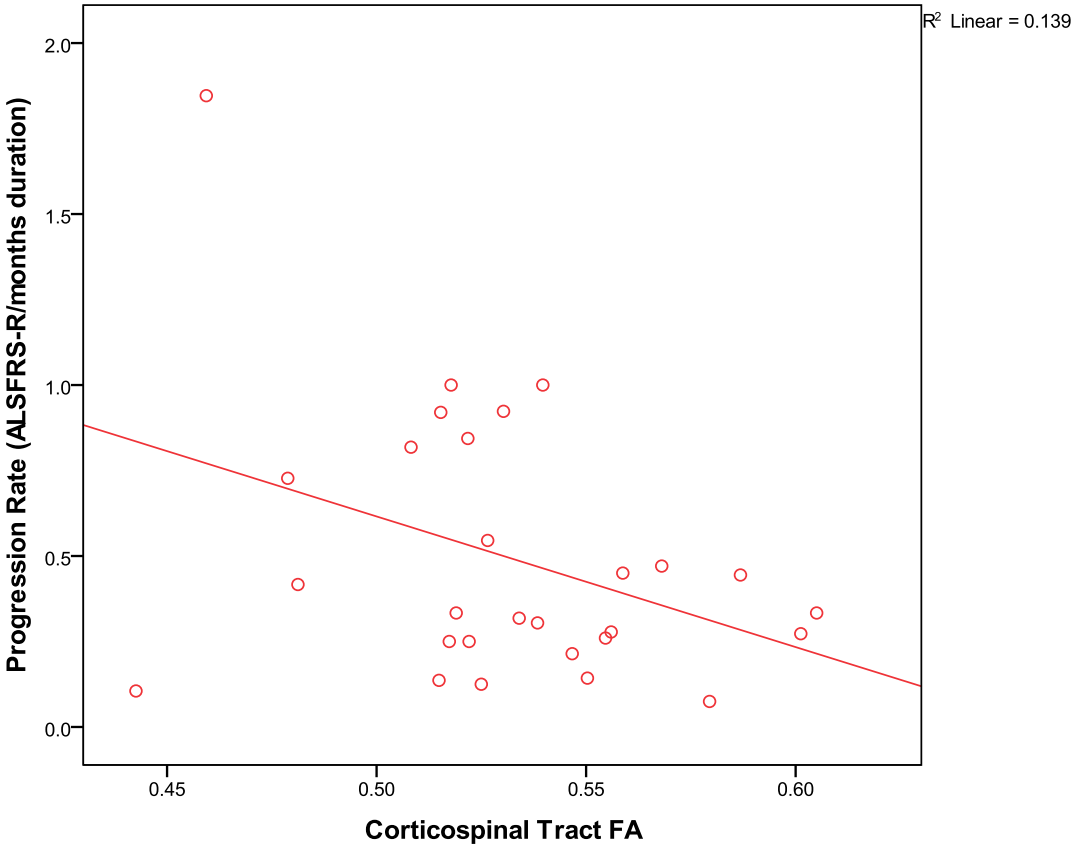


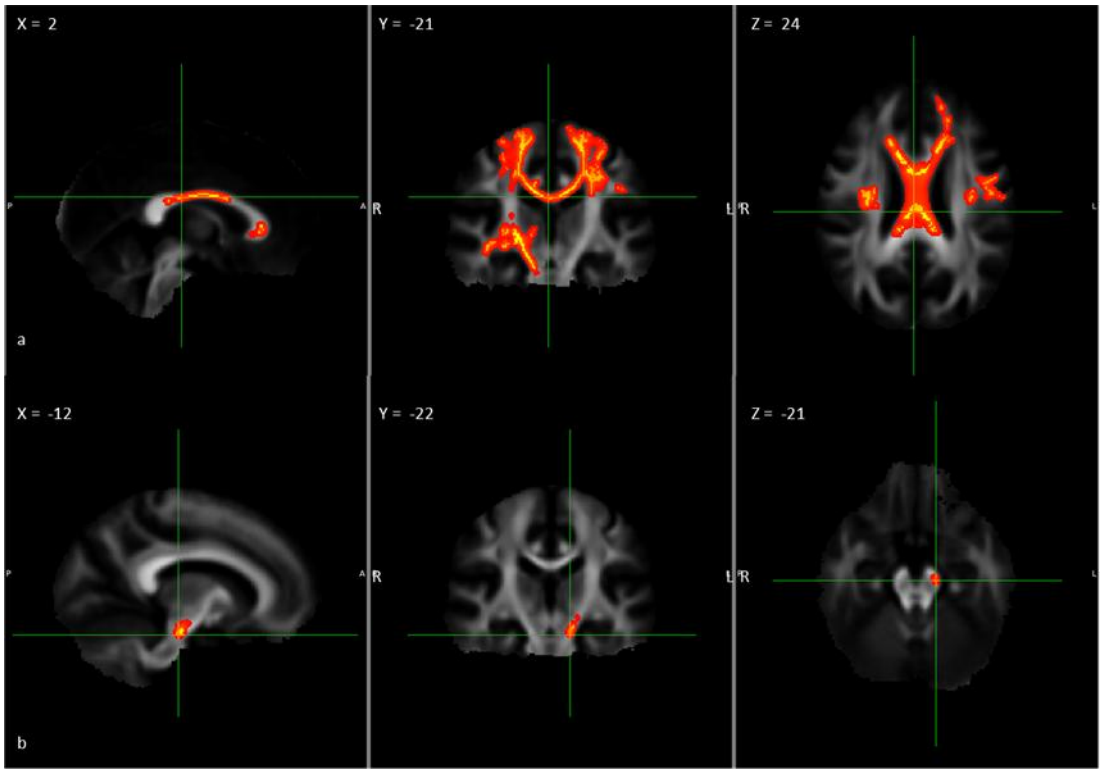
Figure 16. Association between disease progression rate and corticospinal tract integrity



6.3.6 TBSS group analyses

Voxel-wise group comparisons of ALS patients' and healthy controls' mean FA maps revealed two large significantly different clusters for the condition control FA > patient FA. Cluster 1 contained 13094 voxels with the highest intensity voxel located in the motor segment of the corpus callosum (Figure 17a); p = 0.004. Cluster 2 contained 207 voxels with the highest intensity voxel located in the corticospinal tract (Figure 17b); p = 0.048. No significant differences were revealed in the condition patient FA > control FA.

Figure 17. Group analysis of skeletal voxel FA showing location of highest intensity voxel within cluster 1 (a) and cluster 2 (b)

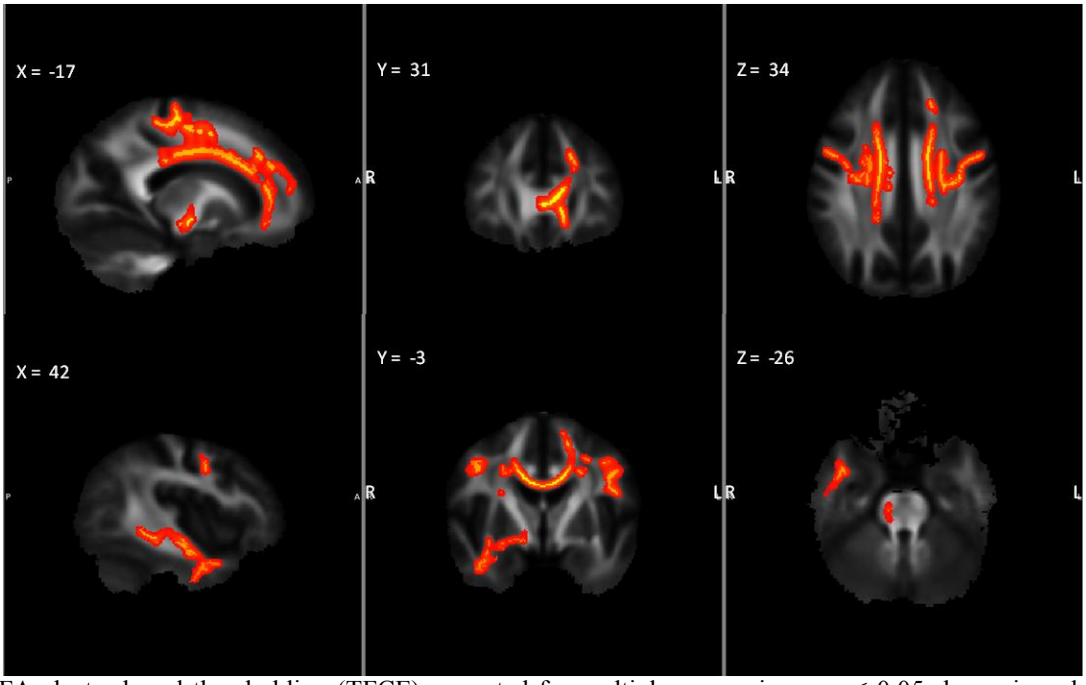


Panel a (top) = cluster 1, panel b (bottom) = cluster 2. FA cluster based thresholding (TFCE) corrected for multiple comparisons, $p \leq 0.05$ shown in red-yellow. Background: greyscale mean FA map for all participants. Crosshairs indicate highest intensity voxel; anatomical location given in MNI coordinates.

As can be seen in Figure 18, and Figure 19a, cluster 1 included large portions of the central and anterior corpus callosum, and extended dorsally to involve white matter underlying bilateral precentral gyri, and anteriorly into superior frontal gyrus white matter and anterior corona radiata. The cluster also extended ventrally from the corpus callosum with clear involvement of the corticospinal tract, and furthermore into right hemispheric temporal regions implicating the inferior longitudinal, inferior fronto-occipital, and uncinate fasciculus, as well as ventral (hippocampal) cingulum and superior temporal lobe white

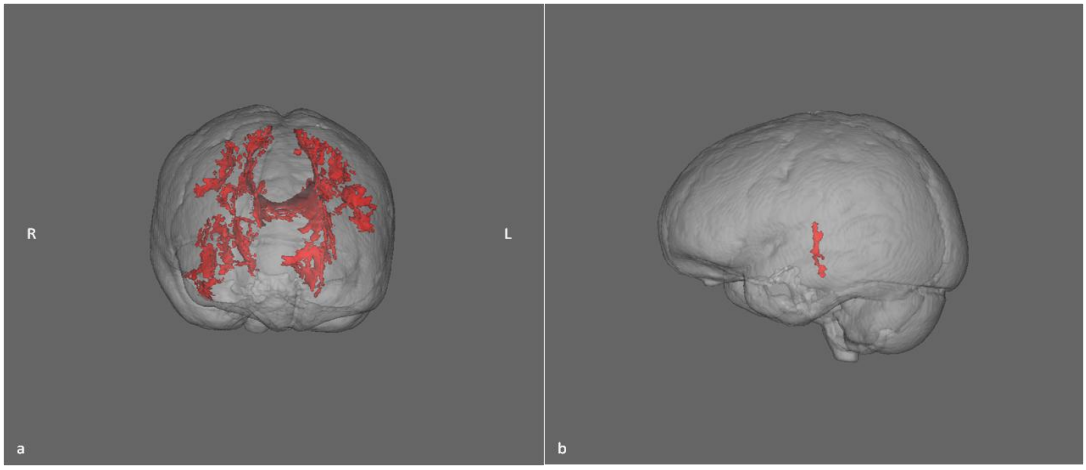
matter. By contrast, as shown in Figure 19b, cluster 2 was localised to the corticospinal tract.

Figure 18. Group analysis of skeletal voxel FA showing extent of cluster 1



FA cluster based thresholding (TFCE) corrected for multiple comparisons, $p \leq 0.05$ shown in red-yellow Background: greyscale mean FA map for all participants. Anatomical location given in MNI coordinates.

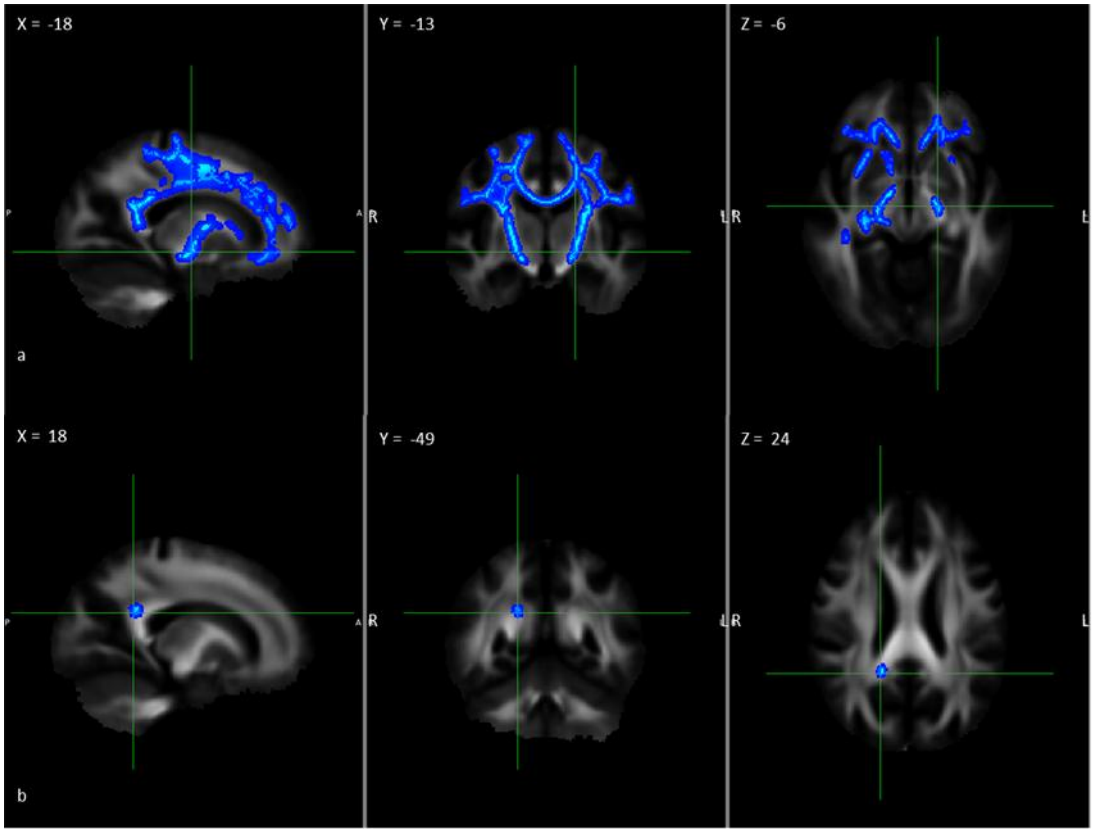
Figure 19. Three-dimensional rendering of FA cluster 1 (a) and cluster 2 (b)



Panel a (left) = cluster 1, panel b (right) = cluster 2. FA cluster based thresholding (TFCE) corrected for multiple comparisons, $p \leq 0.05$ shown in red. Background: standard MNI T1 1mm template.

Voxel-wise group comparisons of ALS patients' and healthy controls' mean ⟨D⟩ maps revealed two large significantly different clusters for the condition patient ⟨D⟩ > control ⟨D⟩. Cluster 1 contained 22385 voxels with the highest intensity voxel located in the left posterior limb of the internal capsule (PLIC) corresponding to the corticospinal tract (Figure 20a); $p = 0.008$. Cluster 2 was small containing only 23 voxels with the highest intensity voxel located in the right splenim (Figure 20b); $p = 0.05$. No significant differences were revealed in the condition control ⟨D⟩ > patient ⟨D⟩.

