The Nature of Language Impairment in Motor Neurone Disease

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Declaration

I declare that this thesis is my own composition, and that the material contained in it describes my own work. It has not been submitted for any other degree or professional qualification. All quotations have been distinguished by quotation marks and the sources of information acknowledged.

Phillipa Rewaj

Abstract

Background: Language impairment associated with Motor Neurone Disease (MND) has been documented since the late 19th century, yet little is understood about the pervasiveness or nature of these deficits. The common clinical view among healthcare professionals is that communication difficulties can be attributed solely to the motor speech disorder dysarthria. Recent literature raises the possibility of more central processing deficits. Impairments in naming ability and comprehension of complex grammatical constructs have been frequently reported in some patients with MND. However, there is now growing evidence of spelling impairment, which could suggest the contribution of a more phonologically based deficit. In addition, the close relationship between MND and frontotemporal dementia (FTD) raises questions about the connection between the language impairments seen in MND patients and those documented in patients with the primary progressive aphasia (PPA) syndromes associated with FTD.

Aims: This thesis examines the nature of speech and language deficits in people with MND and the extent to which expressive communication impairment can occur above and beyond dysarthria. In particular, the study explores: i) to what extent these language impairments can be attributed to deficits in working memory, executive functioning and/or disease severity; ii) what spelling errors can reveal about the integrity of lexical, phonological and orthographic processing; iii) whether similar patterns of impairment can be seen in PPA syndromes; iv) the relationship between language impairment and bulbar onset; and v) the impact these findings have on clinical management of MND patients.

Methods: MND patients from across Scotland with changes in speech and/or language were tested using a neuropsychological battery of experimental and standardised tests of naming, spelling, syntactic comprehension, prosody and phonological and orthographical awareness. Patients were also screened for levels of dysarthria, executive functioning and working memory deficits, and results compared to those of matched controls.

Findings: As a group, MND participants performed significantly worse than matched controls on measures of naming, spelling, orthographical awareness, grammatical comprehension, affective prosody and verbal fluency, but not working memory. However, based on patterns of individual impairment, of which spelling impairment formed a distinctive marker, the patient group divided into dichotomous subgroups, with 44% of participants categorised as 'linguistically impaired', while the remainder displayed little to no impairment. Those participants identified as linguistically impaired did not differ significantly from other MND participants on measures of disease severity, disease duration or dysarthria severity, although significantly more bulbar onset than limb onset participants were linguistically impaired. Spelling error patterns were suggestive of deficits at both a lexical and sublexical level, and were comparable to those reported in PPA literature. These findings suggest that dysarthria may be masking linguistic deficits in almost half of dysarthric MND patients, and highlight the importance of multidimensional assessment of language for effective clinical management.

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This thesis is dedicated in loving memory of my mother Catherine Rewaj.

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Shine silently

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Chapter 1: Introduction

Motor Neurone Disease – A purely motor disorder?

1.1 Motor Neurone Disease (MND)

First described by French neurologist Charcot in 1869 (Charcot & Joffroy, 1869), Motor Neurone Disease (MND) is the name given to a collection of progressive, degenerative disorders that affect the neurones of the upper and/or lower motor neurone systems. Motor neurones are the nerves responsible for carrying messages from the brain to the muscles about how and when to contract. Upper motor neurones (UMN) are contained within the brain, brainstem, and spinal cord and send axons (nerve fibres) to the lower motor neurones (LMN) running from the spinal cord. LMNs then send motor axons into the peripheral cranial and spinal nerves, resulting in muscle contractions. While MND damages and destroys both UMNs and LMNs, both types are not always simultaneously affected and presentation varies between individuals dependant on the subtype of the disease and onset location.

Amytrophic Lateral Sclerosis (ALS) is the most common type of motor neurone disease affecting approximately 85% of all people with MND, and is often used synonymously with the term MND, particularly in the United States (K. Talbot, 2002). ALS can affect limb and/or bulbar (those required for speech and swallowing) muscles and results from damage to both the UMNs and LMNs. Damage to the UMNs causes muscle stiffness or spasticity (increased muscle tone), while damage to the LMNs causes muscle weakness, atrophy and flaccidity (decreased muscle tone). Average life expectancy for an individual with ALS is approximately 3-4 years from onset of symptoms, and is more common in men than women (Leigh et al., 2003). Progressive Bulbar Palsy (PBP) is the second most common type of MND, accounting for approximately 25% of MND cases (ibid.), and is dominated by LMN damage to the cranial nerves supplying the bulbar muscles. Initial and predominant symptoms are distorted or 'slurred' speech (dysarthria) and difficulties swallowing (dysphagia). Life expectancy for someone with PBP is around 6 months to 3 years on average, and is more common in women than men (Kiernan et al., 2011).

Progressive Muscular Atrophy (PMA) and Primary Lateral Sclerosis (PLS) are the two rarest forms of MND affecting approximately 10% and 1% of the MND population respectively (K. Talbot, 2002). While PMA is caused by damage to the LMNs alone, conversely PLS results from damage solely to the UMNs. Both PMA and PLS are more common in men than women, and average life expectancy is longer than for the more common subtypes: PMA approximately 5 to 10 years from onset; PLS living a relatively average lifespan providing it does not develop into ALS (Leigh et al., 2003). As a collective disease, MND affects around 6 to 8 people per 100,000 at any one time, and according to 2011 statistics there were approximately 130 new diagnoses and just over 400 people living with the condition in Scotland (MND Scotland, 2011).

1.2 Communication Impairment in MND

1.2.1 Speech

The presence of communication impairment in MND has been well documented over the years, frequently attributed to the motor speech disorder 'dysarthria'. Estimates vary on the prevalence of dysarthria in MND, but figures range from 50-80% of patients developing motor speech problems at some point in the disease trajectory (Li, Alberman, & Swash, 1990; Tomik & Guiloff, 2010; Traynor et al., 2000).

1.2.1.1 Dysarthria

Dysarthria is a collective name for a range of neurogenic speech disorders characterised by impairment in the strength, speed, range, steadiness, tone, or accuracy of movements required for control of the respiratory, phonatory, resonatory, articulatory, and prosodic aspects of speech production (J.R. Duffy, 2005). In the same way that other muscles in the body are affected differently dependent on the type of motor neurones affected, impairment of the articulators can also present variably. Damage to the UMNs causes spasticity in the muscles, which, in turn, results in what is known as spastic dysarthria. The most salient speech characteristics associated with spastic dysarthria, as identified by Darley, Aronson & Brown's seminal work are (in order of frequency): imprecise consonants; monopitch; reduced stress; harshness; monoloudness; low pitch; slow rate; hypernasality; strained-strangled quality; short phrases; distorted vowels; pitch breaks and breathy voice (Darley, Aronson, & Brown, 1969a). Spastic dysarthria is commonly associated with PLS. When, on the other hand, damage is solely to the LMNs, as with PMA, muscles become flaccid, causing flaccid dysarthria. Key characteristics of flaccid dysarthria include (in order of frequency): hypernasality; imprecise consonants; breathy voice; monopitch; nasal emission; audible inspiration; harsh voice quality; short phrases; and monoloudness (Darley et al., 1969a).

However, most commonly both UMNs and LMNs are affected in MND which results in a mixed spastic-flaccid dysarthria. While mixed spastic-flaccid dysarthria is a recognised and described form of dysarthria, due to the mixed nature of its presentation and the potential fluctuation in predominant symptoms dysarthria may not be perceived to be mixed throughout the disease progression, and much variability exists. Characteristic features, as outlined by Darley and colleagues include (in order of frequency): imprecise consonants, hypernasality, harsh voice quality, slow rate, monopitch, short phrases, low pitch, strained-strangled quality and breathiness (Darley, Aronson, & Brown, 1975). While articulatory characteristics occur due to weakness and spasticity of the lips, tongue and jaw, changes in voice quality arise as a result of palatal and laryngeal changes. Phonatory disturbances can be the first clinical symptom, particularly in bulbar onset cases, and diagnostic procedures can often begin through referrals to ENT (Hillel et al., 1995). Indeed research has shown that even among highly intelligible patients there can be a high frequency of voicing errors suggestive of early laryngeal vulnerability (Riddel, McCauley, Mulligan, & Tandan, 1995). Furthermore there has been some suggestion of gender differences in phonatory symptoms, with men being susceptible to greater changes in laryngeal function than women (J. F. Kent et al., 1992; Riddel et al., 1995). In addition, respiratory insufficiency can result in reduced voice volume and short phrases, impacting on prosodic speech patterns (R. D. Kent, 2000). All of these symptoms contribute to the gradual deterioration in speech intelligibility, progressing to the point where augmentative and alternative communication (AAC) is often required.

1.2.1.2 Apraxia of Speech

Another motor speech disorder that has only recently been suggested as a possible contributor to the communication impairment in MND is apraxia of speech (AOS). First described by Darley in the 1960s as an impairment of motor speech planning, AOS reflects a reduced capacity to programme the motor commands necessary for movement of the articulators to result in phonetically and prosodically normal speech (J.R. Duffy, 2005). Articulatory errors not attributable to muscle weakness and prosodic abnormalities are the characteristic features of AOS (Ogar, Slama, Dronkers, Amici, & Gorno-Tempini, 2005). Other hallmark features include: effortful groping towards articulatory positions; greater difficulty with consonants over vowels; inconsistent and variable errors often more complex than the target; and perseverative and anticipatory errors (Darley et al., 1975). Additionally, a substantial proportion of people with AOS also exhibit nonverbal oral apraxia – a difficulty imitating or performing to command non speech actions of the articulators (e.g. clicking tongue, smacking lips) (J.R. Duffy, 2005). Most commonly associated with vascular lesions, AOS has also been identified in neurodegenerative diseases including cortiocbasal degeneration (CBD)(Lehman Blake, Duffy, Boeve, Ahlskog, & Maraganore, 2003; Rosenfield, Bogatka, Viswanath, Lang, & Jankovic, 1991), progressive supranuclear palsy (PSP) (B. Boeve et al., 2003; Josephs et al., 2005) and primary progressive aphasia (PPA) (Gorno-Tempini et al., 2004; Hart, Beach, & Taylor, 1997; Josephs et al., 2006).

The existence of AOS as a contributor to communication impairment in people with MND is a controversial and little reported issue. Initial reports of AOS as a sign of motor neurone disease came from Duffy's 2006 retrospective summary of 80 patients with a variety of degenerative neurological conditions for whom AOS was a predominant communication disorder (J.R. Duffy, 2006). 7 of the 80 patients described had MND, and the characteristics of these patients were described in detail in a further report (J. R. Duffy, Peach, & Strand, 2007). They reported that all 7 patients had three or more speech features consistent with AOS and which were unlikely to be attributable to dysarthria. These features included distorted substitutions, irregular articulatory breakdowns, difficulty with sequential motion rates (e.g. repetition of /pətəkə/), vowel distortions and articulatory groping. In addition, they refer to earlier studies reporting nonfluent aphasia in MND, such as Caselli and colleagues (Caselli et al., 1993), where speech is described as being "effortful" and "stuttering-like", and suggest that these reports may also be indicative of the presence of AOS.

A more recent single case report describes one patient with bulbar onset MND-FTD with spastic dysarthria and asymmetric orofacial apraxia (Lobo, Pinto, Rocha, Reimao, & de Carvalho, 2013). The patient demonstrated a left facial paresis on examination of voluntary movements (e.g. lifting eyebrows, showing teeth) on command and on imitation, however automatic movements such as smiling were symmetrical. Interestingly the patient also showed behavioural and cognitive changes including apathy, mild executive dysfunction and agrammatic writing with reduced vocabulary. However, while latterly the patient was anarthric and dysphagic, she demonstrated no other neurological features and was without weakness, muscle atrophy or respiratory symptoms and repeated electrodiagnostic investigations resulted in normal conduction study values with no loss of motor units or spontaneous activity, making a MND diagnosis questionable. However both of these studies are suggestive of the presence of a communication disorder beyond the limits of dysarthria.

1.2.2 Language

However, the ability to communicate is not limited to the motor elements of speech. Indeed before the movements for speech sounds can be programmed and executed, concepts must be transformed into words and correct speech sounds selected and sequenced (further discussion regarding the cognitive neuropsychological model of language processing will be presented in chapter 4). While language processing in MND has, in general, often only been studied as part of wider cognitive testing, increasingly reports of linguistic deficits are being recognised as evidence towards a distinctive impairment profile.

1.2.2.1 Naming and Fluency

One of the most reported language impairments in people with MND is covered under the umbrella term 'word retrieval' deficits. Commonly within cognitive testing confrontation naming and verbal fluency measures have been administered to gain insights into language and executive functions respectively, although the strong language component of letter and category fluency tasks has given rise to their use as a measure of language abilities also. Indeed, for many early studies of language function in MND, confrontation naming, verbal fluency and language sections from assessments such as the Mini-Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) have been the only measure of language processing used (Strong, Grace, Orange, & Leeper, 1996). While increasingly other domains of language processing are being included in assessment, confrontation naming and verbal fluency measures are still amongst the most frequently used.

One of the earliest studies to examine naming and fluency in MND was a study of nineteen patients conducted by Talbot and colleagues (P. R. Talbot et al., 1995). Assessment using the Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 1983) revealed no significant difference in performance between MND patients and controls in confrontation naming, and there was also no significant difference in performance to controls on letter fluency. However, a larger study of 146 patients conducted by Massman and colleagues the following year found 11.7% of the patients tested on various neuropsychological measures performed at or below the 5th percentile on the BNT, while 21.2% of patients performed at or below the 5th percentile on letter fluency measures (Massman et al., 1996). Similar results were reported by Strong and colleagues where patients performed significantly worse than controls on measures of confrontation naming and single word comprehension as tested with the Peabody Picture Vocabulary Test (PPVT-III) (Dunn & Dunn, 1997) (Strong et al., 1999). Errors were characterised by both verbal paraphasias (e.g. 'yell' for funnel) and semantic paraphasias (e.g. 'nut' for acorn). More recently Taylor and colleagues found naming deficits in a cohort of 51 patients with performance worse than controls on the BNT (Taylor et al., 2013).

Abrahams and colleagues also found conflicting results across two studies examining the relationship between verbal fluency and linguistic abilities. A group of 22 MND patients were compared to controls on letter and category fluency, a computerised sentence completion test based on the Hayling sentence completion test (Burgess & Shallice, 1997), phonological loop functions (phonological similarities effect and word length effect) and the GNT (Abrahams et al., 2000). They found no significant difference between groups on category fluency, spoken letter fluency, phonological loop functions, sentence completion test and GNT, with the only difference in performance between groups occurring with written fluency. They argue that this suggests verbal fluency deficits are as a result of attentional deficits or an impairment in the central executive component of working memory and not in phonological loop functions or linguistic abilities. However, this contrasts sharply with a later study conducted by the same group comparing twenty-eight ALS patients with controls on measures of executive and memory functions and the same naming and sentence completion tests (Abrahams et al., 2004). Again there was no significant difference between patients and controls on sentence completion test, yet on this occasion MND patients were significantly worse than controls on GNT. Patients were also significantly worse on written and spoken letter fluency but not category fluency, which could suggest that there is some effect of orthography and/or phonology on performance rather than semantics. Cooper and colleagues examined the lexical-semantic differences on performance of generative naming in sixteen MND patients, testing whether patients displayed specific impairments for living/non living in category fluency measures (Cooper et al., 2008). Although there was no overall difference between patients and controls as a whole group, they identified a subgroup of three patients who were significantly worse than controls, and also produced significantly more errors in the living category over non living.

The variability in reports regarding verbal fluency and naming abilities could, in part be due to this suggestion that there may be a distinct subgroup of linguistically impaired patients. Rackowicz and Hodges tested eighteen patients and found no significant difference between patient and control groups on Hodges' semantic battery naming test (Hodges, Salmon, & Butters, 1991), however patients were significantly worse than controls on the Graded Naming Test (GNT) (McKenna & Warrington, 1983) (Rakowicz & Hodges, 1998). Additionally, five of the eighteen (28%) were identified as language impaired, three with additional dementia, and were distinguishable from the rest of the group through naming performance, with errors characterised by predominantly semantic paraphasias or circumloctions. In one of the first studies specifically focussed to examining language function in MND, Cobble also used the GNT, amongst other tests of language, to assess a group of nine patients (Cobble, 1998). She found that although patients were significantly worse than controls on GNT, scores were still within norms. Furthermore, Cobble's study also identified a subgroup of three patients who were impaired across all linguistic measures used. Naming performance, as measured through the BNT, has also been used to identify the presence of progressive aphasia in MND patients (Lomen-Hoerth et al., 2003).

Several studies report marked anomia as one of the initial presenting symptoms of an MND/progressive aphasia syndrome. Doran and colleagues tested three patients with rapidly progressive aphasia and MND on various language measures, including letter fluency, category fluency, and picture naming and naming to description (Doran, Xuereb, & Hodges, 1995). All three demonstrated marked anomia and low verbal fluency scores, particularly with letter fluency. Despite these marked deficits, two of the patients attained only mildly impaired scores on the MMSE, while the other was within the normal range. Word finding difficulties were also the presenting symptom of a case described by Catani and colleagues who after six months developed dysphagia and dysarthria accompanied by fasciculations of the tongue (Catani et al., 2004). Testing over the course of a year at 3, 9 and 15 months post onset revealed progressive and rapid decline in all language functions, with non-verbal cognitive functions relatively preserved in comparison to language. The fluency and content of speech was reduced, characterised by anomia and circumlocutions, and was particularly deficient in syntactic words. Similar to the cases presented by Doran and colleagues, letter fluency was worse than category fluency. With regards confrontation naming, he displayed similar patterns of impairment across both spoken and written naming, and was particularly impaired in the naming of actions over objects.

1.2.2.2 Action and Object Processing

Dissociation in action and object processing is another frequently reported characteristic of the linguistic impairment observed in MND patients. One of earliest studies to report a noun-verb processing dissociation in MND patients was that conducted by Bak and Hodges (T. Bak & Hodges, 1997). They reported three patients in whom noun and verb comprehension was assessed and were found to display a specific deficit in the comprehension of verbs over nouns. One of the three was also tested on a noun and verb naming test and showed a striking impairment and verb-noun dissociation, correctly naming only 13% of verbs, while being able to name 63% of nouns correctly. These findings have been reported elsewhere in the literature (Catani et al., 2004), and were also supported by a further study by Bak and colleagues where performance was not only significantly worse than controls, but also a group of matched Alzheimer's Disease (AD) patients, who, in addition, did not show the verb-noun dissociation seen in MND patients (T. H. Bak, O'Donovan, Xuereb, Boniface, & Hodges, 2001).

Another commonly used set of tests designed to assess noun and verb processing are the Pyramids and Palm Trees (PPT) (Howard & Patterson, 1992) and Kissing and Dancing (KDT) (T.H. Bak & Hodges, 2003) tests of semantic association. While the PPT is a test of nonverbal semantic association for nouns, the KDT is a similarly designed test for verbs. Bak and Hodges reported four cases of MND/aphasia/dementia who were assessed on the PPT and KDT (T. H. Bak & Hodges, 2004). All four of the patients tested performed significantly worse on the KDT than the PPT. More recently Taylor and colleagues reported similar findings in a larger group of 51 patients where performance on the KDT was significantly worse than controls, however there was no significant difference between the groups on the PPT (Taylor et al., 2013). These findings suggest the presence of a central, nonverbal deficit in the concept of verbs over nouns.

Researchers have attempted to explain this dissociation of performance by considering it as a deficit not of verbs over nouns, but of actions over objects. Grossman and colleagues tested 34 patients on word-description matching and associativity judgements with actions and objects, finding that 72.7% of patients performed significantly worse on measures requiring action knowledge than object knowledge (Grossman et al., 2008). Of particular interest was that this difficulty on action processing measures was correlated with cortical atrophy in the motor cortex on imaging, while object processing was not. Other studies unrelated to MND research have shown activation in motor-related cortical areas during the processing of action words (Hauk, Johnsrude, & Pulvermuller, 2004; Pulvermuller, 2005; Willems, Hagoort, & Casasanto, 2010), supporting the theory of "embodied" cognition (Clark, 2006). As MND is a neurodegenerative disease affecting motor-related cortical regions it is argued that this may explain the specific impairment processing verbs over nouns (T. H. Bak & Hodges, 2004; Grossman et al., 2008).

1.2.2.3 Syntax and Discourse

Another area that has consistently shown to be impaired and perhaps related to the verb processing deficit is that of sentence comprehension and production. Several case studies have reported agrammatical speech and writing similar to that observed in nonfluent aphasia, in conversation (Ferguson & Boller, 1977b; Ichikawa, Koyama, et al., 2008), in picture description (T. H. Bak et al., 2001) and in the writing of sentences to dictation (Piquard et al., 2006), characterised by a reduction in the use of prepositions, incorrect morphology, and perseverations. Furthermore, deficits in the processing of syntax are not confined to production. In one of the earliest studies to assess syntactic processing in MND Doran and colleagues reported on three patients with rapidly progressive aphasia who underwent neuropsychological and language testing including assessment using the Test for Reception Of Grammar (TROG) (D. V. M. Bishop, 1983) (Doran et al., 1995). The TROG examines the comprehension of increasingly complex syntactic structures, with participants required to select the correct picture from a choice of four to presented sentence. Testing of language comprehension in the Doran et al. study revealed that patients demonstrated a more severe impairment with syntactic than semantic comprehension, as tested through a simple picture-word matching task.

This finding has since been consistently reported throughout the literature, both using the TROG (T. H. Bak et al., 2001; Rakowicz & Hodges, 1998; Taylor et al., 2013), and other measures of auditory sentence to picture matching (Cobble, 1998). On analysis of patterns of impairment according to sentence type, Bak and colleagues highlight that errors were dependent on syntactic complexity and not necessarily sentence length, indicating a specific linguistic deficit and not as a product of attentional difficulties (T. H. Bak et al., 2001). This was further supported through post mortem findings revealing pathological changes in Brodmann areas 44 and 45 (Broca's area), associated with language processing and, interestingly, the recognition and production of actions (Fadiga & Craighero, 2006; Fadiga et al., 2006).

Limited in depth analysis of discourse based on picture descriptions of the Boston Cookie Theft image (Goodglass & Kaplan, 1983) has produced conflicting results. A study by Roberts-South and colleagues examining changes in discourse production analysed spoken Boston Cookie Theft description samples for discourse productivity (mean length of utterance (MLU), total words, total utterances) and discourse content (correct information units – those words that were intelligible and relevant to the picture) (Roberts-South, Findlater, Strong, & Orange, 2012). They found that discourse productivity was less impaired than discourse content. Although there was no difference in the total number of words or utterances produced in comparison to controls, this did not necessarily translate into more meaningful content. Taylor and colleagues reported no significant difference in Complexity Index (mean number of clauses per utterance) analysis of Boston Cookie Theft picture descriptions in comparison to controls (Taylor et al., 2013). However this analysis method does not measure for accuracy of content and could account for the difference in findings.

1.2.2.4 Reading and Writing

A growing body of evidence is accumulating to suggest a specific and significant spelling impairment in people with MND. Perhaps as a consequence of deteriorating speech and a reliance on writing as an alternative method of communication, this impairment was first brought to light through anecdotal evidence in case reports. Most notably a large number of these reports have come from Japan. The Japanese writing system consists of two types of letters: the phonetically based and graphically simple kana phonograms and the graphically complex kanji ideograms (Ichikawa, Hieda, Ohno, Ishihara, & Kawamura, 2012). Roughly speaking, kana words correspond to regular words in alphabetical languages due to their direct phoneme to grapheme relationship.

Kanji letters however convey a particular meaning but may have more than one pronunciation and the combination of kanji letters to form a kanji word usually has only one pronunciation attached to the meaning, thus making them roughly comparable to irregular words in that they must be processed via a lexical-semantic route (ibid.).

Ichikawa and colleagues report on what is arguably the earliest mention of spelling errors in MND, a case report by Watanabe in 1893 (Ichikawa, Miller, & Kawamura, 2011). In this case report, a predominance of kana errors were made in both spontaneous writing and writing to dictation, often writing a word correctly in kanji, but incorrectly in kana. However he could copy letters well and reading appeared unaffected, although there was some suggestion of a phonological processing deficit as evidenced through difficulty identifying the number of written syllables. In recent years, increasing reports supporting this dissociation of better persevered writing in kanji over kana have emerged. Several retrospective case review studies have reported substitution and omission of kana letters with relatively persevered kanji formation (Ichikawa et al., 2010; Ichikawa, Koyama, et al., 2008; Ichikawa, Ohno, Murakami, Ohnaka, & Kawamura, 2011; Ichikawa, Takahashi, Hieda, Ohno, & Kawamura, 2008; Yabe et al., 2012). In further support of Watanabe's original report Satoh and colleagues identified 3 patients from a group of 16 tested who, in addition to kana omission, also demonstrated an impairment a on moraic segmentation task, similar to syllable segmentation, perhaps suggestive of phonological processing deficit. However all participants performed normally on measures of reading, memory, reasoning and executive functions (Satoh, Takeda, & Kuzuhara, 2009).

The dissociation of kana and kanji dysgraphia is particularly interesting for several reasons. Firstly kanji is usually learned later than kana in the Japanese education system (Ichikawa et al., 2010). This being the case, it would be expected that kanji may be more susceptible to impairment due to age of acquisition effects (Ellis & Lambon Ralph, 2000). Secondly, kanji are graphically more complex. If spelling impairment was an effect of fatigue, it would be expected that again kanji would be more susceptible to error. Thirdly, while most patients were reported to produce kana errors with relatively preserved kanji, some studies also report the opposite observation (Ichikawa, Koyama, et al., 2008). Ichikawa and colleagues retrospectively reviewed 14 MND cases without overt spoken aphasia. A dissociated pattern of impairment was shown across patients in the production of kana and kanji errors, with those producing more kana errors showing significant association with frontal lobe atrophy on imaging, while a predominance of kanji errors was associated with temporal lobe atrophy (Ichikawa et al., 2010). Double dissociation between kana and kanji has also been reported in stroke patients with frontal lobe lesions (Sakurai, Matsumura, Iwatsubo, & Momose, 1997).

Similar to the evidence from Japanese literature, reports of spelling errors in MND patients using alphabetical languages first emerged through case reports. One of the earliest case reports of spelling errors in MND in alphabetic language was that by Ferguson and Boller (Ferguson & Boller, 1977b). They report two bulbar onset MND patients who, in using writing as an alternative method of communication, displayed spelling, syntactic and perseverative errors. Ferrer and colleagues reported a similar case study of a woman who displayed spelling and caluculation errors (Ferrer, Roig, Espino, Peiro, & Matias Guiu, 1991). However, where the initial symptoms in Ferguson and Boller cases were dysarthria, dysphagia and fasciculations, spelling errors were the first symptom for the patient presented by Ferrer and colleagues, who later developed dysphagia and muscle wasting due to MND.

The study by Caselli and colleagues was another early and influential study in the identification of aphasia in MND (Caselli et al., 1993). They documented seven patients with predominantly bulbar symptoms and rapidly progressive aphasia. Of the five who had enough hand function to allow legible writing all five displayed writing that was paraphasic and halting, both in spelling to dictation and writing in response to questions. Doran and colleagues also observed five MND patients with rapidly progressive aphasia of which two were noted to produce spelling errors combined with word finding difficulties and occasional reading errors (Doran et al., 1995). Despite these reports and the strong suggestion of a specific spelling deficit, some have dismissed findings of omissions and insertions in spelling as "more likely to be associated with upper limb weakness affecting motor movements for writing rather than due to a language processing deficit" (Cobble, 1998). While it is possible that letter omissions could attributed to upper limb weakness, the same cannot plausibly said for letter insertions where extraneous effort would be required. This is particularly relevant when it is considered that the two patients who produced spelling errors in Cobble's study were also impaired on tests of semantic association, auditory comprehension of sentences and the GNT. Most recently the study by Taylor and colleagues examining associations between language and executive functioning in a group of fifty-one MND patients revealed that patients were significantly worse than controls on the Graded Difficulty Spelling Test (Baxter & Warrington, 1994), and also on the Spot the Word lexical decision test (A. Baddeley, Emslie, & Nimmo-Smith, 1993) (Taylor et al., 2013).

However, while these studies have made major contributions to the recognition of spelling errors as a marker of linguistic impairment in MND, little qualitative analysis has been conducted into the nature of these errors. One study which has attempted to investigate the nature of these errors was that conducted by Lucchelli and Papagno in their case study of a woman with "slowly progressive anarthria" who it was later found had symptoms and EMG patterns suggestive of MND (Lucchelli & Papagno, 2005). Initially presenting with distortions, syllable omissions and transpositions in speech, her speech output became progressively worse over the course of four years, to the point where she was reliant on writing as her main method of communication. Her written and spoken word comprehension was normal, however her writing displayed errors consisting mainly of transpositions and deletions and was explored in depth. Her spontaneous writing showed agrammatic errors, while her written naming was characterised by letter deletions, substitutions and a few insertions and transposition errors. She made no non-responses and only one lexical-semantic error ('pentola' (pot) for padella (pan)). There was no effect of grammatical class, frequency or length, but a serial position effect, with more errors in the middle of words than at the beginning or end, was observed. Spelling to dictation revealed a similar error pattern, with no difference in performance when spelling words and nonwords. They argue that, in the absence of lexical-semantic errors and preserved comprehension, her spelling impairment is unlikely to be linguistic in nature. Instead they suggest that these errors reflect impaired subvocal rehearsal due to her dysarthria. Subvocal rehearsal is part of the phonological loop mechanism of the working memory model outlined by Baddeley and Hitch, whereby words are rehearsed to prevent decay before being produced (A. D. Baddeley & Hitch, 1974). Lucchelli and Papagno argue that subvocal rehearsal is essential to enable phonemes to be converted and assembled into graphemes when writing and that her impaired articulation prevents this from happening, giving rise to spelling errors (Lucchelli & Papagno, 2005).

Zago and colleagues also suggested that similar spelling errors observed in a group of sixteen MND patients could be due to a deficit in the subvocal rehearsal mechanism, impacting on the ability to correctly sequence and assemble graphemes when writing, again suggestive of a working memory impairment (Zago, Poletti, Corbo, Adobbati, & Silani, 2008). Certainly the errors patterns described by Lucchelli and Papagno and Zago and colleagues are consistent with a graphemic buffer deficit (Caramazza, Miceli, Villa, & Romani, 1987). Yabe and colleagues identified an association between Japanese writing errors and dysfunction in the anterior cingulate gyrus which they suggest could indicate a working memory or attentional deficit (Yabe et al., 2012). However, they also reported normal performance on digit span and trail making tests, which would indicate preserved working memory and visual attention respectively. Furthermore, attentional or working memory deficits cannot necessarily account for the reported kana-kanji dissociation, particularly in light of the comparative complexity of the frequently preserved kanji. Thus whether these reported spelling errors represent a deficit in working memory and/or attention or a central linguistic deficit is still unclear. Certainly the association between language and cognitive function in MND is a closely related issue.

1.3 Cognition and Association with Frontotemporal Dementia

Many of the cases presented above have been associated with and presented in the context of wider cognitive changes. Increasingly a relationship between MND and frontotemporal dementia (FTD) is being recognised and explored.

1.3.1 Frontotemporal Dementia (FTD)

Frontotemporal dementia, also interchangeably termed frontotemporal lobar degeneration (FTLD) is the name given to a group of disorders where degeneration of the frontal and temporal lobes results in a spectrum of cognitive changes. FTD comprises three variants as outlined in the international consensus criteria proposed by Neary and colleagues and diagnosed on the basis of core clinical symptoms, physical signs and investigations (Neary et al., 1998), and a recently identified fourth variant (Gorno-Tempini et al., 2008).