Figure 20. Group analysis of skeletal voxel ⟨D⟩ showing location of highest intensity voxel within cluster 1 (a) and cluster 2 (b)

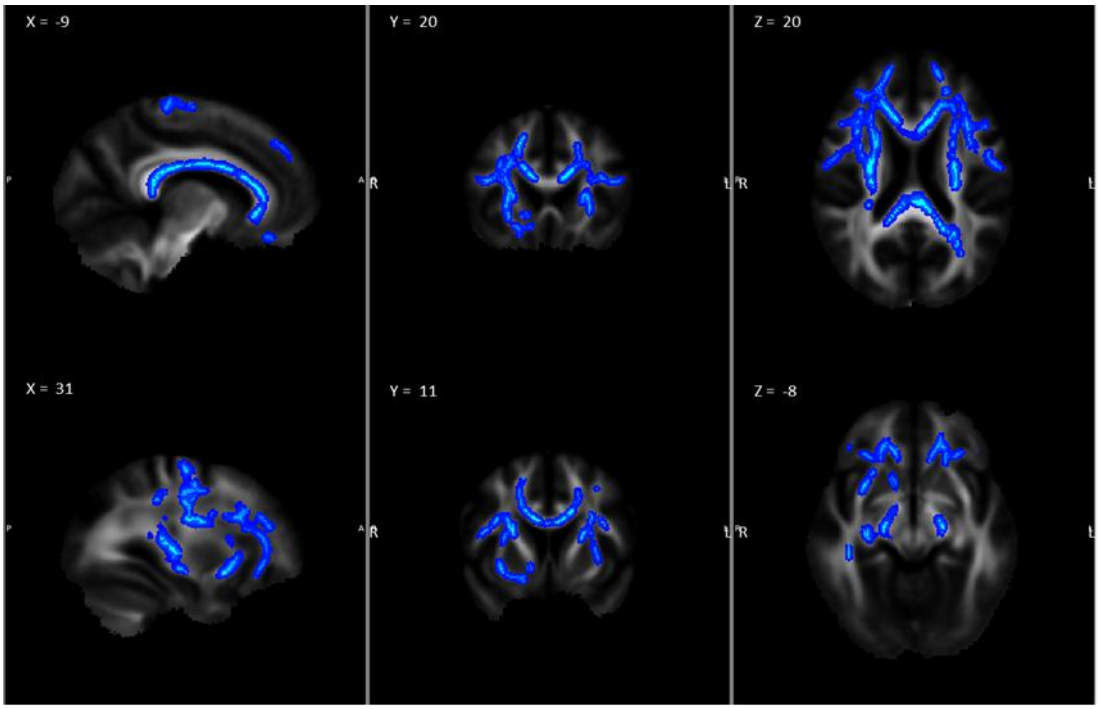


Panel a (top) = cluster 1, panel b (bottom) = cluster 2. ⟨D⟩ cluster based thresholding (TFCE) corrected for multiple comparisons, $p \leq 0.05$ shown in blue-light blue. Background: greyscale mean FA map for all participants. Crosshairs indicate highest intensity voxel; anatomical location given in MNI coordinates.

As can be seen in Figure 21 and Figure 22a and b, cluster 1 comprised large portions of the corpus callosum including bilateral genu and left splenium, and extended dorsally to involve white matter underlying bilateral precentral gyri and superior corona radiata. In addition, the cluster extended anteriorly into bilateral inferior, middle and superior frontal gyrus white matter as well as anterior corona radiata. The cluster also extended ventrally from the corpus callosum with clear involvement of the corticospinal tract, and further into right hemispheric temporal regions implicating the inferior longitudinal, inferior fronto-occipital and uncinate

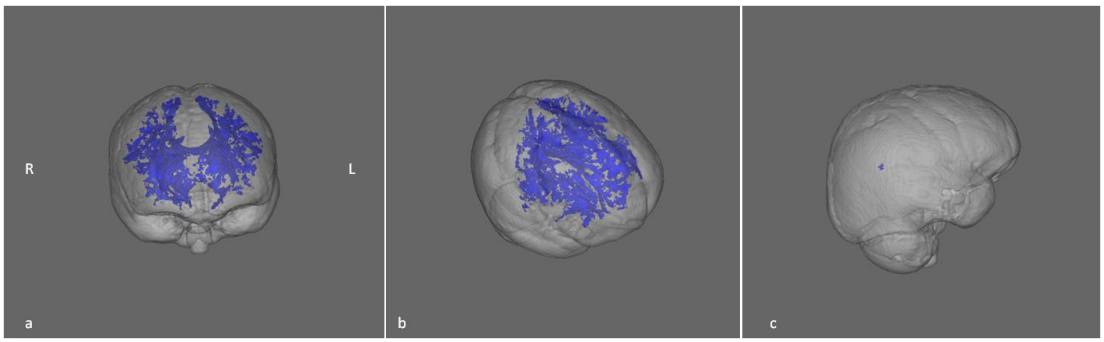
fasciculus, as well as ventral (hippocampal) cingulum. By contrast, as shown in Figure 22c, cluster 2 was localised to the right splenium.

Figure 21. Group analysis of skeletal voxel ⟨D⟩ showing extent of cluster 1



⟨D⟩ cluster based thresholding (TFCE) corrected for multiple comparisons, $p \leq 0.05$ shown in blue-light blue. Background: greyscale mean FA map for all participants. Anatomical location given in MNI coordinates.

Figure 22. Three-dimensional rendering of ⟨D⟩ cluster 1 (a and b) and cluster 2 (c)

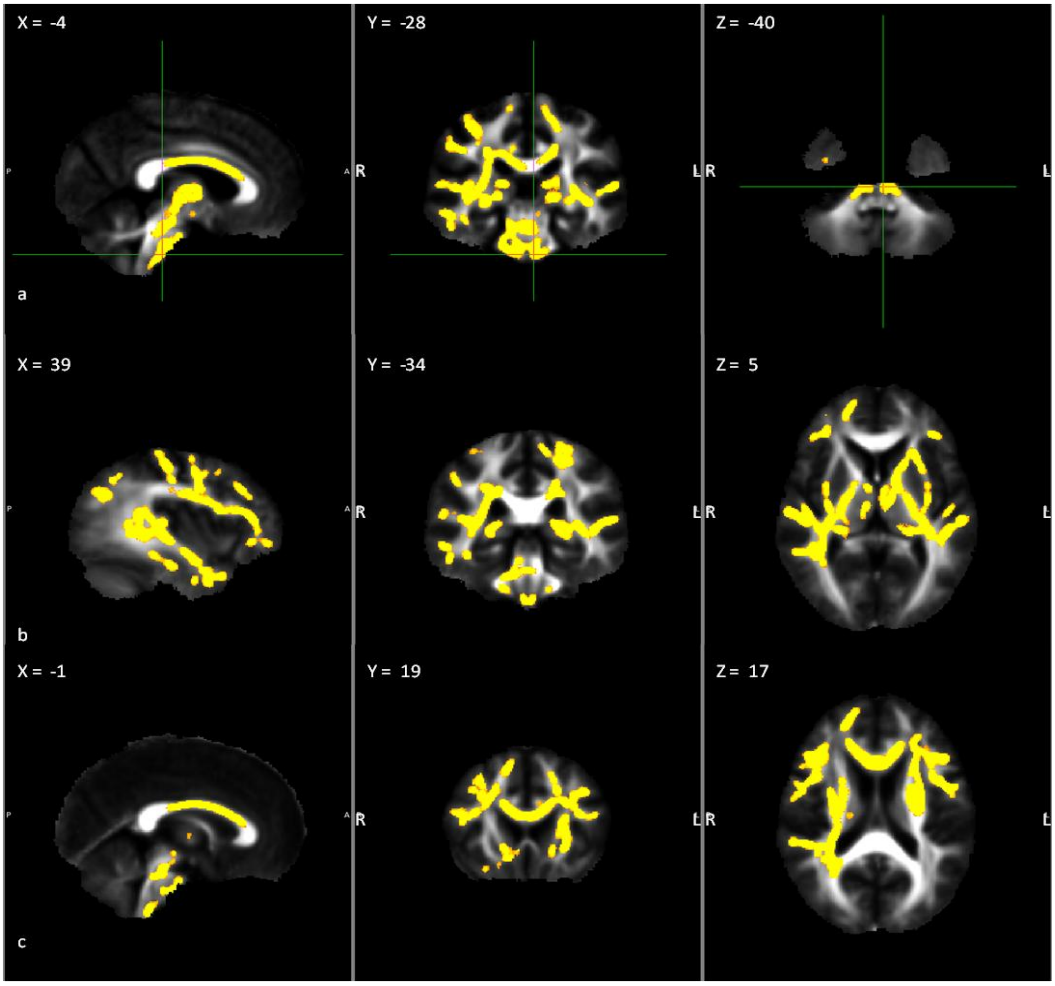


Panels a and b (left and middle) = cluster 1, panel c (right) = cluster 2. ⟨D⟩ cluster based thresholding (TFCE) corrected for multiple comparisons, $p \leq 0.05$ shown in blue. Background: standard MNI T1 1mm template.

6.3.7 TBSS correlates

Correlational analyses between patient performance in cognitive tests and FA and ⟨D⟩ maps revealed a significant association between fluency indices (*fi*) in the Spoken Letter Fluency Test and FA values. When the cluster threshold was set at $p = 0.05$, a single large cluster was revealed containing 32891 voxels with the highest intensity voxel located in the corticopsinal tract (Figure 23a); $p = 0.006$. Figure 23 (a, b, and c) shows that the cluster extended dorsally from lower portions of the corticopsinal tracts through the thalamic nuclear complex and internal and external capsules, and into central and anterior portions of the corpus callosum, as well as involving white matter underlying the postcentral and precentral gyri. Moreover, the cluster extended anteriorly to involve bilateral inferior, middle and superior frontal gyri white matter, and into temporal regions implicating right inferior longitudinal fasciculus and inferior fronto-occipital fasciculus, as well as bilateral fornix and white matter underlying the superior and medial temporal gyri.

Figure 23. Skeletal FA voxels correlated with ALS patient letter fluency indices at p = 0.05. Location of highest intensity voxel (a), and extent of cluster (b and c)

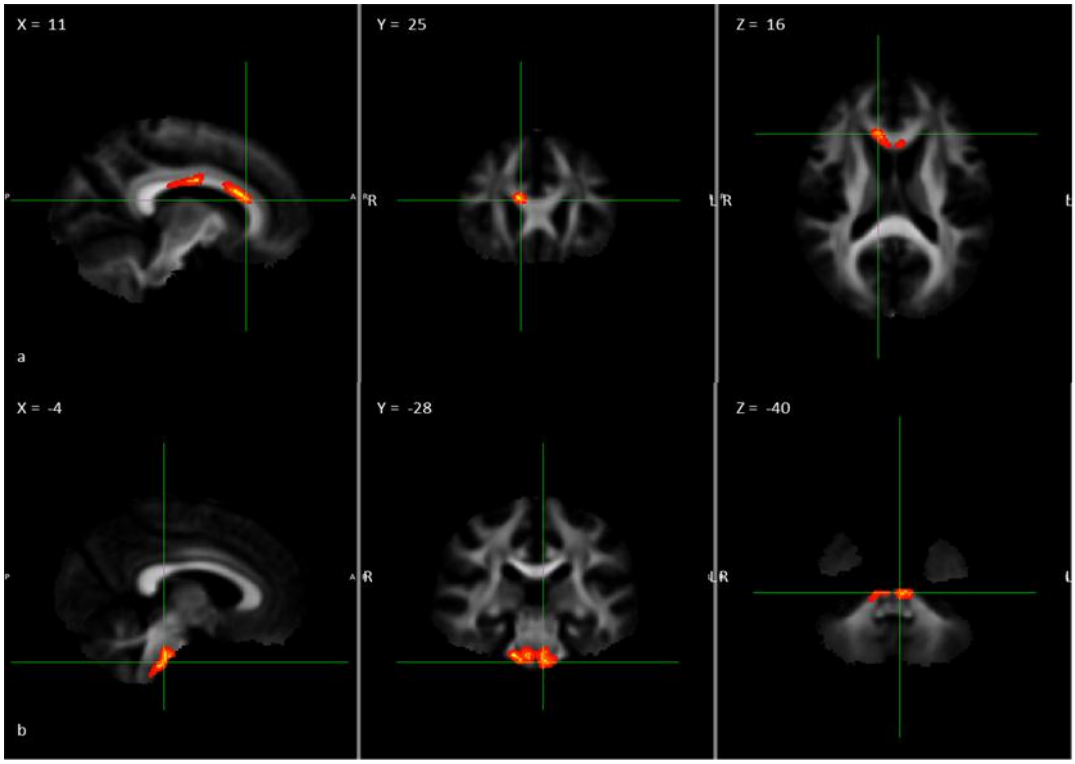


Panel a (top) = highest intensity voxel, panel b (middle) = temporal aspect of cluster, panel c (bottom) = anterior aspect of cluster. FA cluster based thresholding (TFCE) corrected for multiple comparisons, $p \leq 0.05$, corrected for effects of age, shown in yellow. Background: greyscale mean FA map for all participants. Crosshairs indicate highest intensity voxel; anatomical location given in MNI coordinates.

To identify the white matter regions most associated with fluency index scores, the cluster threshold was subsequently set at p = 0.001 which revealed 2 significant clusters. Cluster 1 contained 1385 voxels with the highest intensity voxel located in the anterior portion of the

corpus callosum (Figure 24a); p = 0.008. Cluster 2 contained 456 voxels with the highest intensity voxel located in the left corticospinal tract (Figure 24b); p =0.006.

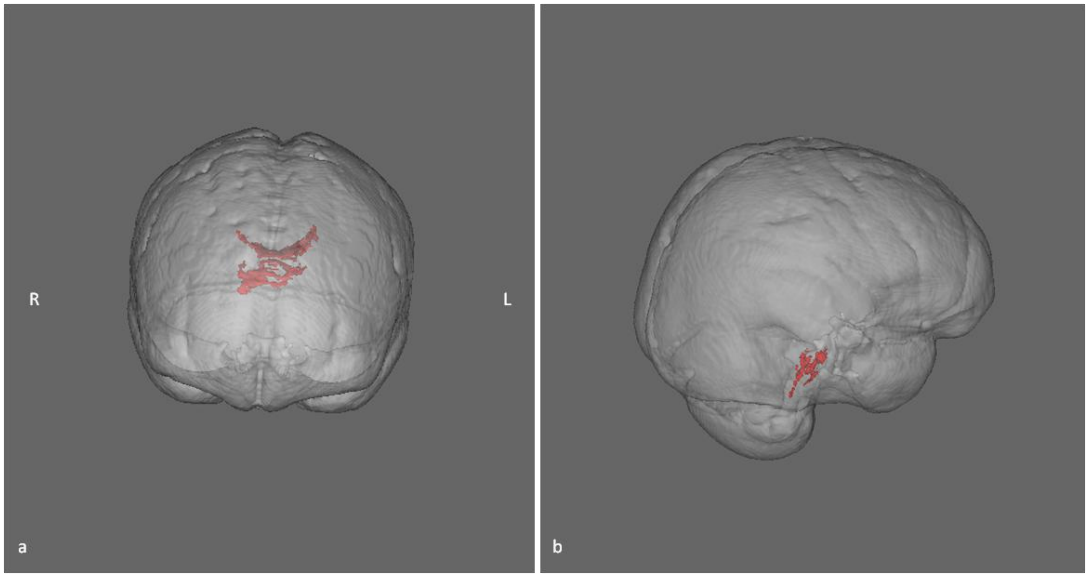
Figure 24. Skeletal FA voxels correlated with ALS patient letter fluency indices at p = 0.01. Location of highest intensity voxel in cluster 1 (a), and cluster 2 (b)



Panel a (top) = cluster 1, panel b (bottom) = cluster 2. FA cluster based thresholding (TFCE) corrected for multiple comparisons, $p \leq 0.05$, corrected for effects of age, shown in red-yellow. Background: greyscale mean FA map for all participants. Crosshairs indicate highest intensity voxel; anatomical location given in MNI coordinates.

Figure 24a and Figure 25a show that cluster 1 was localised to anterior and central portions of the corpus callosum while cluster 2 was localised to bilateral corticospinal tracts (Figures 24b and 25b). No further correlations were found between any cognitive tests and voxel FA or $\langle D \rangle$ in ALS patients.

Figure 25. Three-dimensional rendering of FA cluster 1 (a) and cluster 2 (b) correlation with letter fluency indices



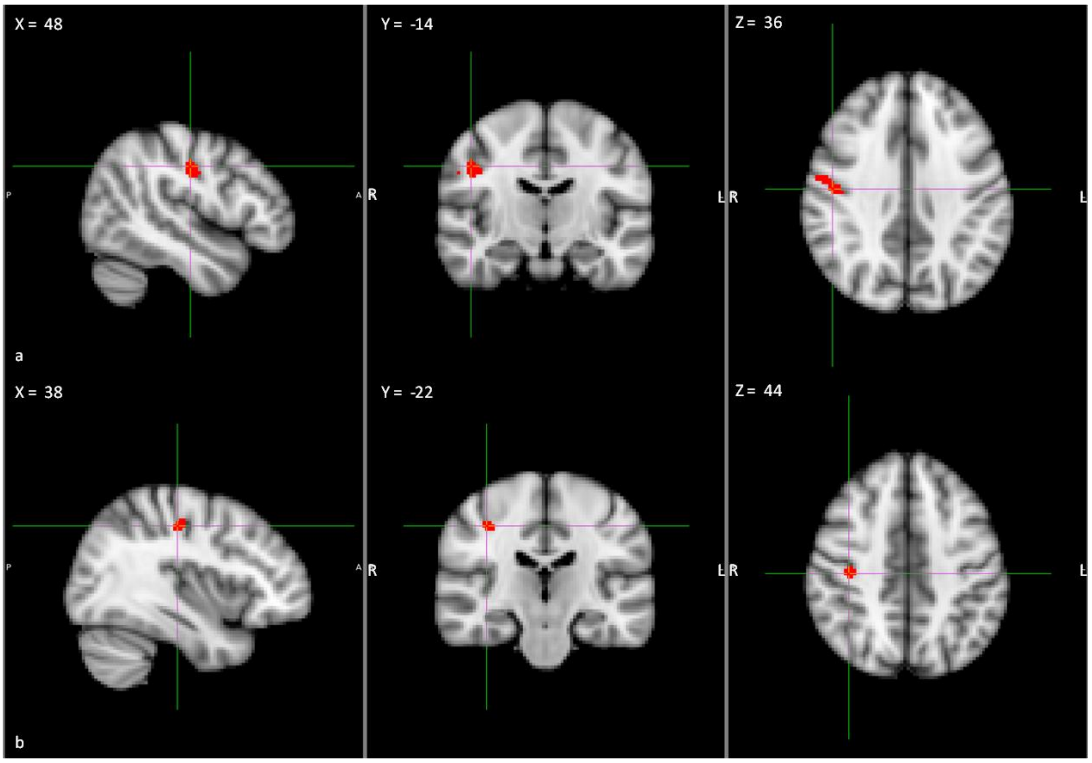
Panel a (left) = cluster 1, panel b (right) = cluster 2. FA cluster based thresholding (TFCE) corrected for multiple comparisons, $p \leq 0.05$, corrected for effects of age, shown in red. Background: standard MNI T1 1mm template.