1.3.1.1 Behavioural Variant FTD (bvFTD)

While not primarily identified with language impairment, some alterations in communication may be observed. Five core criteria define the bvFTD: insidious onset and gradual progression of symptoms; early decline in social interpersonal conduct; early impairment in regulation of personal conduct; early emotional blunting; and early loss of insight (Neary et al., 1998). As the name suggests, it is primarily identified with a marked change in behaviour, and may include behaviours such as a loss of manners, intrusions into personal spaces, physical , verbal or sexual disinhibition, apathy and a loss of empathy and sympathy (Henri-Bhargava & Freedman, 2012). Similar changes can reflect in communication, primarily affecting pragmatics, with speech becoming minimal or overly verbose. While the disinhibited patient may be tangential and dominate conversation, the apathetic patient will rarely initiate conversation and withdraw (Orange & Hillis, 2012). However linguistic impairment is not a primary characteristic of bvFTD.

1.3.1.2 Primary Progressive Aphasia (PPA)

The other variants of FTD are grouped under the term primary progressive aphasia (PPA). First described by Mesulam (Mesulam, 1982), it denotes a cluster of disorders whereby gradual language decline is seen over a period of at least two years and in the absence of any other cognitive functions (Croot, 2009). Originally divided into fluent and non-fluent subtypes, debate surrounded the ability to define and agree upon what was meant by 'fluent' (Orange & Hillis, 2012). Thus recent consensus criteria was developed out of the original Neary criteria defining language subtypes as nonfluent/agrammatic variant PPA, semantic variant PPA and logopenic PPA (Gorno-Tempini et al., 2011).

1.3.1.2.1 Semantic Variant PPA/Semantic Dementia (SD)

Associated with atrophy in the ventral and lateral areas of the anterior temporal lobes (Gorno-Tempini et al., 2004), two core clinical features define the semantic variant of PPA, both of which must be present to confirm diagnosis: impaired confrontation naming; and impaired single-word comprehension (Gorno-Tempini et al., 2011). While naming deficits may be present in the other PPA subtypes, the severity of the impairment, combined with single word comprehension deficits, particularly for low frequency items, separates the semantic variant from the others (ibid.). Furthermore, these features are the characteristic manifestations of what is essentially a wider impairment of semantic memory, also affecting non-verbal stimuli including as object, person and environmental sounds (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000; Hodges, Bozeat, Lambon Ralph, Patterson, & Spatt, 2000). Speech and writing is generally 'fluent' in terms of motor speech and grammatical construction, although content may be meaningless. Analysis of errors reveals semantic substitutions in naming (e.g. 'dog' or 'animal' for 'cat') , and errors in reading and writing are often characteristic of surface dyslexia and dysgraphia, whereby phonological rather than lexical processing routes are used and irregular words are regularised (e.g. 'yacht' spelled 'yot' and 'sew' read /su/) (N. Graham, L., 2000; Henri-Bhargava & Freedman, 2012).

1.3.1.2.2 Nonfluent/Agrammatic Variant PPA/Progressive Nonfluent Aphasia (PNFA)

Associated with left inferior frontal and insular atrophy (Gorno-Tempini et al., 2004), two core clinical features define the nonfluent variant of PPA, of which at least one must be present for diagnosis: agrammatism in language production; and effortful, halting speech with inconsistent errors characteristic of apraxia of speech (Gorno-Tempini et al., 2011). Patients with PNFA use approximately two-thirds less words per sentence resulting in a reduced mean length of utterance (MLU), with sentences becoming grammatically simpler, omitting articles, auxiliary verbs and prepositions and containing a greater proportion of nouns (Ash et al., 2009). Naming deficits are also apparent in PNFA, but errors are typically phonemic paraphasias (e.g. 'hotapitamus' for hippopotamus), rather than semantic as seen in the semantic variant, and often complain of a 'tip of the tongue' feeling (Rohrer et al., 2008). While the presence of speech sound errors in PNFA is a hallmark of the disorder, the cause of these errors is debated. Apraxia of speech is often cited to be present, and can be the initial symptom of PNFA, frequently occurring with oral and limb apraxia (Gorno-Tempini et al., 2004; Josephs et al., 2006; Rohrer, Rossor, & Warren, 2010). However, it has been reported that errors occurring early in PNFA are more phonemic than phonetic or articulatory in nature, suggesting that some of these 'apraxic' errors may be more linguistic in nature (Ash et al., 2010). Other features include impaired comprehension of syntactically complex sentences with spared single word comprehension and spared object knowledge, in contrast to the semantic variant (Gorno-Tempini et al., 2011). Dyslexia and dysgraphia may also be present, with spelling errors being non-phonologically plausible and including omissions and transpositions of letters (Kartsounis, Crellin, Crewes, & Toone, 1991).

1.3.1.2.3 Logopenic Variant PPA/Logopenic Progressive Aphasia (LPA)

Associated with abnormalities in the left temporo-parietal junction (posterior temporal, supra-marginal and angular gyri), logopenic progressive aphasia is the most recently described and little researched variant of PPA (Gorno-Tempini et al., 2011). The two core clinical features of LPA required for diagnosis are impaired single-word retrieval in spontaneous speech and naming; and impaired repetition of sentences and phrases (ibid.). Speech rate is slow due to word finding difficulties although grammar and articulation is preserved (Gorno-Tempini et al., 2008). Naming difficulties are usually less severe than in the semantic variant, with errors circumlocutory and phonemic in nature (Gorno-Tempini et al., 2004). In addition, spared single word comprehension and lack of agrammatism distinguish LPA from the semantic and nonfluent variants respectively. Language deficits in PPA are thought to be due to a impairment in the phonological loop functions, accounting for the dissociation in impaired sentence repetition with preserved repetition of short single words and the accompanying performance on digit, letter and word span tasks (Gorno-Tempini et al., 2008).

1.3.2 The MND-FTD Relationship

Cognitive and behavioural changes have been documented in MND since the 1890s (Marie, 1892; Pilcz, 1898; Resegotti, 1907), while studies dating from the 1930s have reported histopathological evidence of MND with frontal lobe degeneration (Gozzano, 1936; I. S. Wechsler & Davison, 1932). However these early cases were widely dismissed as co-incidental, and the idea of MND as a purely motor disorder continued in the English-speaking world until the late 20th century (T. H. Bak, 2010; Zago, Poletti, Morelli, Doretti, & Silani, 2011).

Early investigations into the prevalence of these frontotemporal cognitive changes in MND reported very low levels, with some studies suggesting figures as low as 5% (Murphy, Ahmed, & Lomen-Hoerth, 2012). This was due, in part, to the use of assessments designed to identify Alzheimer's disease type impairments such as episodic memory and spatial orientation and which did not test for frontal impairments of executive functioning. More recent prevalence rates of cognitive impairment in MND as reported in the literature have shown wide discrepancy, ranging between 17% (Gallassi et al., 1989) and 50-60% (Ringholz et al., 2005; Strong et al., 2009), however a figure of between 28-35% is becoming more consistently reported (Murphy et al., 2012). In 2009 a consensus criteria for the clinical characterisation of cognitive impairment in MND was created, consisting of six main subtypes (Strong et al., 2009) (see Table 1.1).

Type	Subtype	Characteristics
ALS/FTD	ALS/bvFTD	ALS patients meeting the Neary (Neary et al., 1998) or Hodges (Hodges & Miller, 2001) criteria for FTD
	ALS/PNFA	ALS patients meeting the Neary criteria for PNFA
	ALS/SD	ALS patients meeting the Neary criteria for SD
ALS with behavioural impairment (ALSbi)		ALS patients with at least two non-overlapping supportive diagnostic features from the Neary or Hodges criteria for FTD
ALS with cognitive impairment (ALSci)		Evidence of cognitive impairment at or below the 5th percentile on at least two test of cognition sensitive to executive functioning
FTD-MND like		A primary diagnosis of FTLD with evidence of MND type degeneration, but insufficient to be classified as MND
ALS/dementia		ALS in association with dementia not typical of FTD (e.g. Alzheimer's Disease)
ALS/parkinsonism dementia complex		ALS concurrent with dementia and/or parkinsonism occurring in hyperendemic foci of the Western Pacific

Table 1.1: Subtypes of cognitive impairment in MND according to the 2009 consensus criteria. Adapted from (Strong et al., 2009)

The most notable development with the introduction of these criteria is the inclusion of the two subtypes of impairment (ALSbi and ALSci), classifying those that do not meet the criteria for the MND-FTD status (Murphy et al., 2012).

With the exception of the latter two subtypes (ALS/dementia and ALS/parkinsonism dementia) it is considered that these criteria, while delineating clear subtypes, represent a continuum of impairment with pure MND at one end, pure FTD at the other and the newly defined MNDbi and MNDci subtypes bridging the gap between MND and MND-FTD (see Figure 1.1). Indeed most patients with some degree of cognitive impairment falling within the MND-FTD overlap will not fulfil the criteria for ALS/FTD diagnosis (Henri-Bhargava & Freedman, 2012)

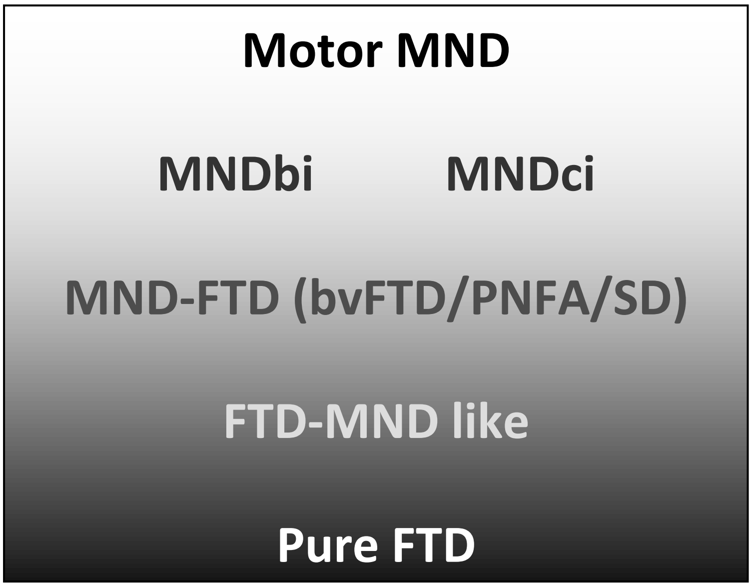


Fig 1.1: MND-FTD continuum hypothesis. Adapted from (Zago et al., 2011)

It is estimated that approximately 5-15% of MND patients display severe cognitive changes, meeting the criteria for some variant of FTD (Phukan et al., 2012; Ringholz et al., 2005). However, a much larger proportion, in the region of 35%, fit the 'ALS with cognitive impairment' category (Phukan et al., 2012; Ringholz et al., 2005). In addition to the language deficits outlined earlier, the strongest evidence of cognitive impairment comes from studies of frontal executive function. Executive function includes the ability to plan and organise information, shift attention, inhibit behaviour and negotiate social-emotional relationships. As discussed previously, verbal fluency has been the most frequently investigated measure of executive function, with the majority of studies consistently finding impairment (Abrahams et al., 2004; Abrahams et al., 2000; Massman et al., 1996; P. R. Talbot et al., 1995; Taylor et al., 2013). Other areas of executive function such as set shifting, cognitive inhibition and attention have also been found to be impaired in MND patients (Lomen-Hoerth et al., 2003; Phukan et al., 2012; Pinkhardt et al., 2008). Findings regarding working memory have been less consistent, with some studies reporting impairment on digit span tasks (Rakowicz & Hodges, 1998), while others reported no deficit (Phukan et al., 2012; Zaehle et al., 2013). The integrity of memory functions have also been variably documented. Reports of impaired immediate and delayed recall with intact recognition suggest that there may be an impairment in the ability to encode information rather than a memory deficit (Mantovan et al., 2003; Phukan et al., 2012). Deficits of social and emotional cognition have also been found, though not necessarily related to executive functioning (Elamin, Pender, Hardiman, & Abrahams, 2012; Girardi, Macpherson, & Abrahams, 2011).

1.4 The Nature of Language Impairment in MND

However, it has been questioned where the language impairment documented in MND lies in this spectrum of cognitive impairment. Are the deficits characteristic of the ALS/PNFA or ALS/SD subtype? Certainly a number of similarities can be seen in reports of the language impairment profile of PNFA. A number of studies have documented a dissociation in action and object processing in PNFA, with patients having greater difficulty in the comprehension and production of verbs, similar to findings regarding MND patients (Rhee, Antiquena, & Grossman, 2001; C. K. Thompson, Lukic, King, Mesulam, & Weintraub, 2012). In a direction comparison of MND and PPA patients, Hillis and colleagues found that while fluent variant primary progressive aphasia (or semantic dementia) patients were significantly worse in naming nouns, both those with nonfluent progressive aphasia and those with MND were worse when naming verbs (Hillis, Oh, & Ken, 2004). In addition, significantly impaired production and comprehension of grammatical structure, as reported in MND research, have also been reported in PNFA (Code, Muller, Tree, & Ball, 2006; Grossman & Ash, 2004; Knibb, Woollams, Hodges, & Patterson, 2009). Furthermore, the comparison with PNFA could also account for evidence of AOS in MND. Included in the Neary consensus criteria as a possible indicator of PNFA, AOS has been commonly reported in PNFA, occasionally co-occuring with buccofacial and limb apraxia (Gorno-Tempini et al., 2004; Rohrer et al., 2010). However, further investigation of the language deficits in MND are need to ascertain whether the language profile fits that of PNFA, or whether other features characteristic of the semantic or logopenic PPA variants are also present.

Or do the language deficits in MND fit within the ALS with cognitive impairment category? As a large number of the studies above have found verbal fluency deficits in conjunction with language impairment, it could be suggested that there is some association between the two deficits, thus joint categorisation within the ALS with cognitive impairment subtype would be appropriate. However the nature of the connection between executive dysfunction and language impairment is unclear. Some studies have suggested that the relationship between poor performance on measures of both executive and language functions could indicate that language impairment is merely a result of executive dysfunction (Abrahams et al., 2000; P. R. Talbot et al., 1995). However more recent studies have argued that the two functions are, to some extent, dissociable in MND and therefore support the suggestion of a separate language impairment (Abrahams et al., 2004; Taylor et al., 2013).

The argument for language impairment in MND as a separate subtype, in line with the ALSc and ALSbi variants, is one supported by Bak (T. H. Bak, 2010). Indeed the finding of a subgroup of participants impaired on language measures in a number of studies, and reported mixed PNFA and SD characteristic features would support this suggestion (Cobble, 1998; Rakowicz & Hodges, 1998). However, in order to explore this hypothesis, further investigation is needed into the prevalence and nature of language deficits in MND, particularly beyond the realm of naming impairments.

Furthermore, while it is increasingly apparent that dysarthria is not always the only contributor to communication impairment in MND, many researchers have investigated the suggestion that there may also be a connection between cognitive and/or language impairment and bulbar onset and/or dysarthria. Studies have found that bulbar onset patients perform consistently poorer than non bulbar onset patients across a range of cognitive measures, most notably measures of executive functioning (Abrahams et al., 1997; Schreiber et al., 2005). Similar findings have also been reported regarding spelling impairment, with a greater number of errors being produced by those with bulbar disease onset (Ichikawa, Koyama, et al., 2008; Ichikawa, Takahashi, et al., 2008). However others have found no significant difference between bulbar and non bulbar patients in performance on cognitive measures (Cooper et al., 2008; Rakowicz & Hodges, 1998; Ringholz et al., 2005). Indeed, in a review of a number of studies Raaphorst and colleagues concluded that there was not enough evidence to support the suggested relationship between bulbar onset and cognitive dysfunction (Raaphorst, de Visser, Linssen, de Haan, & Schmand, 2010). Some researchers have also argued that there is a greater degree of cognitive impairment in dysarthric patients over non dysarthric patients, although the extent to which this can be explain by other factors such as disease duration, respiratory function and onset site is uncertain (Massman et al., 1996; Sterling et al., 2010). Thus a number of questions about the nature of language impairment in MND have not yet been addressed and require further investigation.