6.3.8 VBM grey matter between group analyses

Whole brain voxel-wise group comparisons of ALS patients' and healthy controls' volumetric data failed to show significant group differences for either the control volume > patient volume condition or patient volume > control volume condition. Based on areas showing significant group differences in the white matter ROI analysis, the following VBM ROI templates were created and tested for group effects; frontal pole, medial frontal gyrus, inferior frontal gyrus, motor region (pre-central and post-central gyri), cingulate gyrus and temporal gyri (medial temporal gyri, superior temporal gyri and parahippocampal gyri).

Voxel-wise group comparisons in the motor ROI revealed two large significantly different clusters for the condition control volume > patient volume. Cluster 1 contained 122 voxels with the highest intensity voxel located in right pre-central/post-central junction (Figure 26a); p = 0.009. Cluster 2 was small containing 29 voxels with the highest intensity voxel also located in right pre-central/post-central junction (Figure 26b); p = 0.024. No significant differences were found in the patient volume > control volume condition.

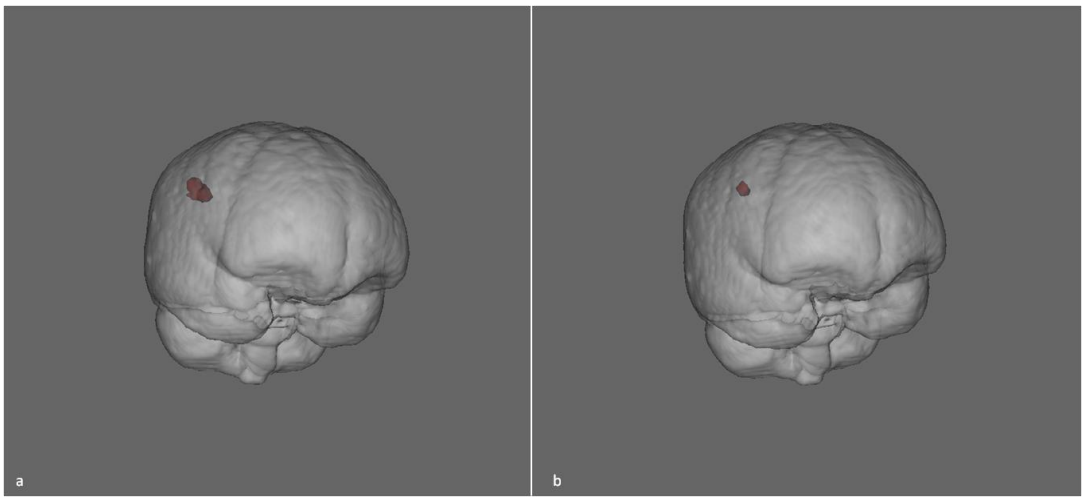
Figure 26. Group analysis of voxel volumes in motor ROI showing location of highest intensity voxel within cluster 1 (a) and cluster 2 (b)



Panel a (top) = cluster 1, panel b (bottom) = cluster 2. FA cluster based thresholding (TFCE) corrected for multiple comparisons, $p \leq 0.05$, corrected for effects of age, shown in red. Background: standard MNI T1 2mm template. Crosshairs indicate highest intensity voxel; anatomical location given in MNI coordinates.

Figures 26 and 27 show that both cluster 1 and cluster 2 were localised to the junction between the right pre-central and post-central gyri, with the larger cluster occupying a more lateral aspect.

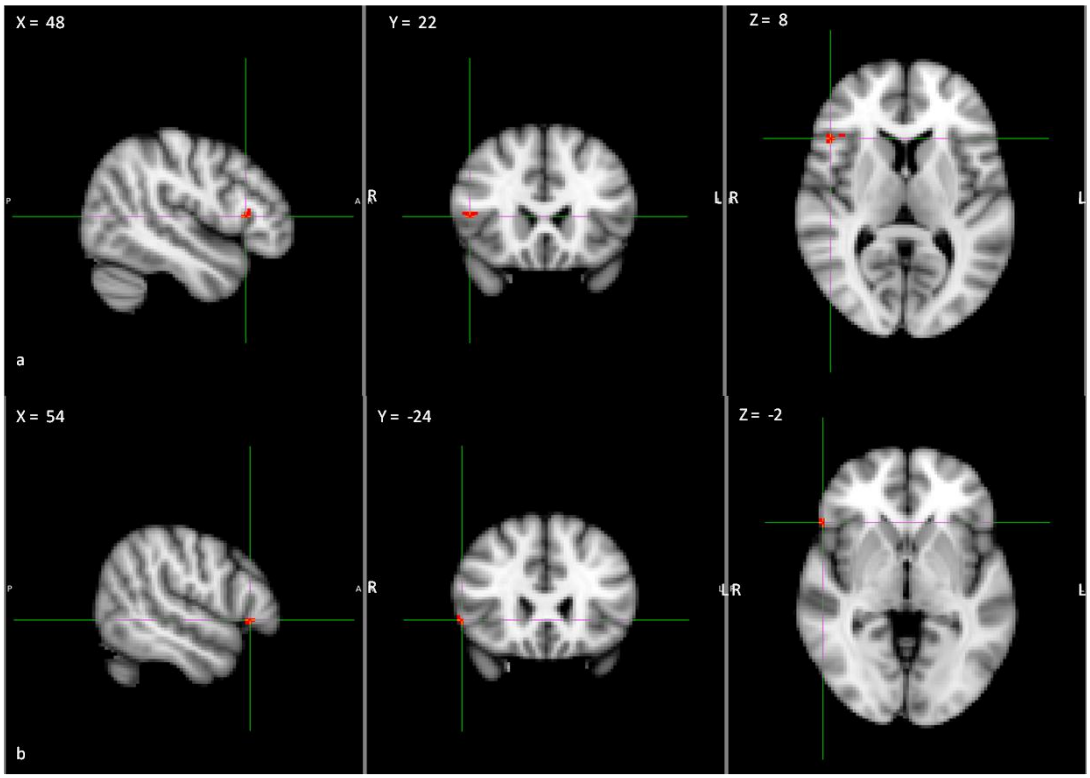
Figure 27. Three-dimensional rendering of VBM analysis in motor region showing cluster 1 (a) and cluster 2 (b)



Panel a (left) = cluster 1, panel b (right) = cluster 2. VBM cluster based thresholding (TFCE) corrected for multiple comparisons, $p \leq 0.05$, corrected for effects of age, shown in red. Background: standard MNI T1 1mm template.

Voxel-wise group comparisons in the inferior frontal gyrus ROI revealed two large significantly different clusters for the condition control volume > patient volume. Cluster 1 was small containing 22 voxels with the highest intensity voxel located in right inferior frontal gyrus (Figure 28a); $p = 0.025$. Cluster 2 was very small containing 10 voxels with the highest intensity voxel also located in right inferior frontal gyrus (Figure 28b); $p = 0.044$. No significant differences were found in the patient volume > control volume condition.

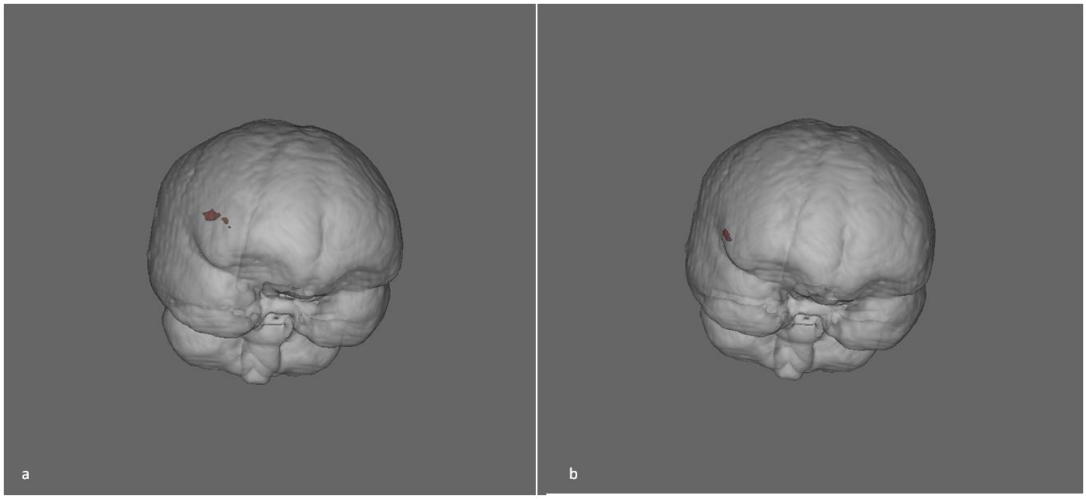
Figure 28. Group analysis of voxel volumes in inferior frontal gyrus ROI showing location of highest intensity voxel within cluster 1 (a) and cluster 2 (b)



Panel a (top) = cluster 1, panel b (bottom) = cluster 2. FA Cluster based thresholding (TFCE) corrected for multiple comparisons, $p \leq 0.05$, corrected for effects of age, shown in red. Background: standard MNI T1 2mm template. Crosshairs indicate highest intensity voxel; anatomical location given in MNI coordinates.

Figures 28 and 29 show that both cluster 1 and cluster 2 were localised to the right inferior frontal gyrus, with the larger cluster occupying a more dorsal aspect.

Figure 29. Three-dimensional rendering of VBM analysis in inferior frontal gyrus showing cluster 1 (a) and cluster 2 (b)



Panel a (left) = cluster 1, panel b (right) = cluster 2. VBM cluster based thresholding (TFCE) corrected for multiple comparisons, $p \leq 0.05$, corrected for effects of age, shown in red. Background: standard MNI T1 1mm template.

No significant group differences were found in any of the other VBM ROI analyses. No significant correlations were found between patient whole-brain or ROI voxel volumes and performance in cognitive tests.

6.4 Summary

The white matter ROI analyses revealed extensive changes in structural integrity in ALS patients relative to healthy controls. The ALS patient group showed increased ⟨D⟩ and reduced FA in anterior corona radiata and in white matter underlying superior, middle, and inferior frontal gyri, as well as in white matter underlying temporal gyri. In addition,

changes were evident in the anterior thalamic radiation which connects the thalamus to areas of the prefrontal cortex, as well as in the anterior and ventral portions of the cingulum, which connects subcallosal regions to the frontal lobes and hippocampus respectively. The observed pattern of impoverished integrity in prefrontal associative fibres and cingulum, with preserved integrity in parietal and posterior regions is largely consistent with a previous study showing volumetric white matter reductions in similar regions using less refined automated volumetric estimations (Abrahams et al., 2005). In agreement with other studies (Abrahams et al., 2005; Agosta et al., 2007; Sarro et al., 2011), reduced structural integrity was observed in the corpus callosum which has been suggested to be one of the most consistent MRI findings in ALS (Filippini et al., 2010). Substantial changes were observed in the corticospinal tracts, indicative of upper motor neuron pathology which has been consistently shown in previous DTI investigations (Abe et al., 2004; Ciccarelli et al., 2006; Agosta et al., 2010). Moreover, ALS patients have reduced FA in the corona radiata which projects primarily to motor regions of the cortex providing further evidence of upper motor neuron pathology. Reduced white matter integrity was also found in ROI sampling of the uncinate fasciculus which connects the temporal lobes and amygdala to orbitofrontal and inferior regions of the prefrontal lobes, a result which is consistent with other studies in ALS (Sato et al., 2010; Agosta et al., 2010) and FTD (Matsuo et al., 2008). Concordant with a recent DTI investigation (Sarro et al., 2011), ALS patients showed reduced structural integrity in the inferior longitudinal fasciculus, one of the long association bundles connecting the temporal and occipital lobes.

The pattern of results revealed in the TBSS analysis was largely consistent with those revealed by the ROI analysis. Analysis of voxel FA and ⟨D⟩ values showed that ALS patients had reduced structural integrity relative to healthy controls in motor regions

corresponding to the corticospinal tracts and white matter underlying the pre-central and post-central gyri which corresponds to the corona radiata region in the ROI analysis. Reduced white matter integrity was also found in the corpus callosum; notably in the FA analysis this was restricted to central and anterior portions whereas the ⟨D⟩ analysis revealed changes throughout the corpus callosum including the genu and splenium. Such findings are consistent with a multitude of studies employing VBM style analysis of diffusion data (e.g. Sach et al., 2004; Agosta et al., 2007) as well as those employing TBSS (e.g. Ciccarelli et al., 2009; Prudlo et al., 2012). Moreover, the fact that the highest intensity voxel in the ⟨D⟩ analysis was located in the PLIC lends further support to the meta-analysis of Li et al. (2012) who showed that the PLIC was the most sensitive region of the corticospinal tract for detecting white matter damage in ALS. Consistent with the ROI investigation, changes in ALS patients were observed in prefrontal regions; reduced FA was found in superior frontal gyrus and anterior corona radiata, and in the ⟨D⟩ analysis changes were extended to the inferior and middle frontal gyri. These findings are concordant with previous investigations employing TBSS, particularly those of Sage et al. (2009) and Ciccarelli et al. (2009) who reported reduced FA in multiple prefrontal regions including white matter fibres underlying superior, inferior, and dorsolateral prefrontal cortex as well as the hippocampal formations. White matter integrity reductions were also revealed in several temporal regions in the TBSS analyses, with changes predominantly located in the right hemisphere. Significant group differences were observed in FA and ⟨D⟩ clusters implicating major white matter tracts of the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus in addition to association fibres underlying superior temporal gyrus. Previous investigations employing both TBSS and tractography techniques have reported similar involvement of major longitudinal tracts (Sarro et al., 2011; Prudlo et al., 2012). Finally, in agreement with the ROI analysis and previous investigations (Sage et al., 2009; Senda et al., 2011), reduced structural integrity was observed in ventral/posterior cingulum, although

corresponding changes in anterior portions were not observed. Of note, there was a distinct lack of FA or ⟨D⟩ changes in both the ROI and TBSS analyses in posterior regions (posterior parietal or occipital regions).

The TBSS analysis employed in the current investigation may suggest that ⟨D⟩ is more sensitive to white matter changes in ALS than FA; the ⟨D⟩ analysis involved more significant voxels than the FA analysis in the major clusters (22385 vs 13094) and encompassed more regions. Other investigators (Agosta et al., 2007; Canu et al., 2011) have also found ⟨D⟩ to be more sensitive to prefrontal white matter changes, although Sage et al. (2007, 2009) reported more changes in FA. However, although ⟨D⟩ may be the more sensitive diffusion parameter, more correlations (in ROI and TBSS analyses) were observed between cognitive measures/disease parameters and FA suggesting that FA changes may be more relevant to functional changes in ALS.

In terms of correlations between MRI parameters and cognitive performance in ALS, the white matter ROI analysis appeared to be the most sensitive measure. Average Dual Task Cost scores correlated with FA values in middle frontal gyrus white matter, whereby poorer performance was associated with lower white matter integrity. The middle frontal gyrus (or dorsolateral prefrontal cortex) is thought to be highly influential in the regulation of executive processes such as strategy formation, set-shifting and working memory (Stuss, 2002; Royall et al., 2002) and was previously identified as a site of dysfunction in ALS in functional imaging (Abrahams et al. 1996; 2004). The neural correlates of dual tasking are hotly debated (Erickson et al., 2005), however the white matter region identified by the current study correspond wells to the prefrontal areas that were suggested to reflect central

executive activity in functional imaging studies of dual tasking in healthy adults (D'Esposito et al., 1995). Moreover, subsequent functional imaging studies have demonstrated the importance of the bilateral frontal gyri (including the dorsolateral prefrontal cortex) in managing and coordinating response selection and interference (MacDonald et al., 2000; Wager & Smith, 2003), and it is possible that the white matter findings presented in this study underpin dysfunction in these processes. It has also been suggested that executive functioning is best understood in terms of interactions between networks of regions (Collette & Van der Linden, 2002), and that dual tasks impose higher processing demands on cortical areas already involved in the component single tasks. Thus, it is also possible that the correlation with white matter underlying dorsolateral prefrontal cortex may be a reflection of the high demands on working memory that are required to maintain performance on the DDR task whilst completing a concurrent task.

Of particular interest is the finding that performance in the dual task was associated with different white matter pathways than the commonly reported letter fluency deficits. Scores in the Spoken Letter Fluency Test (*fi*) were associated with low FA in the corpus callosum in the ALS cohort. A previous study has implicated volumetric reductions in anterior portions of the corpus callosum amongst other prefrontal and temporal regions in ALS patients with impaired letter fluency (Abrahams et al., 2005); the results of the current study further builds on these findings to demonstrate a direct correlation between fluency performance and structural integrity of the corpus callosum. Further support for the importance of corpus callosum integrity to ALS cognition is provided by Sarro and colleagues (2011) who reported correlations between corpus callosum FA and performance in another test of executive functioning, namely the Trail Making Task. Moreover, an early structural investigation by Yamauchi and others (1995) suggested that pathology in the

anterior portion of corpus callosum was associated with cognitive and behavioural changes. Although the methods employed by our corpus callosum segmentation analysis were unable to differentiate between discrete portions of the corpus callosum, trends in the ROI analysis toward low FA in the genu, but not splenium, may indicate the presence of an anterior gradient of corpus callosum involvement as postulated by others (Filippini et al., 2010). Indeed, the TBSS analysis of FA indicated greater involvement of anterior corpus callosum, and subsequent correlational analyses revealed significant association between this region and performance in the Spoken Letter Fluency Test (*fi*). Such consistency between the ROI and TBSS analyses suggests that the relationship between corpus callosum integrity and letter fluency performance is robust. Furthermore, the observed correlation between letter fluency performance and corticospinal tract integrity in both the ROI and TBSS analyses suggests that fluency performance may be sensitive to disease severity. This may be related to the propensity for patients with bulbar onset to show more upper motor neuron degeneration, as well as being more likely to exhibit cognitive impairment (Abrahams et al., 1997). However, some longitudinal studies have suggested that cognitive impairment occurs early in the disease and does not progress at the same rate as motor dysfunction (Schreiber et al., 2005). Nevertheless, the fact that letter fluency was the only cognitive measure to correlate with ROI and TBSS analyses, with the same regions implicated by both techniques, is further evidence that fluency impairments are one of the core deficits that characterize cognitive change in ALS. Thus, performance in these two tests of executive functioning appears to be underpinned by different white matter pathways; letter fluency appears to be sensitive to changes in the corpus callosum and particularly regions linking the prefrontal cortices, whereas dual tasking seems to be sensitive to white matter disruption in a specific prefrontal region, namely the middle frontal gyrus.

In addition to correlations with tests of executive functioning, a correlation was observed between patient performance on the Reverse Digit Span task and increased ⟨D⟩ in the hippocampal portion of the cingulum, as well as in uncinate fasciculus. The hippocampal portion of the cingulum is traditionally associated with episodic and long-term memory (Köhler et al., 1998), indeed it has been shown to correlate with cognitive functioning in Alzheimer's disease (Nakata et al., 2009). Increasingly however, the hippocampus has been shown to have a role in working memory paradigms (Ranganath & D'Esposito, 2002), and together with the posterior cingulate has been associated with tasks assessing multiple cognitive domains suggesting that it may be a crucial structure in complex cognitive circuitry (Kantarci et al., 2011). Moreover, neuropathological studies in ALS patients with and without dementia have shown abnormalities in the hippocampus (Okamoto et al., 1991; Takeda et al., 2009). Reduced integrity in uncinate fasciulus has commonly been associated with memory impairment and naming deficits in other disorders such schizophrenia and epilepsy (Kubicki et al., 2002; Diehl et al., 2008; Papgno et al., 2011). However, a recent study by Tartaglia and colleagues (2012) in FTD patients revealed that uncinate fasciculus integrity was associated with the number of errors made in a modified version of the Trail Making Task which places considerable demands on working memory (Sanchez-Cubillo et al., 2009) and the results of the current study may reflect a similar association in ALS patients.

In the present study, correlations were also observed between impairment in the Logical Memory scales and inferior longitudinal fasciculus integrity. Memory dysfunction in ALS has been previously highlighted (Raaphorst et al. 2010), although typically related to secondary executive retrieval dysfunction. Here correlations were observed in the patient sample not only in measures of immediate memory, but also in retention and recognition,

and as such are unlikely to be explained through an executive dysfunction alone. This suggests a primary memory deficit in some ALS patients that is associated with disruption to a major white matter pathway connecting temporal regions to posterior cortical regions. Although changes in the inferior longitudinal fasciculus have been reported in a previous investigation into ALS (Sarro et al., 2011), performance in a test of executive functioning (Trail Making Task) not memory was associated with integrity in this tract. Thus, although the functional significance of the inferior longitudinal fasciculus remains unclear, there is evidence that this tract is related to cognitive change in ALS, and further investigation of this relationship should be considered by future studies.

In addition to association with cognitive measures, the white matter ROI analyses also revealed a significant correlation between corona radiata integrity and rate of disease progression, as well as a strong trend between corticospinal tract integrity and rate of disease progression. Similar findings have been reported by other investigators assessing white matter integrity with a variety of diffusion imaging techniques (Ciccarelli et al., 2006; Agosta et al., 2010; Bastin et al., 2013). Of interest, and as has been the case in other studies (e.g. Agosta et al., 2007), disease severity as measured by the ALSFRS was not associated with corticospinal tract or corona radiata integrity suggesting that this measure is not as robust as disease progression indices which take into account functional severity and disease duration. Despite these inconsistencies, the correlation between motor tract integrity and clinical and functional/cognitive measures suggests that DTI techniques have the potential to provide useful biomarkers of disease progression.

In comparison to the ROI and TBSS analyses of diffusion data, the VBM analyses of T1-weighted images showed considerably less evidence of cortical involvement. Indeed, only when ROI masks were applied to the VBM analyses were volumetric reductions in ALS patients revealed in right hemispheric motor cortex and inferior frontal gyrus. Nevertheless, previous investigations employing VBM have also reported cortical atrophy in motor cortex and inferior frontal gyrus amongst others regions (Ellis et al., 2001; Kassubek et al., 2005; Mezzapesa et al., 2007; Agosta et al., 2007). The volumetric reductions revealed by the VBM analysis in current study are also concordant with functional imaging studies in ALS which have shown decreased blood-oxygen response in inferior frontal gyrus (Brodmann Area 44) in response to fluency tasks (Abrahams et al. 2004). Furthermore, this region has been noted as a site of pathological focus in patients with ALS-Aphasia syndrome (Bak et al. 2001). The VBM findings in the current study suggest that grey matter analyses may not be as sensitive to cerebral changes in ALS as white matter investigations with DTI – indeed a similar pattern of results has been found in previous investigations (Abrahams et al., 2005; Canu et al., 2011). Thus, the relative propensity of white matter changes may suggest that white matter pathology is the core deficit underlying cognitive change in ALS and may reflect cortical "disconnection" as has been hypothesised in MS (Dineen et al., 2009).

Chapter 7. Discussion

The current study aimed to investigate whether cognitive impairments observed in ALS patients are characterised by slowed processing speed or executive dysfunction. Moreover, the inclusion of an MS patient group facilitated a comparison between the cognitive profiles exhibited in ALS and MS. In addition, we sought to elucidate whether integrity of specific white matter structures was associated with any observed cognitive deficits in the ALS patient cohort.

7.1 Summary of findings

7.1.2 Patient performance in background neuropsychological assessment

Cognitive domains of executive functioning, short-term memory, working memory, verbal memory, and language were assessed by a range of neuropsychological tests as described in Chapter 2. The two-way analysis between the ALS patients and matched healthy controls revealed that ALS patients exhibited impaired performance in tests of short-term memory (Forward Digit Span), working memory (Reverse Digit Span), verbal memory (Logical Memory scales), and executive functioning (Spoken Letter Fluency Test *fi* and D-KEFS Sorting Test), whilst confrontation naming (GNT) performance remained intact. Analysis of individual patient z-scores showed that 7/29 ALS patients presented with impairments in at least two tests of executive functioning, compared to 2/29 patients who presented with impairments in the Logical Memory scales or GNT in the absence of executive dysfunction.

The pattern of impairment exhibited by the current ALS cohort is largely consistent with the findings of other large scale studies (e.g. Ringholz et al., 2005; Phukan et al., 2012; Elamin

et al., 2013) in that approximately 30% of patients showed evidence of cognitive impairment, predominantly in tests of executive functioning, with a smaller proportion exhibiting impairments in tests of language and memory. However, other studies have suggested that impairments in domains of language (Taylor et al., 2012) and verbal memory (Raaphorst et al., 2010) may be at least as common as those observed in executive functioning. Although the data from the current investigation do not fully support these findings, the current study did not set out to address all aspects of cognitive functioning in ALS, and as such the domains of language and memory were not comprehensively assessed. Nevertheless, there was some evidence to suggest that cognitive impairment in ALS is not restricted to executive dysfunction. Not only did some patients present with memory or language impairments in the absence of executive dysfunction, the pattern of logical memory performance exhibited by the ALS group revealed poor performance in delayed recall and retention conditions which may reflect an underlying consolidation problem (Christidi et al., 2012). Moreover, the finding that patients recalled significantly less digits than controls in forward as well as backward versions of the Digit Span tasks may suggest that ALS patients experience reduced short-term memory capacity in addition to reduced working memory capacity (Conway et al., 2005).

In terms of ALS performance, the three-way analysis between ALS patients, MS patients, and healthy controls revealed essentially the same pattern of results – a subgroup of 25 ALS patients showed impairments in working memory, verbal memory, executive functioning and confrontation naming relative to a group of healthy controls that were matched to the MS patient cohort. Although, some of the group differences observed in the two-way analysis failed to reach significance, namely in Forward Digit Span and Logical Memory Retention, trends towards significance were observed in Forward Digit Span suggesting that

the group differences were still present but may have been masked by the additional statistical constraints associated with having fewer participants and performing post-hoc pairwise comparisons. The most interesting difference between the two-way and three-way analyses was in confrontation naming. Whilst in the two-way analysis ALS patients appeared unimpaired in the GNT, in the three-way analysis age was found to be correlated positively with GNT performance and a subsequent covariate analysis controlling for the effects of age suggested that in fact ALS patients were impaired in the GNT. Such a finding further demonstrates that cognitive deficits are not restricted to executive functioning in ALS, and highlights the importance of controlling for positive age correlations in linguistic assessments.

In terms of MS performance in the background neuropsychological assessments, the MS cohort showed a similar pattern to that exhibited by ALS patients with the same impairments evident in verbal memory (Logical Memory scales), executive functioning (Spoken Letter Fluency Test and D-KEFS Sorting Test), working memory (Reverse Digit Span), as well as a trend towards impairment in short-term memory (Forward Digit Span). However, some differences between the two patient groups were observed; MS patients exhibited additional impairment in the Written Letter Fluency Test, whereas ALS patients presented with impairment in confrontation naming (GNT) that was not observed in the MS patients (although a trend was present). The observed impairment in the GNT suggests that ALS patients may have difficulties with basic word retrieval processes, a deficit which may in turn contribute towards poor performance in the letter fluency tests. Confrontation naming deficits have been shown before in ALS cohorts (e.g. Wicks et al., 2008), but detailed investigations into verbal fluency performance in ALS have shown that letter fluency deficits occur independently of confrontation naming performance (Abrahams et

al., 2000), suggesting that fluency impairments are more likely to reflect executive dysfunction than basic word retrieval problems. Nevertheless, the result of the current investigation highlights the presence of language impairment in ALS which should be taken into account when interpreting performance in other cognitive tests.

In addition, a breakdown of performance in the Logical Memory scales showed that while ALS patients exhibited difficulties in immediate recall, delayed recall and delayed recognition, MS patients exhibited impairments in the delayed recall and retention conditions but not immediate recall or delayed recognition. Such a pattern suggests that although ALS patients may experience consolidation difficulties (as evidenced by retention deficits in the two-way analysis), performance in the Logical Memory scales may also have been affected by encoding and/or retrieval deficits reflecting an underlying executive dysfunction (Mantovan et al., 2003; Lezak et al., 2004). The pattern of performance exhibited by MS patients suggests that verbal memory deficits in MS are more likely to reflect problems with retrieval of information from long term memory. Thus, although the cognitive profiles of ALS and MS appear strikingly similar, there are some subtle differences in performance that may reflect disruption to different underlying cognitive processes. Overall, with regard to the neuropsychological tests employed by the current investigation, the cognitive profile of ALS and MS patients is consistent with predominant executive dysfunction, with further deficits extending to verbal memory in both patient groups, and primary linguistic abilities in ALS.

7.1.2 Patient performance in the experimental tasks

The experimental tasks were developed to assess processing speed and executive functioning, as well as any potential interaction between these functions, independent of motor abilities. This was achieved by developing two processing speed tasks, the VIT task and RSLI task, as well as a dual task paradigm which employed VIT as one component task and Delayed Digit Span as the other. As described in Chapter 3, before the dual task was administered in patient populations, an ageing study was carried out. The ageing study revealed that although VIT performance decreased as a function of age, when individual abilities were calibrated, subsequent dual task performance was unaffected by age as has been reported by previous investigations employing similar paradigms (Cocchini et al., 2002; Logie et al., 2004; Anderson et al., 2011).

In terms of patient performance in the experimental tasks, two-way analyses between the ALS group and matched healthy controls revealed that ALS patients performed almost identically to the control group in both processing speed tasks. Such a result suggested that ALS patients did not exhibit slowed processing of abstract visual information (VIT task) or meaningful visual stimuli (RSLI task). By contrast, the ALS group did show a selective impairment in dual tasking as evidenced by significantly higher Average Dual Task Cost scores than the control group. This effect was revealed despite ALS patients performing comparably to healthy controls in baseline task levels and under single task conditions. These findings not only indicate that ALS patients exhibited a motor independent dual tasking deficit, but also show that this impairment was independent of processing speed (VIT) or short-term memory capacity (Delayed Digit Span).

The three-way comparison between ALS patients, MS patients, and healthy controls revealed the same pattern of results in terms of ALS performance as that of the two-way analysis conducted in the full ALS group; ALS patients displayed normal performance in both processing speed tasks whilst exhibiting a selective deficit in Average Dual Task Cost. MS patients also exhibited significantly higher Average Dual Task Cost scores than the control group alongside normal performance under single task conditions, indicative of a selective dual task deficit. However, within the dual task paradigm, MS patients did show some evidence of processing speed impairment as the group exhibited a trend towards significantly slower baseline VIT level than healthy controls. Further evidence of slowed processing speed in MS patients was revealed by significant group differences in the experimental RSLI task. MS participants made significantly more errors in this task than both ALS patients and healthy controls suggesting that the speed at which they could identify meaningful visual stimuli was slowed. However, with respect to the dual task paradigm, the VIT level was calibrated to each individual's ability suggesting that the observed deficit in dual tasking was independent of processing speed impairment. Of note, MS patients were not impaired in the VIT processing speed task despite showing a trend towards slower baseline VIT level within the dual task paradigm.

As far as we are aware, this is the first study to demonstrate a dual task impairment in ALS patients that is independent of motor functioning. The only previous investigation of dual tasking in ALS was conducted by Schreiber et al. (2005) and employed the divided attention subtest of the Test of Attentional Performance (TAP; Zimmermann & Fimm, 2002), a paradigm in which participants are required to respond to simultaneously presented auditory and visual cues. Outcome measures were reaction times and the number of omitted responses. The authors reported that reaction times in the ALS group were slower than

normative data suggesting the presence of impairment in divided attention. However, not only did this task utilize reaction time data that is susceptible to the confounds of motor dysfunction in ALS, the component tasks were not calibrated for individual performance making it difficult to determine whether any difficulties experienced in the dual task condition are a result of overall task load or to a specific impairment in divided attention (Baddeley et al., 1991).

By contrast, previous investigations into cognitive functioning in MS have set out with the specific aim of investigating dual tasking within the multiple-component model of working memory. D'Esposito et al. (1996) employed a dual task paradigm in which performance in a line judgement task was assessed in single task conditions and under dual task conditions. The line judgement task was in a multiple choice format to allow participants to point to, or verbally identify their responses thereby minimising motor demands. In addition, three secondary tasks designed to impose sequentially greater demands on the central executive; finger tapping, humming of a pre-learned tune, and alphabet recital. Under single task conditions, the authors reported that MS patients performed comparably to controls in all the tasks with the exception of finger tapping, presumably due to motor dysfunction. However, MS patients exhibited a decrement in the line judgement task when it was performed concurrently with humming or alphabet recital. The authors concluded that this finding was indicative of a selective dual task deficit reflecting impairment in the coordinating function of the central executive component of working memory.