1.5 Aims of Thesis

This thesis aims to examine the nature of speech and language deficits in people with MND and the extent to which expressive communication impairment can occur above and beyond dysarthria. In particular, the study explores:

i) to what extent these language impairments can be attributed to deficits in working memory, executive functioning and/or disease severity;

ii) what spelling errors can reveal about the integrity of lexical, phonological and orthographic processing;

iii) whether similar patterns of impairment can be seen in PPA syndromes;

iv) the relationship between language impairment and bulbar onset; and

v) the impact these findings have on clinical management of MND patients.

Chapter two outlines the demographic, medical and background neuropsychological profiles of the MND patient and control participants recruited within this study. Chapter three examines the performance of patients on a number of standard linguistic measures previously used to assess language processes in MND and/or aphasia. These tests include measures of dysarthria, apraxia, naming, reading and prosody. Chapter four examines the performance of patients on a number of experimental linguistic measures designed by the researcher. These tests of minimal pair discrimination, nonword repetition and spelling and word spelling aim to explore the nature of phonological and orthographic deficits suggested to be present in MND patients. Chapter five consolidates and synthesises the findings from across all measures, characterising the emergent pattern of impairment, and particularly examining the performance of three individual patients. Finally chapter six draws conclusions about these findings, relating them to previous studies conducted both in MND and PPA, and making suggestions about the clinical applications of these findings.

Chapter 2: Participants

In order to examine the nature of the communication impairments seen in people with MND, we recruited a cohort of 25 MND patients from across Scotland, between March 2011 and March 2012. All recruitment, data collection and testing methods were approved by South East Scotland NHS Research Ethics Committee and the University of Edinburgh Psychology Research Ethics Committee (see Appendix A). The participants described in this chapter are the same participants from whom the data in all subsequent chapters was collected.

2.1 Selection Criteria

The following criteria were used to select patients for the study:

1. Diagnosis of probable or definite Motor Neurone Disease according to the El Escorial Criteria (Brooks, 1994).
2. Evidence of speech &/or language impairment as reported by MND nurse specialist or other healthcare professional.
3. Absence of any concomitant neurological illness or trauma.
4. No history of alcohol and/or drug abuse.
5. No premorbid learning disability or language disorders.
6. Native speaker of British English.

2.2 Recruitment

2.2.1 Patient

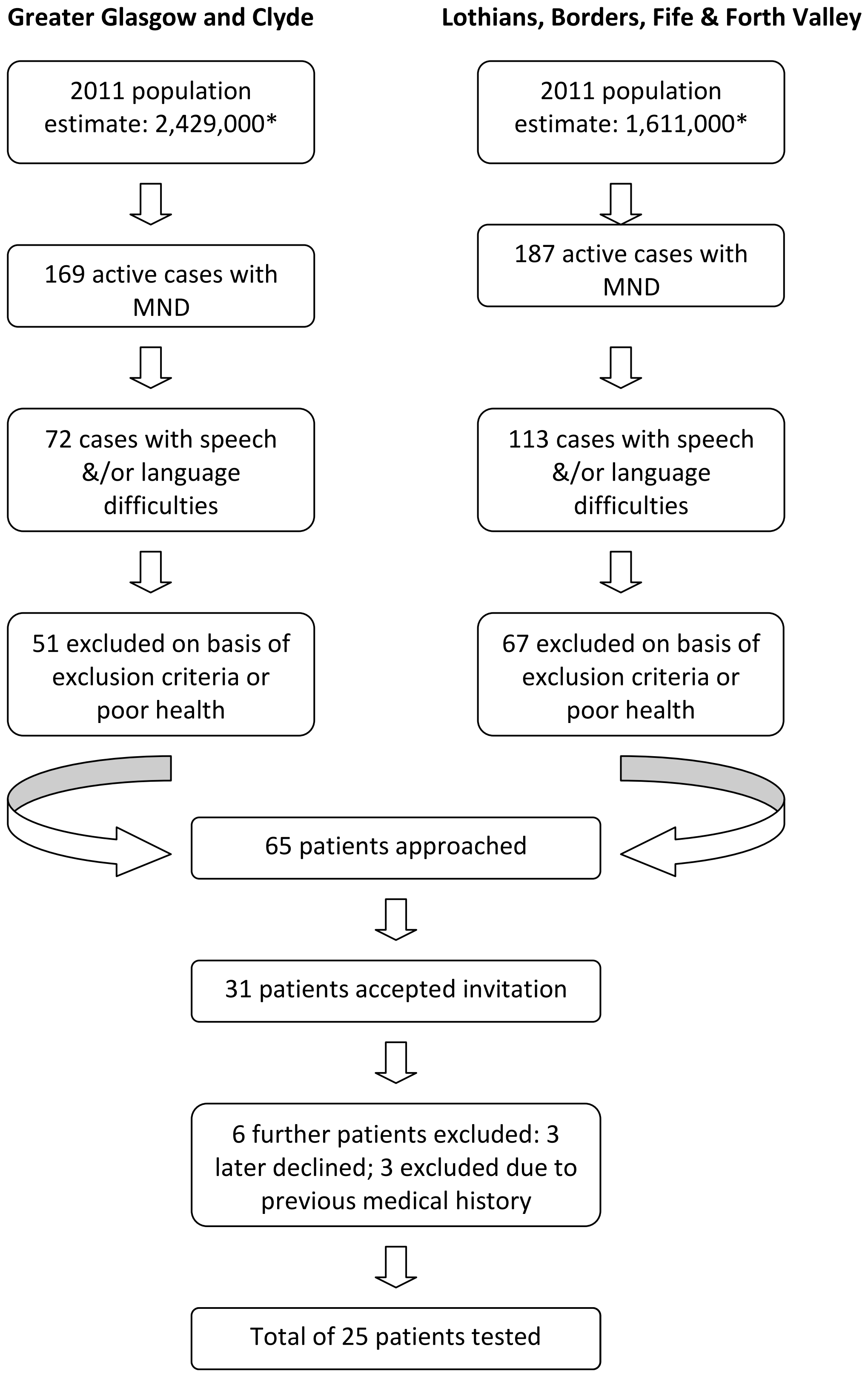
Information about the study and the participant selection criteria was disseminated to the MND care teams in Tayside, Greater Glasgow and Clyde (also covering the West coast of Scotland), and South East Scotland (covering the Lothians, Borders, Fife and Forth Valley). However, while all three centres were originally scoped into recruitment, participants were ultimately only recruited from the latter two centres. Potential participants were identified and initially approached by a member of the clinical care team, primarily the MND nurse specialists. If they expressed an interest in participation, their contact details were passed onto the researcher, and were sent a participant information pack via post or email, explaining further details of the study and what would be required of them (see Appendix B). Willing participants were then contacted directly to arrange commencement of testing. 25 participants with MND were recruited from the two care centres in this way (see Figure 2.1 – population figures taken from 2011 Scotland Census (National Records of Scotland, 2012) . The number of patients recruited equates to approximately 7% of the MND population as a whole for South East Scotland and Greater Glasgow and Clyde combined, and approximately 14% of the MND population with speech &/or language problems in these areas.

2.2.2 Control

Twenty five healthy control participants were recruited from the volunteer Subject Pool panel of the University of Edinburgh Psychology department. In addition, control participants were also recruited through friends of the researcher. Control participants, as a group, were matched as closely as possible to the patient group for number, age, sex and years of education.

2.3 Data Collection

As most patients tested had physical disabilities limiting their mobility, data collection took place at patients' homes in a quiet room with minimal distractions. Controls were tested in an assessment lab at the University of Edinburgh psychology department. Informed, written consent was obtained from all participants before testing commenced, in accordance with the 1964 Declaration of Helsinki. The test battery was administered across a minimum of two sessions, with testing sessions lasting between 45 minutes to 2 hours, dependent on the participant's physical condition and fatigability, which was monitored throughout the testing process. Testing was conducted using a combination of computer and paper based assessment, and sessions were recorded using a Canon HG20 video camera and a Canon DM-100 directional stereo microphone, to enable details of testing to be reviewed if necessary for



* Rounded to the nearest thousand

Figure 2.1: MND participant recruitment figures

further analysis. The entire battery was piloted on three healthy control participants before data collection commenced to test administration time and procedures, and data was collected from ten healthy control participants prior to assessment of any MND participants to ensure confidence in material and testing procedures. The order in which the tests were administered was consistent as far as possible for all participants, with all initial sessions commencing with general and health demographic measurements, followed by experimental linguistic measures, and second sessions consisting of standard linguistic measures followed by neuropsychological measures. However, as some participants required more than two sessions to complete the battery due to issues with fatigue, this ordering was not always consistent and therefore this should be considered in result interpretation

2.3.1 General and Health Demographic Measurements

General and health demographic data was gathered on all patients and controls in order to enable group matching and ensure participants met the study inclusion criteria. Short informal interviews were conducted at the start of the testing procedure and data was collected on participants' age, sex, and number of years of education for group comparison. Furthermore, participants were also asked if they: had any learning difficulties that they were aware of (including spelling ability); were native British English speakers; had any history of neurological illness or trauma; had any history of psychological illness or substance and/or alcohol abuse. For the patient group, additional information about disease onset date, duration, and region/s of onset was also collected.

2.3.1.1 Hearing

Formal assessment of other health measurements was also conducted. As a high proportion of the linguistic assessments used in this study contained verbally presented material, assessing hearing status was important. Action on Hearing Loss reported that in 2010 there were approximately 867,500 adults

(16 and over) with hearing loss in Scotland, of which 768, 500, or 89%, were 50 or over (Action on Hearing Loss, 2011). As people age, hearing deteriorates, most commonly through age-related sensorineural hearing loss termed presbycusis, with those 55 and over losing around 9 decibels each decade (Davis, Ostri, & Parving, 1990). The Royal College of Speech and Language Therapists (RCSLT) outlines auditory discrimination, auditory comprehension and pragmatics, amongst others, as linguistics skills at risk from hearing impairment (Royal College of Speech and Language Therapists, 2010). As the MND population tends to be over 50, with the 1989-1998 Scottish MND register recording an average onset age of 65.2 for men and 67.2 for women, performance on linguistic assessments could be affected by hearing impairment amongst the participants (Forbes, Colville, Parratt, & Swingler, 2007). In order to account for this participants' hearing was measured using the Home Audiometer Hearing Test (Esser, 2013). The software, run through a laptop, runs in a similar way to a professional audiometer whereby a series of tones were played through Sennheiser HD 280 pro headphones at frequencies of 250Hz, 500Hz, 1000Hz, 2000Hz, 4000Hz and 8000Hz, and at varying intensities to ascertain the lowest volume in decibels (dB) an individual can hear at each frequency. The participant is required to press the control key on the keyboard each time they hear a tone, and the tones become increasingly quieter, until the individual can no longer hear the tone and hearing threshold has been reached.

Hearing status was categorised based on the results of the audiogram, following the World Health Organisation (WHO) grades of hearing impairment (World Health Organization, 2013). Audiometric thresholds were averaged across frequencies of 500Hz, 1000Hz, 2000Hz and 4000Hz, and were classified based on performance in the better ear. A margin of error of 10dB was allowed, as the Home Audiometer Hearing Test is reported to be accurate to within 10dB of true hearing level. An average of 25dB or above in the better ear was classified as normal hearing, while an average of 26-40dB in the better ear was classified as a slight impairment. Secondary categorisation was conducted based on whether individual frequency values (again, following the 10dB margin of error) fell within or below the 'speech banana' – the visual representation of where phonemes lie on an audiogram (see Figure 2.2). If one or more frequency values for either ear fell within or below the speech banana area this was classed as an impact on speech perception.

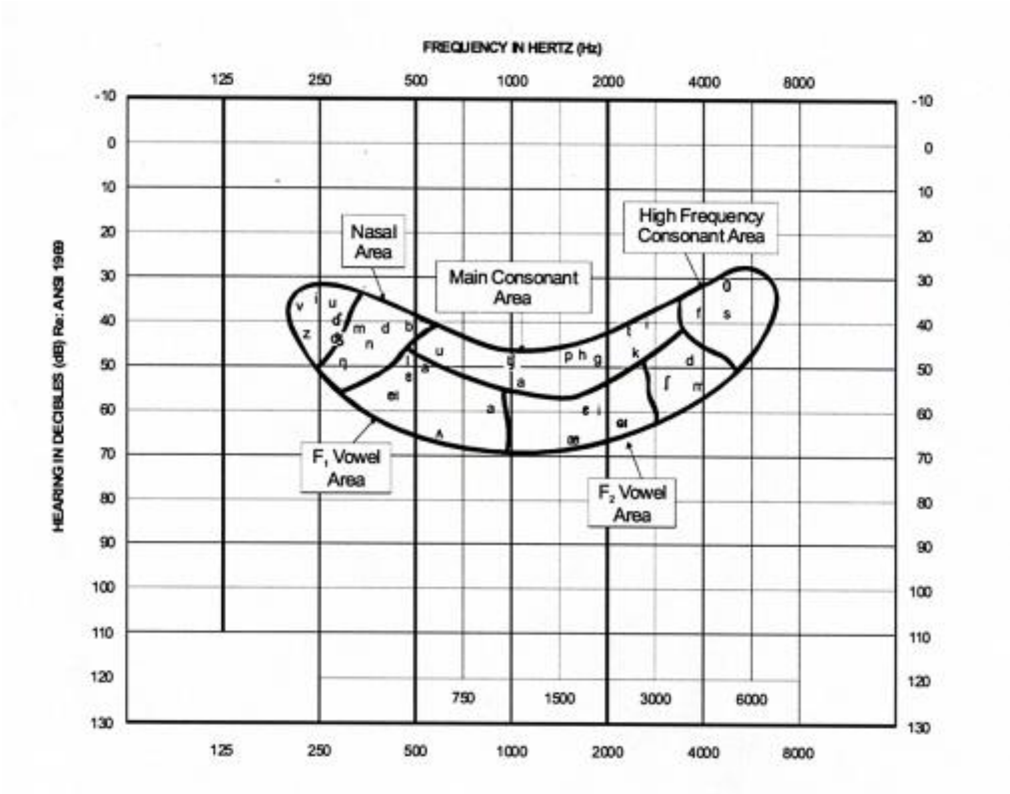


Figure 2.2: Speech Banana (Cochlear, 2013)

2.3.1.2 Mood

Considering the effect of mood upon performance in assessments was also important, as high levels of anxiety and depression have been shown to negatively impact upon cognition, particularly memory (Bierman, Comijs, Jonker, & Beekman, 2005; Kizilbash, Vanderploeg, & Curtiss, 2002). Levels of participants' anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). The HADS is a self assessment Likert scale of fourteen questions. Questions are split 50/50 relating to anxiety and depression, and participants select a response from a choice of four, each scored from 0-3, with a higher score indicating higher levels of anxiety or depression. Two separate scores are given as totals of all anxiety questions and all depression questions, except question D8 'I feel as if I am slowed down', as previous studies have shown this question to be unreliable with MND patients due to responses being confounded by physical impairment (Abrahams et al., 1997; Goldstein, Atkins, & Leigh, 2002). Total sub-scores over 10 are taken to indicate the presence of anxiety or depression that may impact upon performance.

2.3.1.3 Respiratory function

Estimated respiratory function of participants was measured using the Epworth Sleepiness Scale (ESS) (Johns, 1991). The test, originally designed to identify those with potential sleep apnoea, gives a score of daytime sleepiness, which can indicate disruption in night time respiration. Like the HADS, the ESS is a self report Likert scale assessment comprising eight scenarios in which the respondent is to indicate how likely they would be to fall asleep in normal day-to-day life. The participant responds with a score of 0-3, ranging from 'would never doze' to 'high chance of dozing'. A total score greater than 16 indicates a high level of daytime sleepiness, and significantly correlates with a moderate to severe respiratory disturbance index (ibid. 1991). In our patient group, the ESS will give an indication of respiratory dysfunction due to diaphragmatic weakness, something which has been reported to impact on cognitive functioning in MND patients (Newsom-Davis, Lyall, Leigh, Moxham, & Goldstein, 2001).