Thus, the result of dual task paradigm employed by the current investigation lends support to the findings of D'Esposito et al. (1996) by showing a selective dual task deficit in MS,

and in addition extends these findings to ALS patients. Moreover, the findings of the current investigation provide stronger evidence of an independent dual task deficit than previous studies in ALS or MS as the component tasks employed were not affected by motor dysfunction, and were performed under more stringent conditions in which difficulty levels were tailored to each individual's ability. As such, we could be confident that the same cognitive demand was placed on all participants such that the observed performance decrements observed in dual task conditions were likely to reflect a specific problem with the coordination of concurrent tasks.

7.1.3 Structural imaging in ALS

As described in Chapter 6, diffusion tensor and volumetric MRI analyses were carried out in the ALS cohort to investigate structural changes in cerebral white and grey matter respectively. DTI data was analysed by way of an in-house Region-of-Interest (ROI) approach, and Tract Based Spatial Statistics (TBSS), an automated whole brain white matter analysis package. In addition an in-house automatic segmentation tool was employed to investigate corpus callosum integrity. Volumetric T1-weighted data was analysed using Voxel Based Morphometry (VBM).

The ROI white matter analyses revealed reduced structural integrity in ALS patients in predominantly frontotemporal structures including white matter underlying the major frontal and temporal gyri as well as anterior and ventral portions of the cingulum. Further changes were revealed in white matter tracts corresponding to motor functioning (corticospinal tracts), and those linking cortical and subcortical structures (anterior thalamic radiation). Changes were also observed in longitudinal tracts connecting disparate cortical regions;

reduced integrity was revealed in the uncinate fasciculus which connects the temporal lobes and amygdala to inferior aspects of the prefrontal lobes, and inferior longitudinal fasciculus which connects the temporal and occipital lobes. In addition, the corpus callosum analysis revealed significantly reduced integrity in this structure in ALS patients compared to healthy controls. Voxel wise analysis of diffusion data (TBSS) revealed a very similar pattern of results with group comparisons in fractional anisotropy (FA) and mean diffusivity (⟨D⟩) showing a consistent pattern of reduced integrity in ALS patients in sub-gyral white matter in extensive bilateral prefrontal regions, predominantly right temporal regions, and regions corresponding to motor functioning. Moreover, the TBSS analyses highlighted the involvement of major white matter structures of the corticospinal tracts, corpus callosum, hippocampal portion of the cingulum, uncinate fasciculus, inferior longitudinal fasciculus, and occipito-frontal fasciculus. Of note, there was a distinct lack of FA or ⟨D⟩ changes in both the ROI and TBSS analyses in posterior regions (posterior parietal or occipital regions). Moreover, there were no regions in which white matter integrity as indexed by water diffusion parameters was enhanced in ALS patients compared to healthy controls.

The findings of the current investigation are largely consistent with previous studies of white matter integrity in ALS employing a variety of techniques from volumetric white matter analysis (Abrahams et al., 2005), VBM style analysis of DTI data (Sage et al., 2004; Agosta et al., 2007), tractography (Sarro et al., 2011;), and TBSS (Ciccarelli et al., 2009; Prudlo et al., 2012). The majority of changes reported in the above studies highlight the involvement of predominantly frontotemporal regions although it should be recognised that longitudinal tracts such as the inferior and superior longitudinal fasciculus connecting frontal and temporal regions to posterior regions are also commonly implicated (e.g. Abrahams et al., 2005; Sarro et al., 2011). Moreover, the degree of consistency between the

ROI and TBSS analyses suggests that the changes observed in the current investigation are robust, and that DTI data is sensitive to structural pathology in ALS. In contrast to the extensive changes revealed in white matter structures, VBM analysis of T1-weighted data revealed only small and localised volumetric reductions in right hemispheric motor cortex and inferior frontal gyrus. Nevertheless, atrophy in this region has been reported in numerous previous studies (e.g. Kassubek et al., 2005; Agosta et al., 2007; Agosta et al., 2012), as well as being implicated in functional abnormalities in verbal fluency performance, one of the most commonly observed cognitive impairments in ALS (e.g. Abrahams et al. 2004).

The imaging parameters described above were subjected to correlational analyses with performance in the cognitive tests described in Chapter 2 and Chapter 4. Correlations with structural imaging parameters were only performed for those tests (neuropsychological or experimental) which revealed significant group differences between ALS patients and healthy controls. As discussed in detail in Chapter 6 (Section 6.4), several correlations were observed between white matter ROIs and performance in cognitive tests; Average Dual Task Cost correlated with FA values in middle frontal gyrus white matter, performance in the Spoken Letter Fluency Test correlated with FA in the corpus callosum and corticospinal tracts, Reverse Digit Span performance correlated with ⟨D⟩ in hippocampal portion of the cingulum and uncinate fasciculus, and performance in the Logical Memory scales correlated with FA in the inferior longitudinal fasciculus. Compared to the ROI analyses, correlations between cognitive performance in ALS and water molecule diffusion parameters in the TBSS analyses were more limited – as in the ROI analyses, significant correlations between FA and performance in the Spoken Letter Fluency Test were revealed, but diffusion parameters were not associated with performance in any other cognitive task.

7.2 Implications

7.2.1 Executive functioning, processing speed, and attention in motor disorders

The dual task deficits observed in the current patient cohorts can be interpreted in terms of the multiple-component model of working memory (Baddeley & Hitch, 1974; Baddeley, 2000). In the terms of this model, the component tasks of Delayed Digit Span (DDR) and Visual Inspection Time (VIT) would have placed demands on the Phonological Loop and Visuospatial Sketchpad respectively. The component tasks in isolation were unlikely to tax the Central Executive component of the multiple-component model due to their limited processing demands; the DDR task simply required the maintenance of a sequence of digits so that they were available for recall after a 15 second delay, and the VIT task required very basic forced-choice perceptual processing. The ALS and MS patient groups were able to perform comparably to the control groups in both of the component tasks at their own predetermined maximum ability level. Thus, the dual task deficit observed in ALS and MS patients is likely to reflect a specific difficulty in the ability to perform these tasks concurrently. Investigation of dual tasking in healthy adults has demonstrated that dual task costs are low even when two working memory tasks (one verbal, one visuospatial) are performed concurrently, provided the single tasks are tailored to individual ability level (Cocchini et al., 2002). Results of this nature suggest that the domain specific sensory slave systems are able to independently perform additional *processing* functions required by working memory tasks, not just (temporarily) store sensory information. A further consequence of this finding is to suggest that the central role of the central executive in dual task paradigms is the *coordination* of the slave systems, and that dual task decrements observed in the current study may reflect a specific deficit in this attentional ability (Duff & Logie, 2001; Cocchini et al., 2002). Such an interpretation of the dual task impairment

observed in ALS and MS patients is also consistent with a deficit in "sharing attention", one of the proposed components of Norman and Shallice's (1986) Supervisory Attentional System defined by Stuss et al. (1995). According to this account the patient groups in the current study may have deficits in energising and monitoring mechanisms required to ensure that a balance is maintained between the active response sets of two tasks.

However, other researchers have proposed dual task decrements may be a result of slowed processing rather than a decline in attentional capacity (e.g. Salthouse & Somberg, 1982). The paradigm employed in the current investigation addressed this possibility by including a processing speed task as one of the component tasks (VIT task). According to Salthouse (1996), slowed processing may cause dual task interference due to the *Simultaneity Effect* which asserts that if processing speed for a given function is slowed then the information may no longer be available or relevant when it is needed. In this case slowed processing in either of the component tasks may result in there being insufficient time to complete the other task effectively, i.e. before the memory trace decays in Delayed Digit Recall, or before the stimulus disappears in the VIT task. As demonstrated in Chapter 3, younger, middle, and older adults exhibited differences in processing speed with the expected relationship of slowed perceptual encoding occurring with increasing age. Despite this, all age groups were able to perform the dual task to the same ability when individual differences in processing speed were calibrated suggesting that there is no effect of ageing on dual task ability when individual differences in task performance are calibrated. In addition, participants were able to perform a processing speed task, at or close to their maximum ability, concurrently with another task without suffering from a substantial performance decrement. This finding suggests that processing speed is unlikely to be a crucial component of executive coordination as it has no detrimental effect on dual task ability in healthy adults. Thus it is

hypothesised that dual task impairments observed in the patient cohorts reflect an executive dysfunction that is independent of any individual differences in processing speed. Further evidence for this claim is provided by the finding that performance in the experimental VIT processing speed task did not correlate with Dual Task Cost in the ALS or MS groups suggesting that performance in these tasks was not related.

The results of the current investigation also go against the interpretation of dual task impairment in MS offered by D'Esposito et al. (1996). The authors proposed that the functioning of the central executive may rely upon processing speed as dual task decrement scores correlated with PASAT performance in MS patients. It was reasoned that as PASAT performance has traditionally been related to speed of information processing (Gronwall, 1977), one could draw the conclusion that processing speed is also crucial component of the coordinating function of the central executive. However, the results of the current investigation show that MS patients are not impaired in a well validated test of perceptual processing speed (the VIT task), and more over, the observed dual task deficit occurred independently of processing speed ability in this task suggesting that in fact processing speed is not a contributing factor in executive control (at least within the dual task). Of note, this explanation of dual task performance seems particularly unlikely to be relevant to ALS patients as performance in both processing speed measures (VIT task and RSLI task) was comparable to that of healthy controls.

However, MS patients did exhibit impairments in the RSLI processing speed tasks suggesting that executive dysfunction may not account for all cognitive deficits observed in this patient population. The observed pattern of a selective impairment in the RSLI

processing speed task may be explained by the demands imposed by the respective tasks. The VIT task requires the identification of abstract visual stimuli for which there are only 2 choices, therefore it is essentially a simple forced-choice decision task. By contrast, the RSLI task requires the identification of a specific letter, and therefore imposes greater attentional demands as there are multiple potential responses. In addition, there are more distracter stimuli (forward and backward masking) in the RSLI task whereas the VIT task only employs a single backward mask. Thus, the RSLI task may require a further element of inhibitory control as responses to letters other than the target must be suppressed. Further support for this possibility is provided by the correlation between performance in RSLI task and Average Dual Task Cost in MS patients suggesting that an underlying attentional deficit may underpin performance on both tasks. The fact that ALS patients were unimpaired in the RSLI task suggests that the task is not as executively demanding as tasks requiring abstract thought such as letter fluency or sorting tasks. However, good performance in the RSLI task may still require some element of attentional control and MS patients may be more vulnerable to attentional deficits than ALS patients as evidenced by the greater number patients who exhibited impairment in the dual task (8 MS versus 5 ALS). Moreover, such an attentional impairment in MS would certainly explain the commonly reported deficits in tasks such as the PASAT (Fischer, Rudick, Cutter & Reingold, 1999) and Symbol Digit Modalities Test (DeLuca et al., 2004), which although purportedly assess processing speed, undoubtedly require an element of attentional control to keep track of changing task-relevant information and inhibit irrelevant previous responses. Indeed, some investigators have suggested that tasks such as the PASAT are better described in terms of "information processing efficiency" which is defined as involving working memory capacity in addition to speed of processing (Archibald & Fisk, 2000).

In addition to the dual task impairments discussed above, other cognitive deficits observed in the current patient cohorts can also be interpreted in terms of the multiple-component model of working memory. For example the significant group differences (trend in MS patients) observed in Forward Digit Span may reflect disruption of the Phonological Loop which is responsible for maintaining verbal information. The Phonological Loop is comprised of two systems, the phonological store which holds memory traces for a few seconds, and articulatory rehearsal which refreshes the contents of the phonological store through subvocal speech (Baddeley, 1986). Although the current study did not investigate Phonological Loop functioning, a previous investigation reported that ALS patients exhibited the normal Word Length Effect and Phonological Similarity Effect suggesting that articulatory rehearsal and phonological storage processes are intact (Abrahams et al., 2000). Thus, the impairments in Forward and Reverse Digit Span exhibited by ALS patients in the current study may reflect impaired attentional capacity. More specifically, deficits in Reverse Digit Span may be indicative of reduced working memory capacity as additional attentional resources are required to reverse the order of the digits whilst maintaining the original sequence in mind. Moreover, such "high-order" processes of attentional control are also assumed to be crucial for performance in novel or goal directed behaviour such as those assessed by the Spoken Letter Fluency Test and the D-KEFS Sorting Test (Stuss et al., 1995; Baddeley, 1996; Abrahams et al, 2000; Gilbert & Burgess, 2008; Fine et al., 2010).

7.2.2 Sensitivity of letter fluency to cognitive impairment in ALS

The current investigation serves to highlight the sensitivity of letter fluency tests to extra-motor dysfunction in ALS. Not only was the Spoken Letter Fluency Test (*fi*) the most sensitive measure for detecting cognitive impairment in ALS, it was also the only cognitive measure to correlate with both ROI and TBSS white matter analyses. The sensitivity of

letter fluency to cognitive and cerebral changes in ALS may be a reflection of the unique demands imposed by the task. Letter fluency tests remain one of the most commonly used tests of executive functioning (Baldo et al., 2001), and performance is thought to be dependent upon discrete executive processes including; initiation, strategy formation, sustained attention, set-shifting, working memory and inhibition (Troyer et al., 1997; Azuma, 2004; Abrahams et al., 2000; Rende et al., 2002). However, a factor analysis by Fisk and Sharp (2004) revealed that letter fluency tests were not related to performance in tests requiring updating, inhibition, or shifting, and proposed that letter fluency tests may reflect a specific executive ability, namely the efficiency of access to long-term (lexical) memory. Such a process may be interpreted as a function of the 'episodic buffer' which has been proposed to facilitate the transfer of information between working memory and long-term memory (Baddeley, 2000). Moreover, we have demonstrated that ALS patients exhibit impairments in basic linguistic retrieval (confrontation naming), and retrieval from long-term memory (Logical Memory scales). Thus, deficits in letter fluency in ALS may arise due to impairment in any one, or combination of, executive, linguistic, or retrieval processes.

7.2.3 Distinct white matter structures correlate with cognitive performance in ALS

The integrity of different white matter regions and pathways were related to performance in different cognitive tests. Letter fluency and reverse digit span performance were each associated with two anatomically distinct white matter structures, and in both cases, the associated areas were not restricted to prefrontal regions. Such results suggest that performance in executive tasks in ALS is likely dependent on the integrity of pathways connecting distributed brain regions. Indeed the concept that performance in tasks assessing executive functioning is dependent upon distributed brain networks has been suggested by

recent reviews of neuropsychological and neuroimaging studies (e.g. Collette & Van der Linden, 2002; Alvarez & Emory, 2006; Jurado & Roselli, 2007). For example, although letter fluency tasks are sensitive to frontal lobe lesions, and particularly to left dorsolateral and inferior frontal lesions (Stuss et al., 1998; Baldo, Schwartz, Wilkins & Dronkers, 2006; Robinson et al., 2012), patients with non-frontal lesions have been shown to perform as badly as those with frontal lesions (Perret, 1974; Pendleton et al., 1982). Similarly, although there is a propensity for frontal lobe activation during fluency tasks (Frith et al., 1995; Abrahams et al., 2004; Katzev, Tüscher, Hennig, Weiller & Kaller, 2013), other regions such as the thalamus, parietal lobes and temporal lobes are also commonly implicated (Paulesu et al., 1997; Birn et al., 2009). Thus, letter fluency tasks, although sensitive to frontal lobe damage, may not be specific to focal frontal lesions because executive functioning requires coordination of diffuse anatomical and functional cerebral regions. Furthermore, cognitive theorists have also postulated that performance of complex systems such as working memory is less likely to be dependent upon a single anatomical locus, and more likely to be an emergent property of several connected regions (Repovs & Baddeley, 2006).

By contrast, poor dual task performance was associated with low integrity in a specific region of prefrontal white matter (that underlying middle frontal gyrus or dorsolateral prefrontal cortex), which may suggest that this region plays a specific role in the coordination and division of attention. Indeed, some functional imaging studies have highlighted the importance of this region in dual task performance (D'Esposito et al., 1995; Bunge et al., 2002), and neuropsychological studies have shown dual task impairment in the patients with frontal lobe lesions and dysexecutive behaviour (Baddeley et al., 1997), although deficits are also exhibited in patients characterised by temporal lobe involvement

(e.g. Alzheimer's disease; Logie et al., 2004). While some investigators have postulated that specific areas of the prefrontal lobes are crucial for managing and coordinating response selection and interference (MacDonald et al., 2000; Wager & Smith, 2003), others have suggested that dual task performance may dependent upon distributed networks (Collette & Van der Linden, 2002). However, the fact that dual task performance did not correlate with any of the same regions associated with performance in letter fluency or reverse digit span is further evidence to suggest that the processes underpinning these tasks may be functionally distinct.