2.3.1.4 Disease severity

The Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R) (Cedarbaum et al., 1999) is a validated rating instrument designed to monitor overall and individual aspects of disability in people with MND (see Appendix C). The assessment comprises 12 points of questioning examining activities of daily living and individual symptoms which are grouped into four main functions: bulbar; fine motor; gross motor; and respiration. Patients' responses are assigned to a 5 point scale and scored 0-4, with 0 representing the lowest level of functioning and 4 the highest (i.e. normal functioning), with a maximum total score of 48 and a maximum component subscore of 12. In addition to taking particular note of respiratory function, of specific interest to this study is the bulbar score. In conjunction with noting disease onset site, the bulbar score from the ALSFRS will give an indication of the level of overall bulbar impairment, as there has been research to suggest that bulbar symptom onset and deterioration of bulbar functioning can be associated with a fronto-temporal pattern of cognitive dysfunction (Abrahams et al., 1997; Portet, Cadilhac, Touchon, & Camu, 2001; Schreiber et al., 2005). However, this suggestion has also been challenged by others, reporting no correlation with severity or duration of bulbar symptoms, and that patients with bulbar onset did not differ in levels of cognitive impairment (Ringholz et al., 2005).

2.3.2 Neuropsychological Background Assessment

2.3.2.1 Working Memory: Digit Span

To assess working memory, the forward and reverse digit and spatial span tests from the Wechsler Memory Scale Third Edition were used (D. Wechsler, 1997). Digit and spatial span are frequently used measures of working memory, and there is evidence to suggest that reverse digit span performance can be impaired in people with MND(Rakowicz & Hodges, 1998). In the forward digit span assessment participants are read a string of numbers and, following presentation of the full sequence, asked to repeat the numbers back to the researcher. Where participants were unable to verbally repeat the sequence, they were allowed to write down the numbers following presentation of the full sequence. The sequences start with two digits, and the sequence length, or span, increases in number by one in each round. Two trials at each sequence length are given per level, and continue until the participant fails to repeat the sequence correctly on both trials up to a maximum sequence length of nine digits. The maximum number of digits a participant is able to repeat back is the participant's forward digit span. The reverse digit span is administered and presented following the same format, however participants are required to recall the sequence in the reverse order.

Performance on digit span is thought to tap working memory processes of the Phonological Loop (A. D. Baddeley & Hitch, 1974). The phonological loop comprises two parts: the phonological store and the articulatory loop. Verbally presented material enters the phonological store, while the articulatory loop subvocally rehearses the stimuli to prevent decay of the information. The phonological loop has been investigated through performance on working memory tasks in those with communication disorders. It has been reported that while those with the motor speech planning impairment or apraxia of speech show reduced performance on span tasks (Waters & Rochon, 1992), those with intact speech planning processes but with severe dysarthria preventing speech production did not (A. D. Baddeley & Wilson, 1985). This suggests that dysarthria does not impact upon the function of the phonological loop, and in turn verbal working memory, and that any deficit in performance among the MND participants in this study cannot be attributed to dysarthria alone.

2.3.2.2 Working Memory: Spatial Span

The forward and reverse spatial span task assesses nonverbal working memory. Also known as the Corsi block-tapping task, the spatial span is a visual version of the digit span task where participants are presented with a board containing ten identical, unevenly spaced cubes. The researcher taps a number of the blocks in a specified sequence and the participant is required to reproduce the pattern. As with the digit span task, the sequences start with two blocks tapped, and the sequence length, or span, increasing in number by one in each level. Two trials at each sequence length are given per level, and continue until the participant fails to reproduce the tapped sequence correctly on both trials up to a maximum sequence length of nine blocks. The maximum number of blocks tapped in a sequence that a participant is able to reproduce is the participant's forward spatial span. Again, as with the reverse digit span task, the reverse spatial span task is presented in the same format, with participants tapping out the block sequence in the reverse order. However while the reverse digit span task has been shown to be significantly more difficult than the forward digit span task, in a study involving 246 healthy adults aged 50-92, there was no significant difference in performance between the forward and backward spatial tasks (Kessels, van den Berg, Ruis, & Brands, 2008). Furthermore they propose that this dissociation may suggest that while the backwards spatial and digit span tasks both rely on the visuo-spatial sketchpad and phonological loop working memory slave systems respectively, the backwards digit span task also uses the central executive component of working memory.

2.3.2.3 Executive Function: Letter Fluency

Executive functioning was further examined using spoken and written verbal fluency measures. Poor performance on verbal fluency measures is one of the most frequently reported executive functioning deficits in MND (Abrahams et al., 1997; Abrahams et al., 2004; Abrahams et al., 2000; Mantovan et al., 2003; Ringholz et al., 2005). Verbal fluency places heavy demands on the executive functions, requiring participants to generate items from a given cue, and switch between generation strategies, all within a time constraint. In this study participants were given four fluency tasks, two of spoken output and two of written output, each with a constrained and unconstrained condition, similar to that described by Thurstone and Thurstone (Thurstone & Thurstone, 1938). In the two spoken output tasks, participants were given one minute and asked to think of as many words beginning with a particular letter as possible, omitting any proper nouns or numbers. In the unconstrained condition, participants were given the letter 'P' with no further restrictions, while in the constrained condition participants were given the letter 'T', but also told that all words generated must contain only four letters.

In the two written output tasks, the rules remained the same, except participants were given two minutes in which to generate items. For the unconstrained written condition, participants were given the letter 'S', while in the four letter constrained condition participants were asked to generate items beginning with the letter 'C'. Using both spoken and written modalities allowed for more flexibility in terms of the administration of the task in relation to patient motor ability, i.e. if a participant's speech was severely impaired, they were able to complete just the written output task, whilst still enabling a measure of verbal fluency to be obtained. In addition, the impact of motor impairment was further minimised through the use of the verbal fluency index (VFI) when analysing scores (Abrahams et al., 1995). After completing each fluency task, participants were asked to repeat (spoken task) or copy (written task) the items generated, and were timed during this process. The time taken to repeat or copy the items was then subtracted from the time allowed for item generation in each fluency task (either one or two minutes), and divided by the number of items generated:

$$\frac{\text{Generation time allowed} - \text{Repeat/copy time}}{\text{Number of items generated}} = \text{VFI}$$

This index calculation eliminates the motor aspect of the task and reduces the score to an indication of the average amount of 'thinking time' per item generated. The higher the index score, the more time was required to think of items, and therefore is indicative of a greater level of impairment.

2.4 Results

2.4.1 Group Comparisons

2.4.1.1 MND Participants vs Controls

For groupwise comparisons between patients and controls, t-tests were used. Where data was not normally distributed, as determined using Kolmogorov-Smirnov analysis, Mann-Whitney U tests were used. Where data was nominal, Pearson's Chi-Squared test was used. Throughout the thesis significance is reported at a level of $p < 0.05$, with a trend toward significance considered where $p < 0.075$.

2.4.1.1.1 Background

The patient group of 25 consisted of 9 males and 16 females, while the control group of 25 consisted of 8 males and 17 females: there was no significant difference in sex distribution between the groups. There was also no significant difference in age between patients and controls. In addition, there was no significant difference in the number of years of education obtained by the patient and control groups (see Table 2.1).

Variable	MND (n 25)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Age	61.16	10.15	40-79	62.68	9.44	44-80	t = .548, p = .548
Sex	9M; 16F	-	-	8M; 17F	-	-	χ^2 (1) = 0.89, p = .765
Education (years)	11.52	2.4	10-20	12	1.98	10-16	U = 232, z = -1.619, p = .105

Table 2.1: Comparison of MND patients & controls on background measures

2.4.1.1.2 Medical

2.4.1.1.2.1 Hearing

There was no significant difference between the hearing status of the patients (n 20) (Normal Hearing 18; Slight Impairment 2) and controls (n 25) (Normal Hearing 24; Slight Impairment 1) according to the WHO grades of hearing impairment (χ^2 (1) = .643, p = .423). There was also no significant difference between the hearing status of the patients (No Impact 16; Impact 4) and controls (No Impact 16; Impact 9) regarding the impact on speech perception (χ^2 (1) = 1.385, p = .239).

2.4.1.1.2.2 Mood: Hospital Anxiety and Depression Scale (HADS)

Levels of anxiety in the patient group, as measured using the HADS, did not differ significantly from the control group. In addition, levels of depression in patients also did not differ significantly from controls (see Table 2.2).

2.4.1.1.2.3 Respiratory Function: Epworth Sleepiness Scale (ESS)

Levels of daytime sleepiness suggesting respiratory dysfunction were not significantly higher in patients than controls (see Table 2.2).

Variable	MND (n 25)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
HADS A	5.04 (n 23)	3.46	1-12	5.08 (n 25)	2.97	0-10	U = 271, z = -.343, p = .731
HADS D	3.65 (n 23)	3.24	0-13	2.24 (n 23)	2.09	0-8	U = 207.5, z = -1.680, p = .092
ESS	5.76 (n 25)	4.43	0-16	4.88 (n 25)	4.03	0-19	U = 274.5, z = -.740, p = .459

Table 2.2: Comparison of MND patients & controls on measures of mood and respiratory function

2.4.1.1.3 Neuropsychological

2.4.1.1.3.1 Digit Span

There was no significant difference between the forward digit spans of MND patients and controls. In contrast to previous reports (Rakowicz & Hodges, 1998), the reverse digit spans of patients did not differ significantly from controls (see Table 2.3).

2.4.1.1.3.2 Spatial Span

There was also no significant difference between the forward spatial spans of MND patients and controls. Also, the reverse spatial spans of patients did not differ significantly from controls (see Table 2.3).

Variable	MND (n 20)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Forward Digit Span	6.55	0.95	5-8	7.08	1.32	5-9	U = 197.5, z = -1.250, p = .211
Reverse Digit Span	5.05	1.32	3-7	5.52	1.19	3-8	U = 200, z = -1.172, p = .241
Forward Spatial Span	5.45	1.32	3-8	5.44	0.87	4-7	U = 247.5, z = -.061, p = .952
Reverse Spatial Span	4.9	1.21	3-7	5.00	1.04	4-7	U = 242, z = -.191, p = .849

Table 2.3: Comparison of MND patients & controls on digit and spatial spans

2.4.1.1.3.3 Verbal Fluency Indices

The unconstrained spoken verbal fluency index of MND patients was significantly higher (worse) than controls. The constrained spoken verbal fluency index of patients was also significantly higher (worse) than controls (see Table 2.4 & Figure 2.3). In the written modality, the unconstrained verbal fluency index of patients was significantly higher (worse) than controls, while the constrained written verbal fluency index of the patient group was again significantly higher (worse) than controls (see Table 2.4 & Figure 2.3).

Variable	MND			Controls (n 24)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Spoken Unconstrained VFI	7.59 (n 16)	13.63	2.44-58.50	2.41	1.17	.93-6.00	U = 46.5, z = -4.018, p = .000*
Spoken Constrained VFI	10.24 (n 16)	6.46	3.67-29	5.05	2.64	2.10-14.25	U = 69.5, z = -3.383, p = .001*
Written Unconstrained VFI	8.44 (n 24)	20.68	.57-103.00	1.55	1.00	.03-4.53	U = 108, z = -3.712, p = .000*
Written Constrained VFI	26.28 (n 24)	31.73	1.95-116.00	6.56	4.08	.71-18.33	U = 123, z = -3.402, p = .001*

Table 2.4: Comparison of MND patients & controls on verbal fluency indices

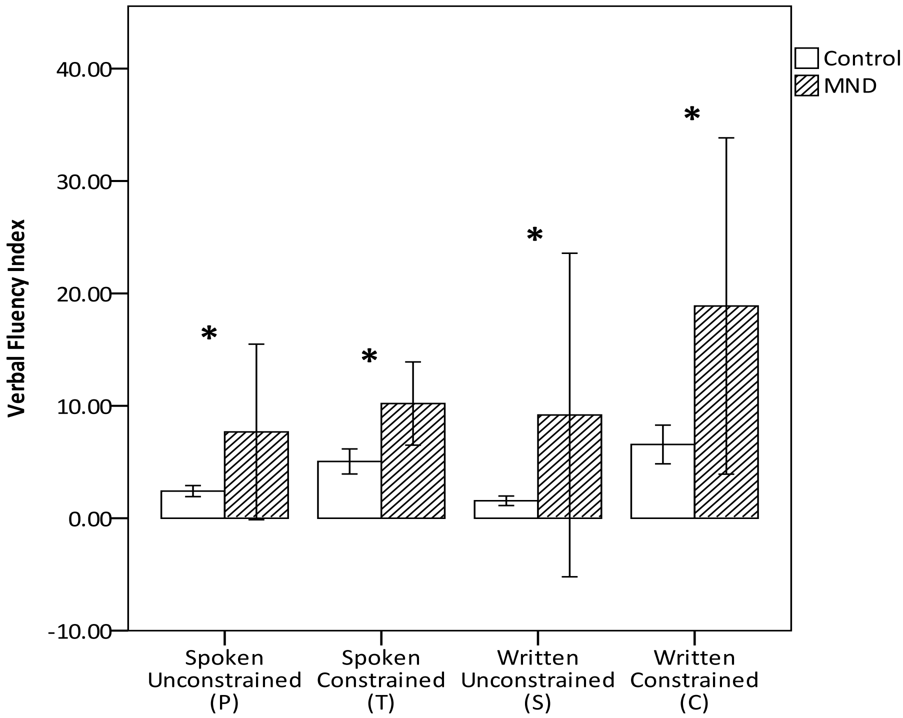


Figure 2.3: Mean verbal fluency scores - * indicates significance (p<.05)

2.4.1.2 Bulbar Onset vs Non-bulbar Onset

Subdivision of the MND group into bulbar and non-bulbar onset groups revealed the following:

2.4.1.2.1 Background & Medical

There was no significant difference in age between the bulbar onset (mean 60.52 years) and non-bulbar onset (mean 62.10 years) groups. Similarly there was no significant difference in the sex distribution in the bulbar (8 Female; 7 Male) and non-bulbar onset (8 Female; 2 Male) groups, or number of years of education (see Table 2.5).

Variable	Bulbar Onset (n 15)			Non-bulbar Onset (n 10)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Age	60.52	10.197	40-77	62.1	10.546	47-79	t = -.371, p = .714
Sex	8F; 7M	-	-	8F; 2M	-	-	χ^2 (1) = 1.852, p = .174
Education	11.33	2.526	10-20	11.8	2.3	10-16	U = 63.000, z = -.702, p = .483

Table 2.5: Comparison of bulbar & non-bulbar onset MND patients on background measures

Comparison of bulbar and non-bulbar onset MND groups on illness duration (in months), HADS anxiety, HADS depression and Epworth Sleepiness Scale also showed no significant difference between groups (see Table 2.6). Additionally there was no significant difference in the hearing status of MND participants in the bulbar onset (Normal 12; Slight Impairment 2) and non-bulbar onset groups (Normal 6; Slight Impairment 0) according to the WHO grades of hearing impairment (χ^2 (1) = .952, p = .329). There was also no significant difference between the hearing status of the bulbar onset (No Impact 11; Impact 3) and non-bulbar onset (No Impact 5; Impact 1) groups regarding the impact on speech perception (χ^2 (1) = .060, p = .807).

The ALSFRS total score was significantly lower (more impaired) in the non-bulbar onset group (mean 27.10) than the bulbar onset group (mean 34.87).

However, there was no significant difference in the ALSFRS bulbar and respiratory scores between the bulbar onset and non-bulbar onset groups (see Table 2.6). This indicates that the significant difference in the total ALSFRS scores can not be attributed to the bulbar and respiratory functions of the MND patients with which we are primarily concerned with in this study.

Variable	Bulbar Onset (n 15)			Non-bulbar Onset (n 10)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Illness Duration	14.87	4.596	7-22	36.1	37.355	7-108	U = 52.000, z = -1.278, p = .201
ALSFRS	34.87	7.745	18-45	27.1	7.279	18-39	U = 35.000, z = -2.223, p = .026*
ALSFRS Bulbar	5.93	3.634	0-11	7.5	3.028	3-10	U = 50.000, z = -1.399, p = .162
ALSFRS Respiratory	11.4	0.632	10-12	10.1	2.183	6-12	U = 55.000, z = -1.190, p = .234
HADS A	5.62 (n 13)	3.525	1-13	4.3 (n 10)	3.401	1-11	t = .901, p = .378
HADS D	4.15 (n 13)	3.997	0-13	3 (n 10)	1.886	1-7	t = .971, p = .371
ESS	6.31	4.837	0-16	5.3	4.473	1-12	t = .417, p = .681

Table 2.6: Comparison of bulbar & non-bulbar onset MND patients on medical measures

2.4.1.2.2 Neuropsychological

Comparison of the bulbar and non-bulbar onset MND groups on the working memory measures shows no significant difference between the groups on any of the digit or spatial span tests (see Table 2.7).

Variable	Bulbar Onset (n 12)			Non-bulbar Onset (n 8)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Forward Digit Span	6.58	0.9	5-8	6.5	1.069	5-8	U = 46.500, z = -.128, p = .899
Reverse Digit Span	5.08	1.443	3-7	5	1.195	4-7	U = 46.500, z = -.120, p = .904
Forward Spatial Span	5.58	1.165	4-7	5.25	1.581	3-8	t = .544, p = .593
Reverse Spatial Span	4.92	1.311	3-7	4.88	1.126	3-6	t = .073, p = .942

Table 2.7: Comparison of bulbar & non-bulbar onset MND patients on working memory measures

There was no significant difference between the bulbar onset and non-bulbar onset groups on both the constrained and unconstrained spoken verbal fluency measures (see Table 2.8). Also, there was no significant difference between the MND subgroups on the written constrained fluency condition, however on the written unconstrained condition the performance of the bulbar onset group was significantly worse than the non-bulbar onset group (see Table 2.8). This is most likely due to the poor performance of bulbar onset participant L146 who was anomalously ≥3 SD below the control mean, while performing at an unimpaired level on all other fluency measures.

Variable	Bulbar Onset			Non-bulbar Onset			Statistics
	Mean	SD	Range	Mean	SD	Range	
Spoken Unconstrained VFI	11.71 (n 8)	20.65	2.52-58.50	4.15 (n 8)	1.45	2.44-6.50	U = 22.500, z = -.998, p = .318
Spoken Constrained VFI	9.05 (n 8)	9.05	3.67-29.00	11.21 (n 8)	4.07	5.89-17.33	U = 17.500, z = -1.525, p = .127
Written Unconstrained VFI	17.22 (n 14)	37.84	2.00-103.00	2.15 (n 10)	1.60	.57-4.88	U = 29.500, z = -2.372, p = .018*
Written Constrained VFI	23.04 (n 14)	37.96	5.36-109.00	15.24 (n 10)	13.84	1.95-39.00	U = 49.500, z = -1.201, p = .230

Table 2.8: Comparison of bulbar & non-bulbar onset MND patients on verbal fluency measures

2.4.2 Individual Patient Characteristics

For measures completed by both control and patient groups, the performance of individual MND participants was compared against the control group mean using z-scores. Z-scores were calculated by subtracting the control mean from each individual patient score and dividing by the control group standard deviation (SD). Performance on measures was taken to be impaired where the z-score fell 2 or more SDs below the control mean, that is, a z-score of ≤ -2.

2.4.2.1 Background & Medical

Table 2.9 shows individual scores for the MND group on background and medical measures. Where comparison is to the control group, individual impairment is marked * for z-scores ≤ -2, and ** for z-scores ≤ -3. However in the case of the HADS and Epworth Sleepiness Scale, as higher scores indicate greater impairment, * represents z-scores ≥ 2 and ** represents z-scores ≥ 3. On the anxiety measure of the HADS, only one MND participant scored over 2 SD above the control mean (G92), while one participant (L121) scored over 2 SD above the control mean on the depression section. A further two MND participants (L107 & L902) scored over 3 SD above the control mean. On the Epworth Sleepiness Scale there was only one participant who scored over 2 SD above the control mean (L902). With regard to hearing status, only two MND participants (L171 & L903) were classified as having a slight hearing impairment according to WHO guidelines, and four (L46, L171, L169 & L903) with hearing levels that may impact upon speech perception. Participant L176 (as marked by ◊ in table 2.9) did indicate he had a hearing impairment in his right ear, however deteriorated before formal assessment could be conducted. In addition, when questioned about pre-morbid spelling ability, only two participants reported that they felt they had never been strong spellers, but also denied any learning difficulties or dyslexia.

	Age	Sex	Onset	Duration	ALSFRS Total	ALSFRS Bulbar	ALSFRS Respiratory	WHO Hearing	Speech Banana Impact	Premorbid Spelling?	ESS	HADS A	HADS D
L120	64	F	UL	12	20	4	8	Normal	No	Normal	1	3	3
L125	62	F	UL	7	39	10	12	Normal	No	Normal	4	1	1
L161	47	F	UL	12	36	10	12	DNC	DNC	Normal	2	9	2
G102	48	F	UL	13	28	10	8	DNC	DNC	Normal	12	4	1
L51	79	F	LL	108	19	3	9	Normal	No	Normal	10	6	4
L46	63	M	LL	102	18	3	11	Normal	Yes	Normal	11	1	1
L121	73	F	LL	28	29	9	11	Normal	No	Normal	8	11	7*
G91	72	F	LL	19	23	7	6	Normal	No	Normal	1	2	3
L174	58	F	LL	24	33	10	12	DNC	DNC	Normal	3	4	4
L176	55	M	LL	36	26	9	12	DNC◊	DNC◊	Not good	1	2	4
G97	53	M	B	18	38	8	10	Normal	No	Normal	6	1	0
G100	60	M	B	18	28	0	12	Normal	No	Normal	5	10	5
L107	76	F	B	7	30	2	12	Normal	No	Normal	0	10	13**
L54	67	M	B	22	18	6	11	Normal	No	Normal	5	DNC	DNC
L146	55	F	B	14	43	8	11	Normal	No	Normal	0	1	1
L171	77	F	B	7	37	2	11	Slight	Yes	Not good	9	4	5
G92	61	F	B	20	43	9	12	Normal	No	Normal	10	13*	4
L165	55	F	B	15	37	2	12	Normal	No	Normal	0	4	3
L169	74	M	B	17	28	5	12	Normal	Yes	Normal	3	5	2
G118	52	F	B	13	45	10	12	Normal	No	Normal	11	5	0
L902	40	M	B	15	39	8	11	Normal	No	Normal	16*	3	9**
L903	64	F	B	16	42	9	11	Slight	Yes	Normal	5	6	1
L904	56	M	B	14	32	1	11	Normal	No	Normal	9	6	2
L901	65	M	B	19	38	11	12	DNC	DNC	Normal	4	DNC	DNC
L900	53	F	B	8	25	8	11	Normal	No	Normal	8	5	9

Table 2.9: Background and medical measurements for individual MND participants
ALSFRS = ALS Functional Rating Scale; ESS = Epworth Sleepiness Scale; HADS = Hospital Anxiety and Depression Scale

2.4.2.2 MND Specific

There were 15 patients with bulbar onset MND, 4 with upper limb onset and 6 with lower limb onset, making the ratio of bulbar onset to non-bulbar onset participants 3:2. The mean disease duration in months was 23.54 (SD 25.99, range 7-108). The mean total score on the ALSFRS-R was 31.76 (SD 8.36, range 18-45), which comprised a mean of 6.56 (SD 3.43, range 0-11) for the bulbar subscore, and a mean of 10.88 (SD 1.563, range 6-12) for the respiratory subscore.

2.4.2.3 Neuropsychological

Table 2.10 shows MND participants who were impaired on the background neuropsychological measures: digit spans, spatial spans and verbal fluency indices. Only four participants fell below 2SD of the control mean on any of the four working memory measures: 2 (L169 & L165) on the reverse digit span and 2 (L46 & L176) on the forward spatial span. Interestingly both MND participants impaired on the measure of verbal working memory belong to the bulbar onset group, while both participants impaired on the measure of nonverbal working memory belong to the non-bulbar onset group.

In keeping with previous research (Abrahams et al., 2004; Abrahams et al., 2000), there were a high number of patients impaired on the verbal fluency measures. 6/16 (37.5%) of patients were impaired on the spoken unconstrained verbal fluency, while 6/16 (37.5%) were also impaired on the spoken constrained measure. In the written modality, 9/24 (37.5%) were impaired on the unconstrained condition, while 10/24 (41.7%) were impaired on the constrained verbal fluency (see Table 2.10).

	Onset	F Digit Span	R Digit Span	F Spatial Span	R Spatial Span	VFI Spoken Unconstrained	VFI Spoken Constrained	VFI Written Unconstrained	VFI Written Constrained
L120	UL								
L125	UL						■		
L161	UL								
G102	UL	DNC	DNC	DNC	DNC	▨	■	■	■
L51	LL					DNC	DNC		
L46	LL			▨		DNC	DNC	■	■
L121	LL	DNC	DNC	DNC	DNC				
G91	LL					■	■		
L174	LL								
L176	LL			▨		▨	■	▨	■
G97	bulbar								
G100	bulbar					DNC	DNC		
L107	bulbar	DNC	DNC	DNC	DNC	DNC	DNC	■	■
L54	bulbar					DNC	DNC	▨	■
L146	bulbar							■	
L171	bulbar	DNC	DNC	DNC	DNC	DNC	DNC		▨
G92	bulbar					▨			
L165	bulbar		▨			DNC	DNC	■	■
L169	bulbar		▨			DNC	DNC		■
G118	bulbar								
L902	bulbar								
L903	bulbar								
L904	bulbar					DNC	DNC	■	■
L901	bulbar	DNC	DNC	DNC	DNC	■	■	■	■
L900	bulbar					■	▨	DNC	DNC

Table 2.10: Table of impairment for MND participants on background neuropsychological measures
N = No Impairment; DNC = Did not complete; ▨ = ≥2 SD below control mean; ■ = ≥ 3 SD below control mean. F = Forwards, R = Reverse

2.5 Discussion

2.5.1 Background & Medical Characteristics

As there was no significant difference on age, sex, and years of education between the patient and control groups, it can be assumed that results on cognitive and linguistic assessments used in this study cannot be attributed to these variables. In particular, it was important that groups were matched for years of education as performance on cognitive and linguistic tests, specifically naming and spelling assessments, can be affected by education level (Henderson, Frank, Pigatt, Abramson, & Houston, 1998; Wood, Giuliano, Bignell, & Pritham, 2006).

Additionally, there was no difference in hearing between patients and controls on both the WHO and speech perception classifications. Although four participants were classified as having hearing levels that may impact upon speech perception, this was lower than in the control group, and is a marker of typical hearing in a population of this age, where higher frequency sounds become more difficult to hear. In terms of speech perception, this may mean high frequency fricative phonemes such as /f/, /s/, and /θ/ may be missed or misinterpreted. In addition, audiograms were not obtained for five MND participants, so the hearing status of these participants is not certain. Therefore consideration for the impact of these hearing impairments will be taken when examining individual performances on the linguistic assessments. However, as control participants also displayed a similar level of impairment as a group, group performance differences cannot be attributed to levels of hearing impairment.

Furthermore, the lack of significant difference between the MND and control groups on the anxiety and depression measures of the HADS suggests that difference in performance between the two groups cannot be attributed to effects of mood disorder. The lack of significant difference on measures of depression between MND patients and controls is a noteworthy finding, and one which has also been reported in the literature. Moore et al. found that only 4/18 MND patients assessed on the HADS and the Beck Depressive Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) were classed as depressed, of which 3 were mildly depressed and 1 moderately so (M. J. Moore, Moore, & Shaw, 1998). This low prevalence of depression amongst people with MND has also been reported in larger (Ganzini, Johnston, & Hoffman, 1999; Rabkin, Wagner, & Del Bene, 2000) and longitudinal studies (Rabkin et al., 2005). This is surprising when considering the rapid progression and poor prognosis of MND, and when it is considered that in other progressive neurological conditions, there is a much higher prevalence of depression (Wicks et al., 2007). Wicks et al. suggest that this discrepancy in prevalence of depression between MND patients, and those with other progressive neurological illnesses may in part be due to the fact that while MND progression is usually relatively rapid, patients with Multiple Sclerosis or Parkinson's Disease will have to endure their symptoms for longer (ibid. 2007). However, there is also a suggestion that there may be some protective factor against depression in people with MND, relating to the function of serotonergic neurones projecting to the frontal and temporo-parietal areas of the cortex (M. J. Moore et al., 1998).

No significant difference between patients and controls on the Epworth Sleepiness Scale suggests that the MND participants, as a group, do not suffer from more symptoms indicative of disturbed respiration than the control group. While the Epworth Sleepiness Scale gives only an indication of symptoms which could suggest respiratory insufficiency, these scores are also supported by the fact that 80% of MND participants scored 11 or 12 (≥92%) on the respiratory subscore of the ALSFRS, indicating normal or near normal respiratory functioning. Therefore, we can also infer that differences in group performance on further measurements are unlikely to be due to poor respiratory functioning in the MND participants.

2.5.2 Neuropsychological Characteristics

As there was no significant difference between MND participants and controls on any measure of working memory used in this study, both verbal and non-verbal, it can be suggested that any differences found between the patient and control groups on linguistic measures cannot be attributed solely to working memory difficulties. However, this does not mean that MND patients individually do not display any working memory deficits. Two participants were impaired on the non-verbal forward spatial span measure, while another two participants were impaired on the verbal reverse digit span measure. Of particular interest is the distribution of these results: while the two participants impaired on the non-verbal measure belong to the non-bulbar onset group, the two participants impaired on the verbal measure came from the bulbar onset group. This could indicate there may be a tendency towards poorer function of the phonological loop in those with bulbar onset MND, while it is the visuo-spatial sketchpad that is more vulnerable in those with non-bulbar onset MND. However, there was no significant difference in performance between the bulbar and non-bulbar onset groups as a whole to support this pattern of findings. Indeed, there is great uncertainty in the literature about the role of memory dysfunction in the cognitive profile of those with MND, as it is inconsistently found within other studies (Raaphorst et al., 2010).

There was marked impairment as a group on all verbal fluency measures, which is in keeping with previous research. Indeed, due its high sensitivity, letter fluency impairment is the most consistently reported cognitive deficit in MND patients (ibid. 2010). The results of this study revealed there was 37.5% impairment on both spoken constrained and unconstrained verbal fluency measures in the MND group, and also on the written unconstrained verbal fluency measure. The written constrained verbal fluency measure showed slightly higher levels of impairment, with 41.7% of the MND group performing two or more SD below the control mean. However, while 9/15 participants with impairment on verbal fluency did so across all conditions completed, 7 were not consistently impaired across the fluency measures, so it is difficult to suggest one measure as more sensitive over the others. However, it is interesting to note that the participants who were impaired on the working memory measures were all impaired on the written constrained letter fluency task, suggesting that this was the most sensitive fluency measure. In terms of accessibility, the written modality was more easily completed by participants as reflected through the higher group number - where participants were unable to write, Augmentative and Alternative Communication (AAC) devices were used to assist in completion of the task.

2.5.3 Bulbar and Non-bulbar Onset Group Characteristics

There was no significant difference between bulbar and non-bulbar onset MND subgroups on any background or medical measures, indicating that the subgroups were also well matched. In addition, any further subgroup analysis on linguistic assessments can be interpreted knowing that there will be no group effect of these measures. This allows for an accurate comparison of cognitive and language functions between bulbar and non-bulbar onset patients and further suggestions about subgroup cognitive profiles to be made.

From the results of the initial neuropsychological measures reported in this chapter, there is little suggestion that there are any significant differences in performance or two distinct profiles. Only one measure, the unconstrained written verbal fluency, revealed any significant difference between the two subgroups, however, as reported, this was likely due to one anomalous result from a bulbar onset participant. The suggested relationship between bulbar onset MND and cognitive impairment will be further investigated throughout the thesis.

Chapter 3: Standard Linguistic Assessment

This chapter outlines the standard linguistic assessments used in this study to investigate the contribution of various aspects of language processing to the communication impairment seen in people with MND. Conducting previously used linguistic assessments not only allows for results to be compared to that of other studies, including related clinical populations, but also acts as a point of comparison for the experimental linguistic assessments outlined in Chapter 4. The areas examined by standard linguistic assessments are motor speech, naming, grammatical comprehension, reading and prosody.