Moreover, performance in the domain of verbal memory was associated with integrity in another discrete white matter pathway as evidenced by the correlation between Logical Memory and the inferior longitudinal fasciculus. The inferior longitudinal fasciculus connects anterior temporal regions to the occipital lobes and recent studies have implicated this structure in semantic memory (Vigneau et al., 2006) and language comprehension (Wong, Chandrasekaran, Garibaldi & Wong, 2011) although its functional significance remains controversial (see Dick & Tremblay, 2012 for a review). Moreover integrity of the inferior longitudinal fasciculus has been shown to correlate with cognitive functioning in ALS, albeit to a test of executive functioning, not memory (Sarro et al., 2011). Verbal memory deficits have been consistently reported in ALS (Raaphorst et al., 2010), and in the current investigation performance in Immediate recall, Delayed recall, and Recognition conditions all correlated with inferior longitudinal fasciculus integrity suggesting that the observed relationship is a reflection of a primary memory deficit in ALS patients. Thus, although the functional significance of the inferior longitudinal fasciculus remains unclear, there is now evidence that this tract is involved ALS as well as FTD pathology (Whitwell et al., 2010) and therefore warrants further investigation.

7.2.4 Cognitive change as a marker of underlying white matter pathology

Although both DTI analyses produced consistent results in terms of identifying structures in which ALS patients had reduced structural integrity, the ROI data was more sensitive to relationships between white matter integrity and performance in cognitive tests. ROI techniques may be more sensitive to correlations with small sub-gyral regions as, unlike in TBSS, native images do not have to be registered to standard templates. However, other correlations with major tracts (e.g. uncinate fasciculus and inferior longitudinal fasciculus) were observed in the ROI but not TBSS analyses suggesting that this may not be the only reason. Another possibility is that the ROI methodology was less statistically conservative; multiple comparison corrections were not applied to correlational analyses as only those cognitive tests and cerebral regions in which there were significant group differences were investigated. By contrast TBSS applies strict multiple comparison corrections as correlations are investigated in a voxel-wise manner for whole brain white matter. Thus, ROI or semi-automated ROI techniques employed by the current investigation may be more sensitive to correlations between cognitive performance and structural integrity in small patient populations.

Nevertheless the ROI and TBSS analyses showed a very good degree of consistency; the regions most strongly associated with letter fluency performance in the TBSS analysis were the same as those revealed by correlations with ROI data, namely the corpus callosum and corticospinal tracts, indicative of a robust effect. Moreover, the anatomical localisation afforded by the TBSS analysis revealed that reduced integrity in the *anterior* portion of the corpus callosum was associated with poor letter fluency performance. As such, the results of

the current investigation suggest that poor fluency performance in ALS may reflect the disruption of pathways between right and left prefrontal areas, as has been suggested by other studies in ALS (e.g. Yamauchi et al., 1995; Filippini et al., 2010), as well as FTD (Matsuo et al., 2008). One possible interpretation of these findings is that fluency deficits may be a sensitive marker of white matter changes in areas that occur frequently and early in ALS, i.e. the corticospinal tract and corpus callosum. By contrast, dual task impairments may be more sensitive to the disruption of more specific prefrontal pathways that affect a smaller subset of ALS patients, and may be a reflection of pathological spread from central areas to more anterior and dorsolateral cerebral areas. Indeed, the corpus callosum has been implicated as a key structure in the mechanism of pathological spread (Eisen, 2009), and thus we may expect callosal abnormalities and verbal fluency deficits to precede anterior and dorsolateral involvement and the associated dual task impairment. However, of the three patients who exhibited impaired performance in the dual task (z-score ≤ 2) only one also exhibited impairment in letter fluency. Moreover, as discussed previously (Chapter4, Section 4.4.3) dual-task and letter fluency performance were not correlated, suggesting that impairments in executive functions are dissociable in ALS patients. Further support for this proposal is provided by research which postulates that executive functions are dissociable at a behavioural and neuroanatomical level (Goldman-Rakic, 1995; Jurado & Roselli, 2007), and particularly by studies which suggest that verbal fluency and dual tasking do not share the same cognitive processes, making them less likely to rely on the same neural pathways (Miyake et al., 2000).

7.2.5 Implications for pathological mechanisms in ALS

As discussed above, the relationships between DTI parameters and performance in cognitive tests suggest that the integrity of white matter structures can be related to functional changes

in ALS. Moreover, white matter integrity in motor regions (corticospinal tract and corona radiata) was associated with an index of disease progression indicating that DTI parameters are also related to clinical disease parameters. However, the question remains as to why changes in grey matter volumes are not observed to the same extent as the changes revealed by the assessment of white matter integrity. One possibility lies in the fundamental difference between DTI and volumetric MRI data. The diffusivity metrics of FA and ⟨D⟩ provide an estimate of white matter integrity, whereas volumetric analyses evaluate cortical structures in terms of absolute volume. Therefore, DTI analyses may be sensitive to small changes in integrity which are too subtle to cause detectable changes in volume. A related point concerns the heterogeneous nature of cognitive impairment in ALS; approximately 30% patients in the current investigation presented with cognitive impairment in standard neuropsychological tests, and as such any volumetric changes present in this relatively small proportion of patients may be lost in whole group analyses – this may explain why the VBM analysis revealed volumetric reductions in primary motor regions as such changes are likely to affect a significant proportion of patients. An upshot of this point is to suggest that the volumetric reductions observed in right inferior frontal gyrus are an important feature of ALS cortical pathology as reductions in this region are seemingly as robust as those observed in motor regions. A final point to consider is the possibility that diffusion abnormalities in white matter may precede cortical atrophy (i.e. volumetric loss) which may occur downstream as a result of more considerable reductions in axonal integrity. As such, the findings of the current investigation appear to be consistent with the "dying-back" hypothesis of ALS pathogenesis which proposes that disease processes begin in the neuromuscular junction and are spread via axonal transport before eventually disrupting the functioning of the upstream neuronal cell (Chou & Norris, 1992 Fischer et al., 2004). However, the degree of cortical involvement revealed by the DTI analyses may be better explained by the notion of focality and contiguous spread recently proposed by Ravits and

La Spada (2009). According to this model, pathology can occur at any level of the motor system (upper or lower motor neurons) before spreading to contiguous regions via transneuronal signalling. Of note, Ravits and La Spada (2009) postulate that disease spread in the upper motor neurons is likely to occur in a medial-to-lateral direction which implicates major inter-hemispheric structures such as the corpus callosum which have been suggested to be crucial in the spread of motor and extra-motor pathology in ALS (Eisen, 2009, Filippini et al., 2010).

Indeed, the pattern of cerebral involvement revealed in the current investigation, as well as those of other studies is concordant with cerebral pathology in ALS. A recent pathological study investigating the presence and severity of TDP-43 proteinopathy (Geser et al., 2008) reported that although a degree of pathology was found in all sampled cortical and subcortical regions, there were marked differences in terms of the percentage of cases exhibiting pathology in different cerebral regions. Within motor, sensory, and regions through which run the corticospinal tract, TDP-43 abnormalities were found in nearly 100% of cases, with high proportions also found in thalamus and subcortical regions involved in motor control (e.g. substantia nigra and cerebellum). In terms of non-motor regions, TDP-43 proteinopathy was reported in cingulate gray matter in approximately 70 % of cases, followed by approximately 60% of cases in midfrontal grey matter, and between 35 – 40% of cases in temporal, hippocampal, and parietal regions. By contrast, only 11% of cases showed TDP-43 pathology in occipital lobe. The pathology gradient observed in this study is broadly consistent with the propensity of changes revealed by the neuroimaging studies described previously, although it should be noted that the Geser et al. (2008) study did include several patients with ALS-FTD. Of particular interest, TDP-43 pathology was more common in grey matter than the corresponding white matter structures. Such findings

provide further evidence to suggest that DTI analyses have considerably greater sensitivity to pathology in ALS than volumetric analyses, although the possibility remains that DTI metrics are sensitive to pathological changes other than those caused by TDP-43 proteinopathy.

Another implication of the correspondence between the structural imaging findings and those of pathological studies is to provide further evidence of a link between ALS and FTD. TDP-43 pathology is not only a hallmark of ALS, it is also the main proteinopathy in cases of frontotemporal lobar degeneration with ubiquinated inclusions (FTLD-U; Geser et al., 2009). According to the TDP-43 clinico-pathological spectrum proposed by Geser et al. (2009), ALS and FTLD exist on opposite ends of a continuum with predominant involvement of the spinal cord at one end, and predominant involvement of cortical areas at the other – cases of ALS with cognitive impairment and ALS-FTD fall somewhere in the middle of the spectrum. Thus, structural MRI, and particularly DTI data from the current study lend support to the postulated continuum between classical ALS and FTD (Lomen-Hoerth et al., 2003; Abrahams et al., 2004; Murphy et al., 2007; Sage et al., 2007; Raaphorst et al., 2010), as it highlights a preponderance for frontotemporal white matter pathology which may play a crucial role in the multi-system involvement observed in this disorder. Moreover, both DTI analyses implicated the involvement of the inferior longitudinal fasciculus and the uncinate fasciculus which have been shown to be preferentially involved in FTD (Whitwell et al., 2010). However, further investigations are needed in which neuroimaging and pathological techniques are combined within the same patient cohort to allow the relationship between ALS, cognitive impairment, and TDP-43 pathology to be investigated directly.

The extent of white matter changes revealed in the current investigation, as well as the observed associations between integrity and cognitive performance suggests that white matter pathology may be the core mechanism underlying functional changes in ALS. Cortical disconnection has been proposed as a mechanism to account for the cognitive impairments observed in other neurodegenerative disorders characterised by white matter pathology such as MS (Dineen et al., 2009), as well as subcortical dementias (Huntingdon's disease; Rosas et al., 2010) and Alzheimers disease (Delbeuck et al., 2003). It is hypothesised that pathological processes resulting in intrinsic damage to white matter structures prevent the communication and coordination of discrete cerebral regions, thus disrupting functional networks. For example, in Alzheimer's disease, convergent evidence has emerged from pathological and DTI investigations to suggest that white matter pathology results in isolation of the hippocampi which may cause the profound memory dysfunction that characterises this disorder (Delbeuck et al., 2003). In terms of ALS, one may expect executive functions to be particularly vulnerable to this kind of pathological process as they are likely to rely upon complex functional networks spread across disparate brain areas. Moreover, comparative analyses between ALS and FTD patients show that while there are only small regions in which FTD patients have worse white matter integrity than ALS patients (corpus callosum and inferior longitudinal fasciculus), there are large (frontotemporal) areas in which FTD patients display greater grey matter atrophy (Lillo et al., 2012). Thus, cortical disconnection as a function of white matter pathology may explain the more subtle cognitive impairments observed in ALS, whereas the more profound impairments exhibited in FTD may be reflection of additional grey matter pathology.

7.2.6 Implications for disease management and patient care

The current investigation has demonstrated that patients with ALS and MS can exhibit impairments in verbal memory, working memory, and executive functioning. Moreover, other studies investigating ALS have shown that deficits in domains of language, behaviour, mood, and social cognition (see Goldstein and Abrahams, 2013 for a review). Although cognitive deficits do not always manifest in either disorder, there is now consistent evidence to show that a significant proportion of ALS and MS patients will develop problems of this nature (Rovaris et al., 2002; Ringholz et al., 2005; Amato et al., 2006; Phukan et al., 2012; Elamin et al., 2013). Cognitive assessment is relatively common place in MS clinical management by way of specifically designed tools such as the Brief Repeatable Battery of Neuropsychological Tests (BRB-N; Rao, 1990) and the Screening Examination for Cognitive Impairment (SEFCI; Beatty et al., 1995), both of which have been shown to provide good sensitivity and specificity to MS cognitive impairment (Sartori & Edan, 2006). However, cognitive assessment and screening is not common place in ALS clinical management as appropriate and validated measures are not currently readily available – at present the screening assessments suggested for use in ALS either have not been specifically designed for ALS populations (e.g. the Penn State screen exam; Flaherty-Craig, Brothers, Dearman, Eslinger & Simmons, 2009), do not adequately control for motor dysfunction (Gordon et al., 2007), or are limited to assessing only one cognitive domain (ALS-Cognitive Behavioural Screen; Wooley et al., 2010). Thus, the first challenge is to develop a cognitive screen that is both sensitive to the heterogeneity of cognitive impairment in ALS and independent of motor and bulbar dysfunction.

In terms of disease management and patient care, even relatively subtle impairments, especially in executive functioning, can dramatically affect an individual's ability to make

decisions and form effective plans and strategies to deal with new situations. Deficits of this nature may hinder adherence to interventions and result in problems learning to perfrom new tasks such as those required for gastrostomy or ventilation purposes (Olney et al., 2005). In cases where more severe impairments are present such as those exhibited by patients with ALS-FTD, individuals may be unable to make decisions regarding their finances and their future, which may ultimately lead to the need for capacity assessment (Goldstein & Abrahams, 2013). Similarly, in addition to the considerable challenges associated with declining motor/bulbar functioning, impairments in memory and language are likely to affect an individual's ability to communicate effectively and function independently (Abrahams, 2013). Therefore, the accurate identification of cognitive deficits is crucial to empower clinicians to employ appropriate interventions and make provisions to educate carers in an effort to ensure that quality of life is maximised for both patients and their families.

7.3 Limitations and future directions

The current investigation was not without limitations. In terms of patient sampling, the ALS cohort were a prevalent rather than incident sample and as a result included a small number of patients (n = 2) with disease duration of over five years, although patients with significant respiratory dysfunction were excluded. However, large population studies of cognitive impairment in ALS using incidence sampling methods have shown similar rates of impairment as those from prevalent samples. They have also revealed a more heterogeneous presentation not only of executive dysfunction but including changes in language and memory (Phukan et al. 2012, Goldstein & Abrahams, 2013) which is consistent with the findings of the current investigation. It should also be noted that the MS group comprised patients with relapse-remitting, primary progressive, and secondary progressive disease

course subtypes. Although cognitive impairment is recognised in all disease subtypes (Foong et al., 2000; Rovaris et al., 2002; DeSonneville et al., 2002), several studies have shown that patients with progressive forms of the disorder are more likely to experience deficits in memory (Calabrese et al., 2000; Gaudino, Chiaravalloti, DeLuca, & Diamond, 2001), executive functioning and attention (Huijbregts et al., 2004, 2006), and processing speed (DeSonneville et al., 2002). As such, the inclusion of relapse-remitting patients in the current study may have resulted in greater cognitive heterogeneity within the current sample and therefore a lower likelihood of detecting cognitive impairment in some of the neuropsychological and experimental tasks. On the other hand, the potential for variation within the MS group may provide greater relevance for comparison with an ALS population in which cognitive heterogeneity is well established.

In addition, we were unable to match the subgroup of 25 ALS patients, MS patients, and healthy controls in terms of age in the three-way comparisons. However, effects of age were investigated and controlled for by covariate analyses and the general consistency between the findings of the two-way and three-way comparisons in both background and experimental tests suggest that age differences were not a major factor. With regard to task design, the processing speed measures were analysed in terms of the number of errors made, a method which proved successful in showing that ALS patients performed comparably to controls in both tasks while MS patients exhibited a selective deficit in RSLI task. However, it would have been of interest to investigate the *qualitative* nature of processing speed performance as well – for example did MS patients make more errors purely in the faster trials, or were errors dispersed more randomly? Such a design may have provided more of an indication as to whether impaired task performance was due to attentional deficits or slowed processing speed. Furthermore, although direct comparisons were made between

ALS and MS patients in terms of cognitive performance, we were unable to attain structural imaging data in the MS cohort and therefore we were unable to determine whether the two groups also shared similarities in terms of white and grey matter pathology. Given, the relatively similar cognitive profiles exhibited by the ALS and MS cohorts, such a comparison may have provided additional insights as to whether the neural correlates of cognitive impairment are also shared.

The current investigation has provided further evidence to show that ALS is a complex multi-system disorder with a considerable degree of heterogeneity in clinical and cognitive impairment. As such, it would be advantageous for future investigations to recruit relatively large cohorts (e.g. n = 100) so that patients can be divided into subgroups based on whether or not they exhibit cognitive impairment. In this way comparisons of structural data may be able to elucidate the specific cerebral changes associated with those patients who exhibit impairments and those who do not. Although recent studies (Phukan et al., 2012; Elamin et al., 2013) have included large samples and identified cognitive subtypes, future studies should investigate multiple aspects of the disease including clinical features, cognition, structural imaging, and pathological examinations, *within* the same cohort. Only in this way can direct associations be made regarding the complex interactions between functional and pathological processes. Moreover, longitudinal studies are needed to investigate whether extra-motor structural changes in ALS, and the associated cognitive deficits, are stable or whether they represent another component of disease spread and pathogenesis. Finally, the current investigation has made an attempt to investigate cognition in ALS in terms of current cognitive models of human behaviour, and subsequent studies should also consider this approach instead of relying purely upon clinical assessment tools which are more difficult to interpret with respect to the underlying cognitive processes.