3.1 Selection of Materials and Methods

3.1.1 Motor Speech Assessment

In order to ascertain the level of motor speech impairment in our MND participants, measurements of both dysarthria and apraxia of speech were taken. While both dysarthria and apraxia of speech are categorised as motor speech impairments, the presentation and cognitive implications differ.

3.1.1.1 Computerised Frenchay Dysarthria Assessment (CFDA)

Dysarthria is the most common communication impairment associated with MND. Indeed all the participants with MND recruited in this study had dysarthria to some degree, as specified by the selection criteria. The primary aim of this study wass to disentangle the contribution of dysarthria from other possible cognitive and linguistic deficits to the overall communication profile. For this reason, the type and severity of dysarthria displayed by each participant was measured using the Computerised Frenchay Dysarthria Assessment (CFDA) (Palmer, Enderby, & Carmichael, 2010). The assessment, based on the published Frenchay Dysarthria Assessment 2 (Enderby & Palmer, 2008), is an experimental computerised tool for analysing motor speech parameters. Run through a Toshiba Portege M750-12F laptop, the assessment software examines eight components of motor speech disturbance: reflexes (cough, swallow, dribble); respiration (at rest, in speech); lips (at rest, spread, seal, alternate, in speech); jaw (at rest, in speech); palate (fluids, maintenance, in speech); laryngeal (time, pitch, volume, in speech); tongue (at rest, protrusion, elevation, lateral, alternate, in speech); and intelligibility (word, sentence, conversation). For each component, participants are either asked to perform orofacial and motor speech tasks e.g. maximum phonation time, variation of pitch and volume, alternating lip/tongue movements, or notes are made based on observations of participants' articulators at rest or reports from participants about reflex based functions (e.g. swallowing). For those tasks scored on speech based performances, recordings are made through the software package and an automatic grade suggestion is made using a hidden Markov Model speech recognition system designed to perform like a naïve listener. Each task is also graded A-E by the researcher based on scoring guidelines given in the instructions and clinical judgement, with A representing normal function and E no function. A dysarthria profile is then compiled (see Figure 3.1), and a suggested diagnosis of the severity and type of dysarthria is calculated according to the key characteristics of the profile.

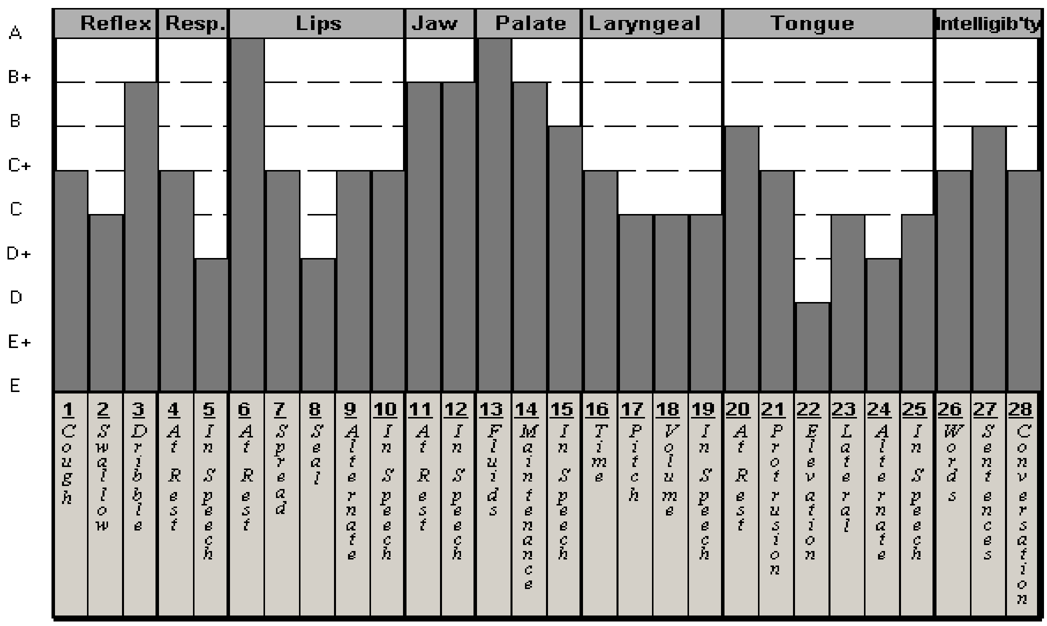


Figure 3.1: Example of Computerised Frenchay Dysarthria Profile for participant L146 – calculated as mild mixed dysarthria

3.1.1.2 Apraxia Screen

As discussed in chapter 1 (see section 1.2.1.2), the existence of apraxia of speech (AOS) as a contributor to communication impairment in people with MND is a controversial and only recently reported issue. Duffy and colleagues (J.R. Duffy, 2006; J. R. Duffy et al., 2007), and more recently Lobo and colleagues (Lobo et al., 2013), have reported on symptoms suggestive of AOS in MND patients, suggesting that early reports of "effortful" and "stuttering-like" speech from Caselli and colleagues may also indicate its existence in MND (Caselli et al., 1993),

Adapted from the Apraxia Battery for Adults 2 (ABA2) (Dabul, 2000) participants were screened using a four part apraxia assessment examining limb, orofacial, and verbal apraxia, the latter of which was divided into imitation and speech samples. For the limb apraxia section participants were asked to imitate five meaningful gestures (e.g. wave goodbye) and five meaningless gestures (e.g. raise little finger), and were graded on a scale of 0-5 according to the guidelines of the ABA2, with 5 representing an accurate, prompt, complete gesture, and 0 representing a complete inability to perform the correct gesture despite further modelling. For the oral apraxia section participants were asked to imitate ten orofacial movements (e.g. smile, pucker your lips), performance of which was graded on the same 0-5 scale used in the limb apraxia section. In the imitation sub-section of the verbal apraxia component participants were required to repeat words with increasing morphological complexity and syllable length (e.g. thick, thicken, thickening). Ten sets of one, two and three syllable words using the same stem were presented to participants from least to most complex and a score of 0-2 was assigned for each item, with 2 representing a correct, prompt repetition, and 0 representing no response, or one that contains the wrong number of syllables or a nonword. Mean scores for each syllable length are calculated, and the mean 3 syllable score is subtracted from the mean 1 syllable score to give the deterioration in performance, with a higher score indicating increased error rate with increased articulatory complexity as distinctive of AOS. Spontaneous, reading and automatic speech samples were also taken in the verbal apraxia component for further qualitative analysis of errors.

3.1.2 Naming Assessment

Naming tests are frequently used measures of language functioning, and have been used in numerous studies examining cognitive impairment in MND. Indeed, one of the earliest studies investigating aphasia in MND found 4 out of 7 patients tested on the Peabody Picture Vocabulary Test had severely impaired naming abilities (Caselli et al., 1993). Assessing word retrieval difficulties, naming tests can give qualitative information about the integrity of semantic, phonological and, when responses are written, orthographic processing systems. However, while naming tests can give an indication of language impairment, when used as the sole measure of language functioning they cannot give a robust analysis of linguistic impairment, and there has previously been an overreliance on naming tests as diagnostic tool for language impairment in cognitive screening studies. Nonetheless their use in combination with other assessments of language functioning can be very valuable. In this study two measures of word retrieval were used: the Graded Naming Test and the Northwestern Naming Test.

3.1.2.1 Graded Naming Test (GNT)

The Graded Naming Test (McKenna & Warrington, 1983) is a commonly used assessment in study of word retrieval in aphasia, and previous studies of people with MND have found significant impairment on the GNT in comparison to control groups (Abrahams et al., 2004; Cobble, 1998; Rakowicz & Hodges, 1998). Other popular naming assessments have been used to test word retrieval skills in people with MND, including the Boston Naming Test (BNT) (Kaplan et al., 1983). One study that used the BNT was that conducted by Talbot and colleagues (P. R. Talbot et al., 1995), where they found no significant difference in performance between MND patients and controls. However, as Cobble argues, the GNT is better able to detect subtle naming difficulties due its decreasing frequency design, created to be sensitive to high level anomia (Cobble, 1998). Indeed, this was reflected in the results of her study where she found significantly poorer performance of MND patients on the GNT in comparison to controls, despite none of the patients exhibiting overt word-finding difficulties in everyday conversation.

This confrontation naming test comprises 30 black and white drawings, with items decreasing in frequency from item 1 'kangaroo', to item 32 'retort' (see Figure 3.2). Items were presented one at a time and participants were asked to give the name for each item. Where participants were unable to respond verbally, written responses were taken. Responses were marked as correct only if named exactly as the target, except for item 25 'yashmak' where 'hijab' was also accepted.

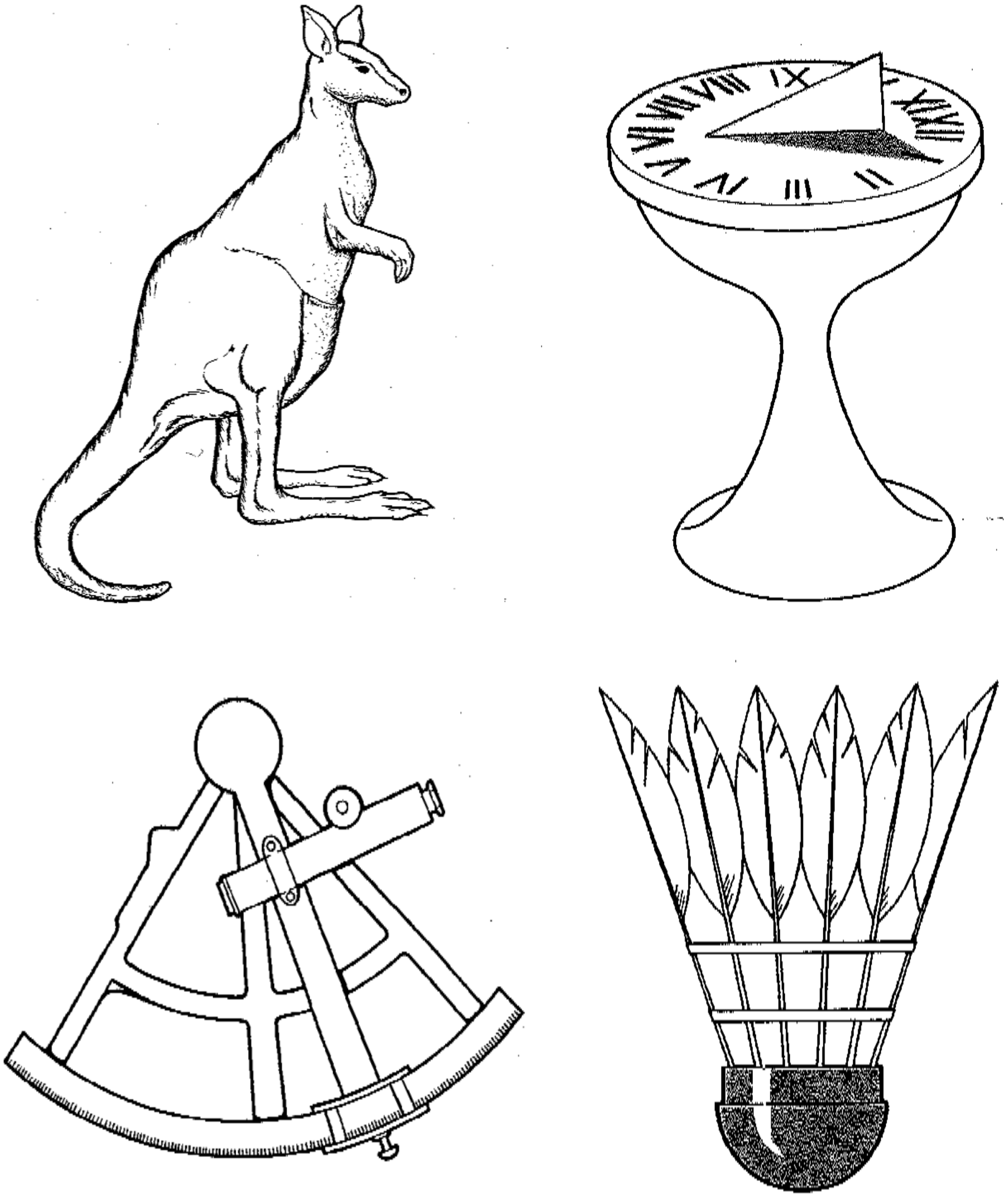


Figure 3.2: Items taken from the Graded Naming Test.
Clockwise from top left: Item 1 Kangaroo; Item 10 Sundial; Item 19 Shuttlecock; Item 26 Sextant

3.1.2.2 Northwestern Naming Test

As an additional measure of word class naming, the Northwestern Naming Test (C.K. Thompson & Weintraub, 2009) was also included. Measuring word class naming performance was important in this study as dissociation between verb and noun naming has previously been shown to exist in people with MND with patients having greater difficulty with naming of verbs over nouns (T. Bak & Hodges, 1997). Bak and colleagues report a group of six patients with MND dementia and/or aphasia who were not only worse at naming verbs than nouns, but were significantly worse at naming both nouns and verbs than both healthy and Alzheimer's Disease control groups (T. H. Bak et al., 2001). They also report that on post-mortem examination there was evidence not only of typical pathological changes to the motor and premotor cortex , but also to Brodmann areas 44/45 (Broca's area), responsible for language production and comprehension, and action recognition and production (Fadiga et al., 2006). Bak and colleagues suggest that as verbs and nouns can be interpreted as actions and objects, through the functional consequence of their semantic difference, this 'action' deficit could indicate a connection between the neural substrates underlying verb representation and the motor cortex. This was also supported by Grossman and colleagues who found that MND patients were significantly more impaired on measures requiring knowledge of actions than objects, and that this deficit correlated with motor cortex atrophy as shown on neuroimaging (Grossman et al., 2008).

The assessment is taken from an experimental battery of tests entitled the Northwestern Naming Battery. The complete battery comprises auditory discrimination, non-word repetition, auditory lexical decision, confrontation naming, auditory comprehension, semantic associates and word repetition. The full version of the confrontation naming test comprises of 72 black and white drawings, and assesses the ability to name verbs, animals, fruits and vegetables, tools, clothing, body parts and colours, and an assortment of items categorised as 'other'. The shortened version of the test was used in this study, comprising 32 items: 16 verbs and 16 nouns, of which 4 are animals, 4 are fruit or vegetables, 4 are tools and 4 are items of clothing (see Figure 3.3). Verb items are depicted as people or animals performing activities, and participants are asked to name the activity. The shortened version of the assessment allows for direct comparison of noun and verb naming as items are balanced in number and frequency. Stimuli was matched for lemma frequency using the CELEX database, however the noun stimuli was not matched with verb stimuli for imageability (C. K. Thompson et al., 2012). The extent to which imageability accounts for word class production deficits is unclear, as while some report that differences in noun and verb production are as a consequence of imageability differences (Bird, Howard, & Franklin, 2002), others have found no role of imageability in word class deficits in aphasic patients (Luzzatti et al., 2002).

Originally designed to be presented on paper, in this study test items were scanned and inserted into a powerpoint presentation and presented via a laptop, with items presented on one slide at a time. As with the GNT, where participants were unable to respond verbally, written responses were taken. Responses were marked as correct only if named exactly as the target, except for the following items: 2 ‘pepper’ where ‘capsicum’ was also accepted; 5 ‘broom’ where ‘brush’ was also accepted; 13 ‘mouse’ where ‘rat’ was also accepted; 19 ‘sweep’ where ‘brush’ was also accepted; and 28 ‘stir’ where ‘mix’ was also accepted.