In conclusion, the current investigation has shown that processing speed is not impaired in ALS, and is unlikely to be related to observed impairments in tests of executive functioning. By contrast, there is more evidence of a processing speed deficit in MS, although the extent to which it is a reflection of a low-level attentional deficit remains to be seen. In addition, both patient groups exhibited impairments in dual tasking that were independent of processing speed and motor dysfunction. Executive dysfunction and particularly deficits in letter fluency remain the most common impairment in ALS, and may reflect the spread of disease pathology into prefrontal white matter structures. Moreover, there is evidence that impairments in different executive functions are related to the integrity of distinct prefrontal white matter tracts. However, further deficits in tests of language and memory suggest that cognitive impairment in ALS may not be restricted to executive functioning, particularly in the light of the observed correlation between verbal memory performance and white matter structures in temporal regions. Finally, DTI techniques are sensitive to cerebral changes in ALS and reflect damage to white matter structures and the disruption of cortical connections which may be the crucial mechanism underpinning cognitive impairment in ALS.

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Appendix A – Ethics favourable opinion letters

Lothian NHS Board

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5 August 2011

Dr Sharon Abrahams
Senior Lecturer in Human Cognitive Neuroscience
Department of Psychology, PPLS
University of Edinburgh
7 George Sq, Edinburgh
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Dear Dr Abrahams

Study title: **Executive dysfunction or slowed information-processing speed in motor disorders; a comparative study.**

REC reference: **11/AL/0369**

Thank you for your letter of 22 July 2011 responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC at a meeting held on 3 August 2011. A list of the sub-committee members is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

- Please state how audio or visual recordings are stored and for how long

NHS Lothian

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Covering Letter		
GP/Consultant Information Sheets	1	02 June 2011
GP/Consultant Information Sheets	1	
Investigator CV		
Other: list of tests		
Participant Consent Form: Healthy volunteers	2	22 July 2011
Participant Consent Form: patients	2	22 July 2011
Participant Information Sheet: patients	1	02 June 2011
Participant Information Sheet: healthy volunteers	1	02 June 2011

NHS
Lothian

Participant Information Sheet: patients	2	22 July 2011
Participant Information Sheet: Healthy volunteers	2	22 July 2011
Protocol	1	02 June 2011
REC application		02 June 2011
Response to Request for Further Information		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

11/AL/0369	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

NHS
Lothian

Dr Janet Andrews
Chair

Email: emily.oconnor@nhslothian.scot.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: Ms Gemma Watson
Ms Karen Maitland, NHS Lothian

South East Scotland Research Ethics Committee 01

Attendance at Sub-Committee of the REC meeting on 3 August 2011

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Janet Andrews	Associate Specialist	Yes	
Mr Lindsay Murray	Health & Safety Manager	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Dr Alex Bailey	Scientific Officer
Ms E Pendleton	

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CPP/MJ /approval

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Director:

Professor David E Newby

Dear Dr Chandran,

Lothian R&D Project No: **2011/W/NEU/03**

Title of Research: Executive dysfunction or slowed information-processing speed in motor disorders; a comparative study.

REC No: 11/AL/0369

CTA No: N/A **Eudract:** N/A

PIS: version 2 dated July 2011 **Consent:** version 2 dated July 2011

Protocol No: version 1 dated May 2011

I am pleased to inform you that this study has been approved for NHS Lothian and you may proceed with your research, subject to the conditions below. This letter provides Site Specific approval for NHS Lothian.

Please note that the study should not begin until R&D receive evidence of GCP training or training in taking informed consent by Lewis Pettit.

Following a Research Ethics Committee final favourable opinion, final copies of all project documentation (with revised version numbers) should be sent, with the Research Ethics Committee letter of favourable opinion, to the R&D office. Management approval will only be valid after favourable opinion has been received.

Following funding award, please send a copy of the funding award letter to the R&D Office for the study file.

Please note that the NHS Lothian R&D Office must be informed if there are any changes to the study such as amendments to the protocol, recruitment, funding, personnel or resource input required of NHS Lothian. This includes any changes made subsequent to management approval and prior to favourable opinion from the REC.

Substantial amendments to the protocol will require approval from the ethics committee which approved your study and the MHRA where applicable.

Please inform this office when recruitment has closed and when the study has been completed.

I wish you every success with your study.

Yours sincerely

Dr Christine P Phillips
Deputy R&D Director

cc Dr S Abrahams, 7 George Square, Edinburgh EH8 9JZ
Paul Dearie, QA Manager

Scotland A Research Ethics Committee

Secretariat
Deaconess House
148 Pleasance
Edinburgh
EH8 9RS
Telephone 0131 536 9026
Fax 0131 536 9346
www.corec.org.uk

NHS SCOTLAND

Dr Sharon Abrahams
Senior Lecturer in Human Cognitive Neuroscience and Clinical Neuropsychologist
The University of Edinburgh
Department of Psychology, PPLS
7 George Square
Edinburgh
EH8 9JZ

Date: 29 May 2008
Your Ref.:
Our Ref.: 08/MRE00/50

Enquiries to: Walter Hunter
Extension: 89026
Direct Line: 0131 536 9026
Email: walter.hunter@lhb.scot.nhs.uk

Dear Abrahams

Study title: **The heterogeneity of cognitive impairment in motor neurone disease**

REC reference: **08/MRE00/50**

The Scotland A Research Ethics Committee reviewed the above application at the meeting held on 22 May 2008. Thank you for attending to discuss the study.

Ethical opinion

The Committee had no ethical concerns with this study, which involved participants in a series of challenging tests. They identified inconsistencies over the duration of these tests from 90 minutes to five tests of 30 minutes each. Adults lacking capacity would not be involved. The age criteria in the recruitment poster differed from the ages set out in the inclusion criteria. There was mention in the participant information sheet for MND of a payment of £6 per hour but this was not included in the other information sheets.

Professor Lees welcomed Dr S Abrahams to the meeting. When asked about the numbers involved Dr Abrahams confirmed there would be 75 MND participants, 15 FTA participants and 75 controls. There would not be a group analysis as some of the tests had not been done and for FTD they would be analysed on a case by case basis. In response to a question about reducing the number of tests Dr Abrahams confirmed this could be possible but would need to be piloted. Dr Abrahams further confirmed there was no replication in tests and that the tests with participants would last 90 minutes followed by a 30 minute interview with the carer. This would be repeated a few weeks later and again after 8 months. All participants involved would receive £6 per hour and if MND participants attend at the University for the tests the payment of expenses would be considered. On storing data on laptops Dr Abrahams advised that only non identifiable information would be stored. Dr

NHS SCOTLAND

Abrahams agreed to correct the inconsistency in the recruitment poster and confirmed that the initial approach to potential participants would come from a member of the treating team. Finally in response to a question on whether FTD cases were aware of their diagnosis Dr Abrahams said this group were difficult cases but they were aware of the diagnosis but for sensitivity reasons this was not mentioned in the information sheet.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation. You should send a copy of the amended recruitment to the poster for the Committee's file.

Ethical review of research sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the research site(s) taking part in this study. The favourable opinion does not therefore apply to any site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at sites requiring SSA.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Application Form Parts A and B		30 April 2008
Investigator CV		30 April 2008
Protocol	1	30 April 2008
Recruitment Poster	1	30 April 2008
Information sheet for Control Participants	1	30 April 2008
Information sheet for Language, Thinking, and Behaviour in different Neurological Conditions	1	30 April 2008
Information sheet for Carers (Language thinking and Behaviour in Motor Neurone Disease	1	30 April 2008
Information sheet for People with FTD	1	30 April 2008
Information sheet for People with MND	1	30 April 2008

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Participant Consent Form: Healthy Control	1	
Participant Consent Form: Carer of FTD - patient	1	30 April 2008
Participant Consent Form: Carer of MND - patient	1	30 April 2008
Participant Consent Form: FTD - Patient	1	30 April 2008
Participant Consent Form: MND - Patient	1	30 April 2008
GP/Consultant information sheet	1	30 April 2008
Letter of invitation to participants - Healthy Control	1	30 April 2008
Letters of invitation to participants - FTD - patient	1	30 April 2008
Letters of invitation to participants - MND- patient	1	30 April 2008
Letter from Sponsor		30 April 2008
Flow chart - Study Procedure	1	30 April 2008

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

Here you will find links to the following:

NHS SCOTLAND

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.
b) Progress Reports. Please refer to the attached standard conditions of approval by Research Ethics Committees.
c) Safety Reports. Please refer to the attached standard conditions of approval by Research Ethics Committees.
d) Amendments. Please refer to the attached standard conditions of approval by Research Ethics Committees.
e) End of Study/Project. Please refer to the attached standard conditions of approval by Research Ethics Committees.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nationalres.org.uk

REC reference number: 08/MRE00/50-Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

Professor Kennedy Lees
Chairman
cc: Dr Anne Langston
Associate Director
Edinburgh Clinical Trials
The Queens Medical Research Institute
47 Little France Crescent
Edinburgh
EH16 4TJ

SFC BRAIN IMAGING RESEARCH CENTRE

Clinical Neurosciences

SCHOOL OF MOLECULAR AND CLINICAL MEDICINE

The University of Edinburgh

Western General Hospital

Crewe Road

Edinburgh EH4 2XU

Tel: 0131 537 2664

Fax: 0131 537 2661

Email Lewis Pettit : L.D.Pettit@sms.ed.ac.uk

Email Dr Bastin: Mark.Bastin@ed.ac.uk

Email Dr Abrahams: s.abrahams@ed.ac.uk

Direct Line to Dr Abrahams: 0131 650 3339

PATIENT INFORMATION SHEET

MAGNETIC RESONANCE IMAGING OF PATIENTS WITH MOTOR NEURONE DISEASE

Research Project: The heterogeneity of Cognitive Impairment in MND: Brain Imaging.

Principal Investigators: **Dr. Sharon Abrahams, Lewis Pettit and Dr Mark Bastin**

Thank you for your interest in this important work.

Medical researchers need to know more about how different regions of the brain may be related to the changes in thinking and behaviour that are present in some people with MND. **In this study, we will use *Magnetic Resonance Imaging* (MRI) to collect images of brain. This imaging data will be used with the data collected from previous interviews to determine which areas of the brain may be affected in MND.**

MRI uses a combination of powerful magnets and radio waves to create very high quality pictures of particular parts of the body without using X-rays. Although MRI techniques are already very well developed for taking pictures of the brain, less is known about how the structure of the brain is altered during illness. This Centre's scanner is dedicated to finding out more about these important questions.

If you agree to join the study, **we will check that it is perfectly safe for you to be scanned**. Although MRI is normally a very safe method of taking pictures, we do not scan people who have a heart pacemaker or who have had surgery involving the insertion of metal clips into the brain, or people who have metal fragments in their eyes, perhaps as a result of their job. Neither will we scan you if there is a chance that you might be pregnant. On the other hand, the metals used in operations such as hip replacements are very rarely a reason not to undergo scanning. The Radiographers will check if you are in any doubt.

When you come to the Centre for your scan, a changing cubicle will be provided. You will be asked to place any metal objects, such as keys, watches, coins and credit cards, in a locker. Please do not wear any make-up or talc, and be prepared to remove contact lenses if you use them.

You will be asked to lie on the scanner bed for up to an hour. While you are in the scanner, a series of pictures of your brain will be taken. The scanner makes quite loud noises while it operates. For your comfort, you will be provided with ear-plugs or headphones, and it may be possible to play music into the Scanner Room if you wish. If at any stage shortly before or during your scan, you become worried, or wish to ask a question, you will be able to speak to one of the Radiographers, who will use an intercom to keep in touch with you.

Of course you do not have to take part in this study, and you may withdraw from it at any time. Please also be aware that this is non-therapeutic research from which you cannot expect to derive any direct benefit, and that participating or not participating in the study <u>will not affect</u> the treatment you would normally receive. Please note that we are required by a medical ethics committee to send a routine report of the scan to your Doctor.

All pictures that are taken within the Centre are entirely confidential, in the same way as all other medical records are. Pictures gathered from the scanner are stored and processed using computers and, after the study is completed, will be copied onto a permanent record which might be studied again at a later time.

Further information on magnetic resonance imaging is available, if you require it, from Mr. David Summers, Consultant Neuroradiologist, Clinical Neurosciences, Western General Hospital, Edinburgh (Tel: 0131 537 2022). He is **not** involved in this study, and so will be able to give you independent advice. Otherwise, the one of the Radiographers will be happy to try to answer any other questions that you might have. They can be contacted at the address shown at the top of the front of this information sheet.

The University has in place a policy that provides an indemnity against legal liability (and includes a no fault compensation section) for accidental injury to any research subject arising out of participation in a clinical trial.

Finally, you will be fully reimbursed for your travelling to the Brain Imaging Centre for this study.

Once again, many thanks.

Dr Sharon Abrahams

Senior Lecturer in Human Cognitive Neuroscience

s.abrahams@ed.ac.uk

Direct Line 0131 650 3339

SFC BRAIN IMAGING RESEARCH

CENTRE FOR SCOTLAND

& DEPARTMENT OF PSYCHOLOGY

PATIENT CONSENT FORM

Research Project: The Heterogeneity of Cognitive Impairment in MND: Brain Imaging.

Principal Investigators: **Dr. Sharon Abrahams and Dr Mark Bastin**

- I have read the Information Sheet that has been provided to me, and this Consent Form, and have been given the opportunity to ask questions about them. I am satisfied that I have all the information that I need to provide **informed consent**.

- I understand that my General Practitioner (GP) will be informed of my participation in this study, and know that he/she will be provided with a routine clinical report.

- I know of no reason why I should not undergo Magnetic Resonance Imaging or take part in the study.

- I know that I am under no obligation to take part in the study and **I can withdraw at any time**.

- **I understand that that is non-therapeutic research from which I cannot expect to derive any direct benefit.**

- **I understand that participating or not participating in the study will not affect the treatment that I would normally receive.**

- I understand and agree that medical images obtained during my scan will be stored and processed using computers and, after the study is completed, that these may be copied onto a permanent record which might be studied again at a later time.

- I understand and agree that information gathered during my scan may be shared with other medical and scientific researchers, subject to strict laws and University of Edinburgh policies intended to safeguard my privacy.

- **I agree to participate in the study**.

Signature of patient

Name of patient (please print in block capitals)

Witnessed by (signature)

Please turn over

Name of witness (please print in block capitals)

Date

Name of Volunteer's GP

GP's address

CHI Number (for use by SBIR Centre staff)

Both copies of this form must be brought to the Centre on the day of scanning. The pink copy is to be retained within the Centre; the patient should retain the white copy.

SFC BRAIN IMAGING RESEARCH CENTRE

Clinical Neurosciences

SCHOOL OF MOLECULAR AND CLINICAL MEDICINE

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Email Dr Bastin: Mark.Bastin@ed.ac.uk

Email Dr Abrahams: s.abrahams@ed.ac.uk

Direct Line to Dr Abrahams: 0131 650 3339

VOLUNTEER INFORMATION SHEET

MAGNETIC RESONANCE IMAGING

Research Project: The heterogeneity of Cognitive Impairment in Motor Neurone Disease: Brain Imaging.

Principal Investigators: **Dr. Sharon Abrahams, Lewis Pettit and Dr Mark Bastin.**

Thank you for your interest in this important work.

Medical researchers need to know more about how different regions of the brain may be related to the changes in thinking and behaviour that are present in some people with Motor Neurone Disease. To do this we also need to collect information from healthy people as a comparative group. **In this study, we will use *Magnetic Resonance Imaging* (MRI) to collect images of brain. This imaging data will be used with the data collected from previous interviews to determine which areas of the brain may be affected in MND.**

MRI uses a combination of powerful magnets and radio waves to create very high quality pictures of particular parts of the body without using X-rays. Although MRI techniques are already very well developed for taking pictures of the brain, less is known about how the structure of the brain is altered during illness. This Centre's scanner is dedicated to finding out more about these important questions.

If you agree to join the study, **we will check that it is perfectly safe for you to be scanned**. Although MRI is normally a very safe method of taking pictures, we do not scan people who have a heart pacemaker or who have had surgery involving the insertion of metal clips into the brain, or people who have metal fragments in their eyes, perhaps as a result of their job. Neither will we scan you if there is a chance that you might be pregnant. On the other hand, the metals used in operations such as hip replacements are very rarely a reason not to undergo scanning. The Radiographers will check if you are in any doubt.

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You will be asked to lie on the scanner bed for up to an hour. While you are in the scanner, a series of pictures of your brain will be taken. The scanner makes quite loud noises while it operates. For your comfort, you will be provided with ear-plugs or headphones, and it may be possible to play music into the Scanner Room if you wish. If at any stage shortly before or during your scan, you become worried, or wish to ask a question, you will be able to speak to one of the Radiographers, who will use an intercom to keep in touch with you.

Of course you do not have to take part in this study, and you may withdraw from it at any time. Please also be aware that this is non-therapeutic research from which you cannot expect to derive any direct benefit, and that participating or not participating in the study <u>will not affect</u> the treatment you would normally receive. Please note that we are required by a medical ethics committee to send a routine report of the scan to your Doctor.

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Finally, you will be fully reimbursed for your travelling to the Brain Imaging Centre for this study.

Once again, many thanks.

Dr Sharon Abrahams

Senior Lecturer in Human Cognitive Neuroscience

s.abrahams@ed.ac.uk

Direct Line 0131 650 3339

SFC BRAIN IMAGING RESEARCH

CENTRE FOR SCOTLAND

& DEPARTMENT OF PSYCHOLOGY

VOLUNTEER CONSENT FORM

Research Project: The Heterogeneity of Cognitive Impairment in MND: Brain Imaging.

Principal Investigator: **Dr. Sharon Abrahams and Dr Mark Bastin**

- I have read the Information Sheet that has been provided to me, and this Consent Form, and have been given the opportunity to ask questions about them. I am satisfied that I have all the information that I need to provide **informed consent**.

- I understand that my General Practitioner (GP) will be informed of my participation in this study, and know that he/she will be provided with a routine clinical report.

- I know of no reason why I should not undergo Magnetic Resonance Imaging or take part in the study.

- I know that I am under no obligation to take part in the study and **I can withdraw at any time**.

- **I understand that that is non-therapeutic research from which I cannot expect to derive any direct benefit.**

- **I understand that participating or not participating in the study will not affect the treatment that I would normally receive.**

- I understand and agree that medical images obtained during my scan will be stored and processed using computers and, after the study is completed, that these may be copied onto a permanent record which might be studied again at a later time.

- I understand and agree that information gathered during my scan may be shared with other medical and scientific researchers, subject to strict laws and University of Edinburgh policies intended to safeguard my privacy.

- **I agree to participate in the study**.

Signature of participant

Name of participant (please print in block capitals)

Witnessed by (signature)

Name of witness (please print in block capitals)

Date

Name of Volunteer's GP

GP’s address

CHI Number (for use by SBIR Centre staff)

Both copies of this form must be brought to the Centre on the day of scanning. The pink copy is to be retained within the Centre; the patient should retain the white copy.

Psychology
SCHOOL of PHILOSOPHY, PSYCHOLOGY and LANGUAGE SCIENCES
The University of Edinburgh
7 George Square
Edinburgh EH8 9JZ
Telephone 0131 650 3440
or direct dial 0131 650
Fax 0131 650 3461
Email Psychology@ed.ac.uk

Participant Information Sheet for Patients

Study title: "Thinking and behaviour in movement disorders; a comparative study".

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The current study investigates processes of thinking in motor disorders and uses some measures which focus on how we pay attention to information and the ability to perform two tasks at once.

Why have I been chosen?

We will be seeing 40 people with motor neuron disease (MND), 40 people with Parkinson's disease (PD), and 40 people with multiple sclerosis (MS). We will also be seeing a total of 40 healthy control participants.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive, now

or in the future. If you wish to discuss the study with somebody else who is informed but independent from the research team, please contact Dr Rob McIntosh; Department of Psychology, PPLS, University of Edinburgh, 7 George Sq, Edinburgh, EH8 9JZ, Tel: 0131 650 3444;
Email: r.d.mcintosh@ed.ac.uk

What will happen to me if I take part?

The study will consist of an interview during which you will undertake a series of simple tasks, some of which will take place on a computer. Please feel free to say no at this stage if you do not wish to participate any further. You are under no obligation to participate.

The interview will last for approx. 2.5 hours. You can take as many breaks as you want and the study can be split across two separate days if you like. The interview can take place at your home at a time of your convenience, or at the Department of Psychology, University of Edinburgh, 7 George Square, if you prefer. Your travelling expenses will be reimbursed if you decide to come to the University of Edinburgh to take part in the study.

If you wish, your G.P will be informed of your participation in this research.

What do I have to do?

You will not have to come off medication or undergo any invasive procedure whatsoever. Most tests are in the form of computer games and puzzles. Some of these tests assess how quickly your brain can do things, some of them test your memory, and some of them test your ability to problem solve and perform two tasks at the same time. The tests have been designed specifically to accommodate for movement problems. If you are unable to move your hands we will assist you in completing the tasks. If you are unable to speak we may skip certain tests that rely on spoken answers. Some of the tests may be filmed to help with data analysis.

What are the possible disadvantages and risks of taking part?

We do not anticipate any health risks from taking part in this study. If you feel distressed at any time during the interview it is important that you let the interviewer know straight away. If you feel distressed after the interview, please contact Dr. Sharon Abrahams 0131 650 3339 (project leader).

What are the possible benefits of taking part?

There will be no direct benefit to you by taking part, and your individual results will not be revealed to you. However, if you wish, we will send you a

summary of the study's findings. It is hoped that this research will improve our knowledge relating to motor disorders and may influence care practices in the future.

What if something goes wrong?

Whilst we do not anticipate any adverse effects from taking part in this study, if you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. The research team will enquire about your educational history to check for any previous or existing problems that could affect the results of the study. Only members of the research team and the clinical team at your hospital will have access to your medical records and notes. The research team will check your medical notes for any prior or existing problems that may affect the results of the study. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. You will be allocated an anonymous ID code during testing which will be used in place of your name in our testing materials, computers or on any future publications.

In the unlikely event that you have given informed consent, but lose the ability to give consent during the study, the information we have already collected about you will be retained and used in the research. As stated earlier, all personal information will be kept strictly confidential.

What will happen to the results of the research study?

The results of the research will be published in appropriate peer-reviewed scientific journals for distribution to other healthcare professionals. Talks and presentations may be made at academic and clinical meetings and conferences. In all cases, your name and personal details will not be identified.

Who is organising the research?

The study is being organised by Dr. Sharon Abrahams and Lewis Pettit from the University of Edinburgh, in collaboration with neurology centers at the Western General Hospital (Edinburgh), and the Royal Infirmary of Edinburgh.

Who has reviewed the study?

This study has been reviewed by the South East Scotland Research Ethics Committee.

Contact for Further Information

If you wish to ask anything further then please contact Lewis Pettit via the address below or on 0131 650 3423 (Lewis.D.Pettit@sms.ed.ac.uk) or Dr Sharon Abrahams 0131 650 3339 (s.abrahams@ed.ac.uk).

Lewis Pettit and Dr Sharon Abrahams
Department of Psychology, PPLS , 7 George Square
Edinburgh, EH8 9JZ

Thank you for reading this information sheet. You will be given a copy to keep. If you have understood the contents of this sheet and wish to take part, please complete the consent sheet on the next page. If you have any questions please feel free to ask them now.

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: "Thinking and behaviour in movement disorders; a comparative study"

Name of Researchers: Dr. Sharon Abrahams & Lewis Pettit

Please tick box

- ☐ I confirm that I have read and understand the information sheet (July 2011, version 2) for the above study and have had the opportunity to ask questions.
- ☐ I understand that I will be filmed/recorded for data analysis purposes.
- ☐ I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
- ☐ I understand that sections of any of my medical notes may be looked at by responsible individuals from *(name of hospital) (location)* or by members of the research team. I give permission for these individuals to have access to my records.
- ☐ Please tick if you would like your G.P. to be informed of your participation in this research.
- ☐ Please tick if you would like to receive a summary of the findings
- ☐ I agree to take part in the above study.

_____	_____	
Name of Patient	Signature	Date
_____	_____	_____
Researcher	Signature	Date

Psychology
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The University of Edinburgh
7 George Square
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Telephone 0131 650 3440
or direct dial 0131 650
Fax 0131 650 3461
Email Psychology@ed.ac.uk

Participant Information Sheet for Healthy Volunteers

Study title: "Thinking and behaviour in movement disorders; a comparative study".

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The current study investigates processes of thinking in motor disorders and uses some measures which focus on processes of attention and your ability to perform two tasks at once.

Why have I been chosen?

We will be seeing a total of 40 healthy control participants. We will also be seeing 40 people with motor neuron disease (MND), 40 people with Parkinson's disease (PD), and 40 people with multiple sclerosis (MS).

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a

decision not to take part, will not affect the standard of care you receive, now or in the future. If you wish to discuss the study with somebody else who is informed but independent from the research team, please contact Dr Rob McIntosh; Department of Psychology, PPLS, University of Edinburgh, 7 George Sq, Edinburgh, EH8 9JZ, Tel: 0131 650 3444;
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The study will consist of an interview during which you will undertake a series of simple tasks, some of which will take place on a computer. Please feel free to say no at this stage if you do not wish to participate any further. You are under no obligation to participate.

The interview will last for 2.5 hours. The interview will take place at the Department of Psychology, University of Edinburgh, 7 George Square. You will be paid £6 an hour as a reimbursement for your time.

If you wish, your G.P will be informed of your participation in this research. In addition, in the unlikely event that the study identifies any medical problems, your G.P will be informed of your participation in this research and advised as necessary.

What do I have to do?

You will not have to take medication or undergo any invasive procedure whatsoever. Most tests are in the forms of computer games and puzzles. Some of these tests assess how quickly your brain can do things, some of them test your memory, and some of them test your ability to problem solve and perform two tasks at the same time. Some of the tests may be filmed to help with data analysis.

What are the possible disadvantages and risks of taking part?

We do not anticipate any health risks from taking part in this study. If you feel distressed at any time during the interview it is important that you let the interviewer know straight away. If you feel distressed after the interview, please contact Dr. Sharon Abrahams 0131 650 3339 (project leader).

What are the possible benefits of taking part?

There will be no direct benefit to you by taking part, and your individual results will not be revealed to you. However, if you wish, we will send you a summary of the study's findings. It is hoped that this research will improve

our knowledge relating to motor disorders and may influence care practices in the future.

What if something goes wrong?

Whilst we do not anticipate any adverse effects from taking part in this study, if you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Only people from the research team will see your information. You will be allocated an anonymous ID code during testing which will be used in place of your name in our testing materials, computers or on any future publications.

What will happen to the results of the research study?

The results of the research will be published in appropriate peer-reviewed scientific journals for distribution to other healthcare professionals. Talks and presentations may be made at academic and clinical meetings and conferences. In all cases, your name and personal details will not be identified.

Who is organising the research?

The study is being organised by Dr. Sharon Abrahams and Lewis Pettit from the University of Edinburgh, in collaboration with neurology centers at the Western General Hospital (Edinburgh) and the Royal Infirmary of Edinburgh.

Who has reviewed the study?

This study has been reviewed by the South East Scotland Research Ethics Committee.

Contact for Further Information

If you wish to ask anything further then please contact Lewis Pettit via the address below or on 0131 650 3423 (Lewis.D.Pettit@sms.ed.ac.uk) or Dr Sharon Abrahams 0131 650 3339 (s.abrahams@ed.ac.uk).

Lewis Pettit and Dr Sharon Abrahams
Department of Psychology, PPLS , 7 George Square
Edinburgh, EH8 9JZ

Thank you for reading this information sheet. You will be given a copy to keep. If you have understood the contents of this sheet and wish to take part, please complete the consent sheet on the next page. If you have any questions please feel free to ask them now.

Control Identification Number for this trial:

CONSENT FORM

Title of Project: "Thinking and behaviour in movement disorders; a comparative study"

Name of Researchers: Dr. Sharon Abrahams & Lewis Pettit

Please tick box

- ☐ I confirm that I have read and understand the information sheet (July 2011, version 2) for the above study and have had the opportunity to ask questions.
- ☐ I understand that I will be filmed/recorded for data analysis purposes.
- ☐ I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
- ☐ Please tick if you would like your G.P. to be informed of your participation in this research.
- ☐ Please tick if you would like to receive a summary of the findings
- ☐ I agree to take part in the above study.

_____	_____	
Name of Volunteer	Signature	Date
_____	_____	
Researcher	Signature	Date

Appendix C – Relationship between depression and cognition in MS

Table 23. HADS depression correlations with background neuropsychological testing

Test	Correlation coefficient (*rho*)	p value
GNT	-0.31	0.182
Spatial Span Fwd	-0.03	0.910
Spatial Span Rev	-0.25	0.259
Digit Span Fwd	0.17	0.428
Digit Span Rev	0.27	0.191
Log. Memory Imm.	-0.05	0.817
Log.Memory Del.	-0.13	0.551
Log. Memory Rec.	-0.24	0.267
Log. Memory Ret.	-0.20	0.341
Brixton (Errors)	-0.13	0.551
Brixton (scaled)	0.08	0.718
Sorting Test (no. of sorts)	-0.17	0.415
Sorting Test (Recog)	-0.08	0.701
Sorting Test (scaled score)	-0.25	0.227
Spoken letter fluency (*fi*)	-0.21	0.306
Written letter fluency (*fi*)	-0.20	0.495

GNT = Graded Naming Test, Fwd = Forward, Rev. = Reverse, Log. = Logical, Imm. = Immediate recall, Del. = Delayed recall, Rec. = Recognition, Ret. = Retention, *fi* = fluency index, No. of sorts = number of correctly identified sorts in the DKEFS Sorting test, Recog = score in the recognition condition of the DKEFS Sorting test.

Appendix D – Dual task pilot study

Participants

In total fifteen healthy young adults (8 males, and 7 females, mean age = 23.3, range = 21 – 30, mean WTAR score = 110.6, range = 96 – 122) were recruited from the university's Volunteer Participant Panel. Seven participants were administered the dual-task using each individual's maximum level of performance in the component tasks. A subsequent eight participants were administered an updated version of the task in which the component tasks were administered at a level one increment below their maximum level (level -1). Participants who undertook this version of the dual task went on to form part of the young participant group in the ageing study.

Procedure

The procedure for the pilot study was identical to that of the ageing study (described in Chapter 3, Section 3.6.3.4), except that the first seven participants were administered the component tasks at their maximum ability level in single and dual task conditions.

Results

Percentage change scores revealed that dual-task costs were relatively high when individuals' were administered component tasks at their maximum level. The average dual-task cost was 5.6% (SD = 7.4) and the range was large (min = -1.9%, max = 18.8%) suggesting that performance was highly variable. For this reason, the dual-task methodology was updated so that component tasks (in both single-task and dual-task conditions) were

administered at a level one below an individual's maximum ability. The updated dual-task methodology was subsequently piloted on a further eight healthy young adults, and revealed a smaller average dual-task cost of 3.6% (SD = 4.0), with a more conservative range (min = -0.3%, max = 12.5%) suggesting that performance under these conditions was more stable and predictable. Indeed, the small dual-task costs observed in the updated dual-task methodology are consistent with those produced by other studies employing similar "preload" methodology (Cocchini et al., 2002; MacPherson *et al.*, 2004). Thus, the updated of version of the dual task paradigm was employed in all subsequent investigations. Full details of the dual-task pilot study are displayed in Table 24.

Table 24. Dual task performance in healthy young participants, means [SD] are presented

	Max. level (n = 7)	**Level -1 (n = 8)**
Baseline DDR level (digits)	6.7 [1.0]	6.3 [0.7]
Baseline VIT level (ms)	38.9 [8.3]	53.1 [10.9]
DDR Single % correct	95.6 [4.2]	97.8 [3.6]
VIT Single % correct	94.6 [5.5]	95.1 [3.9]
DDR Dual % correct	95.1 [5.8]	94.9 [5.6]
VIT Dual % correct	84.9 [13.3]	91.1[6.8]
DDR Dual Task Cost (% change)	0.5 [6.2]	2.7 [5.5]
VIT Dual Task Cost (% change)	10.6 [10.6]	4.3 [4.2]
Average Dual Task Cost (% change)	5.6 [7.4]	3.6 [4.0]

Max. = maximum, ms = milliseconds, DDR = Delayed Digit Recall, VIT = Visual Inspection Time.

Appendix E - Testing Protocol

Participant Number.....

Date.....

Information/Consent.....

Order	Test	Duration	Notes	Score
1	WATR	5 mins		
2	Dual Task	30 mins	Inc. VIT and DS titrations	
3	Letter RSVP	15 mins	Spin laptop screen	
4	HADS	5 mins		
5	Card Sort	15 mins		
6	VIT	15 mins		
7	Written Verbal Fluency	10 mins	S for 5 mins, C4 for 4 mins	
8	Spoken Verbal Fluency	5 mins	P,R,W	
9	wVF control	10 mins		
10	sVF control	5 mins		
		BREAK		
11	Logical Memory	10 mins	Immediate Recall	
12	Brixton	10 mins		
13	Corsi Block	10 mins	Forward	
14	Corsi Block	10 mins	Reverse	
15	Logical Memory	10 mins	Delayed recall/recognition	
16	GNT	5 mins		
17	Digit Span	5 mins	Forward	
18	Digit Span	5 mins	Reverse	
19	Force Respiration	5 mins	ALS only	
20	ALSFRS	10 mins	ALS only	
21	Sleep Apnoea Scale	10 mins	ALS only	