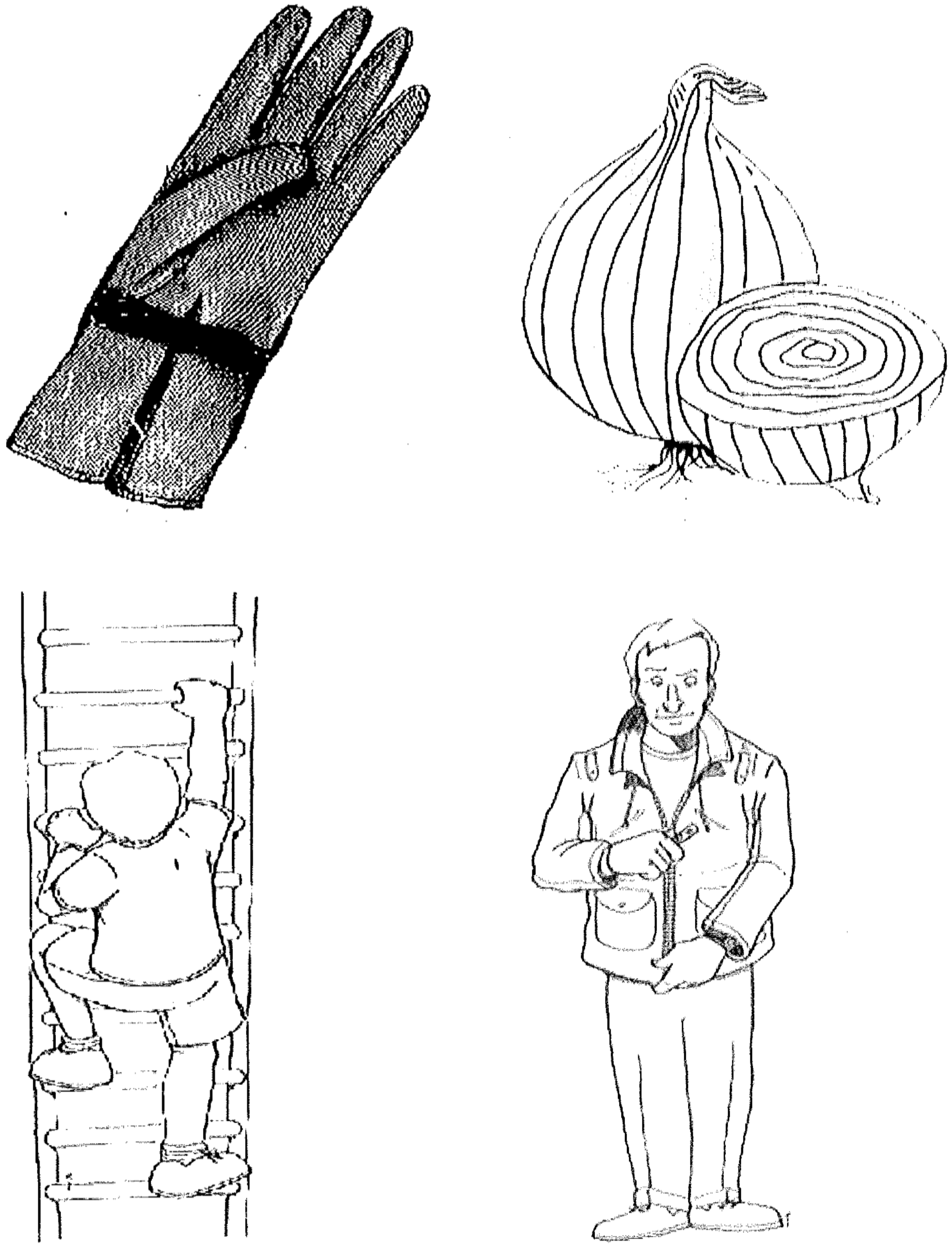


Figure 3.3: Items taken from the Northwestern Naming Test.
Clockwise from top left: Item 1 Glove; Item 14 Onion; Item 17 Zip; Item 30 Climb

3.1.3 Grammatical Comprehension:

Test of Reception of Grammar (TROG)

The Test of Reception of Grammar (D. V. M. Bishop, 1983) was used to assess our participants' understanding of grammatical contrasts. The test, originally designed and standardised for use with children aged 4-12, is also frequently used to assess adults with aphasia, and has previously been used in the MND population. Indeed, several studies have revealed significant impairment of MND patient performance on the TROG in comparison to controls (T. H. Bak et al., 2001; Doran et al., 1995; Rakowicz & Hodges, 1998). A multiple choice test requiring no verbal output, the original version comprises 80 test items presented in an A4 sized book. Participants are presented with a choice of four colour pictures per page, and are asked to select the picture that corresponds to a sentence spoken by the researcher. Each picture is numbered, and participants may respond by pointing to the picture or stating the selected number (See Figure 3.4). The test is divided into 20 blocks of four test items with each block testing a particular grammatical construct, arranged in order of increasing complexity. For the purpose of this study, only the second half of the TROG, blocks K to T, were used as these were shown to be most sensitive to impairment when testing MND participants (T. H. Bak et al., 2001) and enabled us to shorten the overall testing time. The blocks used tested the following grammatical constructs:

K – comparative/absolute e.g. "The knife is longer than the pencil";
L – reversible passive e.g. "The girl is chased by the horse";
M – in and on e.g. "The cup is in the box";
N – post modified subject e.g. "The circle in the star is yellow";
O – *x* but not *y* e.g. "The box but not the chair is red";
P – above and below e.g. "The comb is below the spoon";
Q – not only *x* but also *y* e.g. "Not only the bird but also the flower is blue";
R – relative clause e.g. "The girl chases the dog that is big";
S – neither *x* nor *y* e.g. "Neither the boy nor the horse is running";
T – embedded sentence e.g. "The cat the cow chases is black".

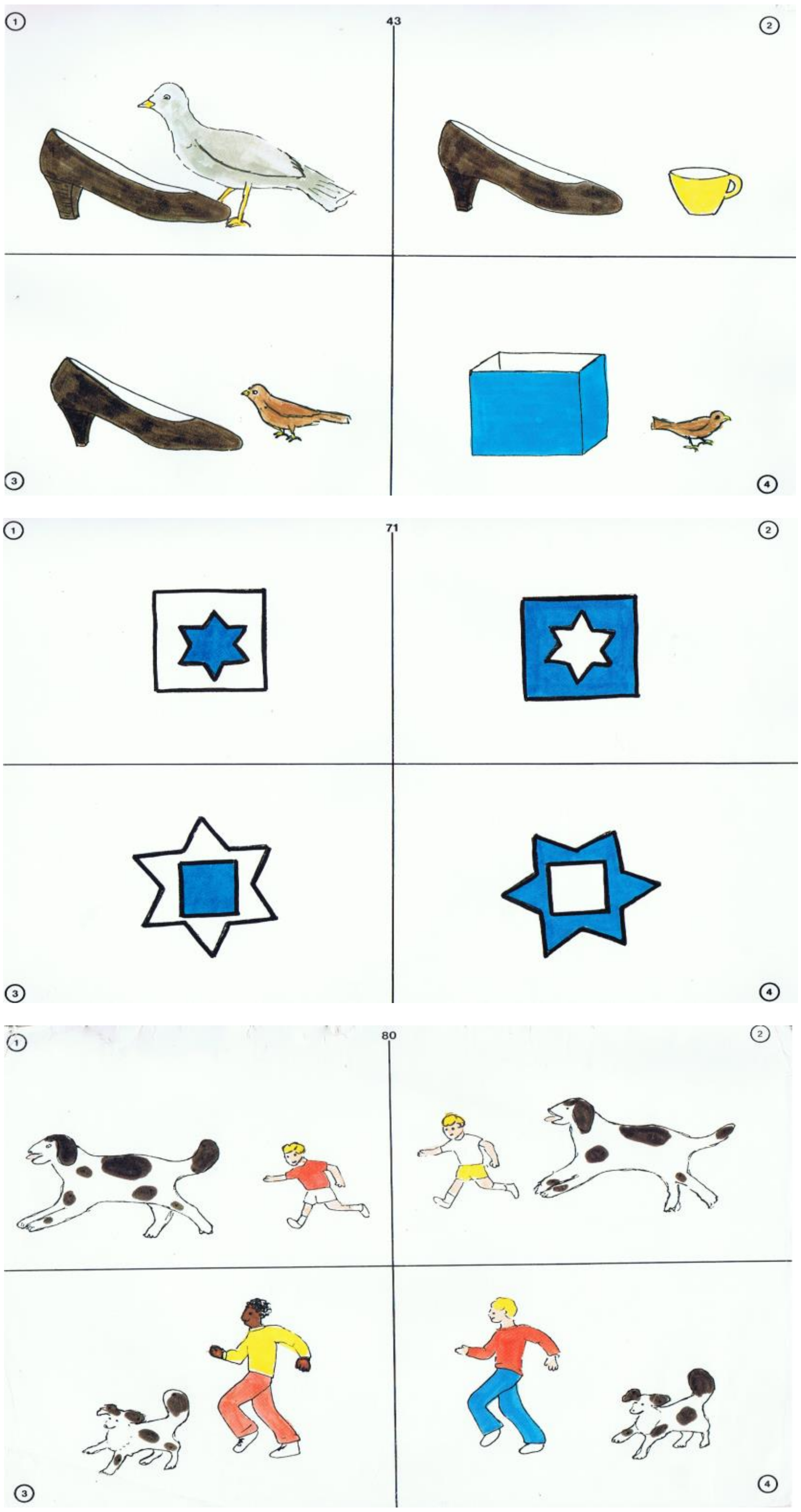


Figure 3.4: Items taken from the Test of Reception of Grammar (TROG).
From top to bottom: Block K Item 43 "The shoe is bigger than the bird"; Block R Item 71 "The square is in the star that is blue"; Block T Item 80 "The boy the dog chases is big"

All sentences were presented to the participants regardless of previous correct or incorrect responses, and each question was scored according to a pass/fail system, with a maximum score of 40.

3.1.4 Reading

To date reading ability has not been explicitly assessed in people with MND. Where some level of reading assessment has been conducted it is most commonly the National Adult Reading Test (NART), as a measure of premorbid IQ in which case scores are usually matched to controls, or in one study, the reading sentences and paragraphs and oral reading and reading comprehension sections of the Boston Diagnostic Examination (BDAE) (Flaherty-Craig, Brothers, Dearman, Eslinger, & Simmons, 2009). Flaherty-Craig and colleagues highlight that the NART, in addition to providing an estimate of verbal IQ, can highlight signs of surface dyslexia. However, many reading tests, including the NART and elements of the BDAE, require verbal output, making their use with a population for whom verbal output is impaired difficult for several reasons. Not only can performance on oral reading tasks be affected by motor speech difficulties, but impaired oral reading can reflect phonological output lexicon or assembly deficits, rather than those at the visual orthographic analysis or orthographic input lexicon levels.

As one of the main language functions under investigation in this study was spelling (as detailed in chapter 4), having an insight into written word comprehension was important. Impairment at the level of visual orthographic analysis or the orthographic input lexicon may impact on the ability to monitor written word production. In addition, some researchers suggest that a common orthographic lexicon serves both spelling and reading (Behrmann & Bub, 1992), which could account for the high correlation of performance on spelling and reading tasks reported in people with semantic dementia (N. L. Graham, Patterson, & Hodges, 2000).

3.1.4.1 Letter String Discrimination (LS)

Adapted from Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) 21 Letter Discrimination: Letters in Words and Nonwords (Kay, Lesser, & Coltheart, 1992), the letter string discrimination test assesses the integrity of visual orthographic analysis. It requires participants to recognise and match individual letters without the necessity to access information about meaning or sound, testing only orthographic knowledge. Participants are presented with 48 pairs of written words and are required to decide if the items in each pair are the same or different. One item in each pair is written in upper case letters, while the other item in the pair is in lower case letters. All items are five letters long, and while 'same' pairs, of which there are 24, differ only in case (e.g. train TRAIN), 'different' pairs, also 24, differ by the substitution or transposition of letters in one item in the pair (e.g. grasp GRASS; acres CARES). Of the different pairs, 12 are substitution pairs and 12 are transposition pairs. When pairs are different, differences occur either in the initial (first letter), medial (third letter) or final (fifth letter) position, of which there are 8 of each type. Half of the pairs are words and half are nonword pairs (e.g. SELIM selim; aihcn AIHCR). The test is administered via powerpoint presentation with one slide per pair in a randomised order, and participants had no time restriction in which to respond. Responses were given either orally, or by pointing to a same/different communication board.

3.1.4.2 Spelling Verification Test (SVT)

The second reading assessment used in this study was an adapted version of the Spelling Verification Test (N. L. Graham et al., 2000). Designed by Graham and colleagues to assess the ability of semantic dementia patients to recognise the correct spelling of words, the assessment tests the integrity of the orthographic input lexicon. In this visual lexical decision test participants are presented with a spoken word target whilst simultaneously shown a written word and asked if the spoken word has been spelled correctly. For example participants would hear the word "girl" and be presented with the written item 'gril'. Stimuli was presented via a powerpoint presentation, with a written word per slide, and the spoken target word played through Sennheiser HD 280 pro headphones. Spoken stimuli was recorded in a professional recording studio by one female from the West coast of Scotland, and one male from the East coast of Scotland and presenters were alternated for each spoken item. The test consisted of 72 monosyllabic items presented in randomised order. Each of the 12 spoken target words were presented four times throughout the assessment with four different written forms: 1) with the written word spelled correctly e.g. "shy" - 'shy'; 2) with a phonologically plausible written nonword e.g. "shy" - 'shie'; 3) with a phonologically implausible written nonword e.g. "shy" – 'sye'; and 4) with a similar written word e.g. "shy" – 'shire'. There were also 24 filler items with correctly spelled written words to the spoken stimuli added to balance the number of 'yes' and 'no' responses. The 12 spoken target words and 24 filler items (36 different spoken targets in total) were split 50/50 for high and low frequency, and also 50/50 for high and low predictability, with predictability referring to spelling regularity of written stimuli as defined by Graham and colleagues (K. S. Graham, Simons, Pratt, Patterson, & Hodges, 2000). There were therefore 18 high frequency - high predictability (HFHP) items; 18 high frequency - low predictability (HFLP) items; 18 low frequency - high predictability (LFHP) items; and 18 low frequency - low predictability (LFLP) items. Responses were either given orally, or by pointing to a yes/no communication board.

3.1.5 Prosody:

Profiling Elements of Prosodic Systems – Children (PEPS-C)

Prosody is another area that has been little investigated in people with MND. Prosody is described as the rhythm, stress and intonation of speech, and can reflect underlying messages including the emotional state of the speaker, the pragmatic implication of the utterance (e.g. question or statement), or other elements of language that may not be encoded by syntax or vocabulary. While a number of studies have explored social and emotional cognition and affective decision making in MND (Girardi et al., 2011; Lule et al., 2005; Papps, Abrahams, Wicks, Leigh, & Goldstein, 2005), there are few that have explored the perception of social and pragmatic communication through prosody. Assessment on the recognition of emotional words and phrases (Papps et al., 2005) and Theory of Mind using the Judgement of Preference task (Girardi et al., 2011) have revealed significant impairment on elements of social cognition in people with MND. Another study by Zimmerman and colleagues found MND patients had deficits in recognition of facial expressions of emotion, but they were not impaired, as a group, on identifying emotions associated with emotionally intoned sentences, although 3 out of 13 participants were below the 95% Confidence Interval for controls (Zimmerman, Eslinger, Simmons, & Barrett, 2007). More recently however, assessment of affective prosody processing using the Aprosodia Battery (Ross, Thompson, & Yenkosky, 1997) revealed MND participants were significantly less accurate at identifying emotion from emotionally intoned words than controls, yet were able to discriminate between intonation and stress patterns in a control condition where phonetic information had been removed (Meier, Charleston, & Tippett, 2010). Furthermore, similar results have been found in people with primary progressive aphasia (Rohrer, Sauter, Scott, Rossor, & Warren, 2012) where not only were participants significantly impaired on recognition of vocal emotions, particularly fear and disgust, but also on perception of linguistic prosody, where participants were required to discriminate between question and statement intonation patterns using the Profiling Elements of Prosodic Systems – Children (PEPS-C) assessment (Peppe & McCann, 2003).

The PEPS-C, originally designed for use with children, assesses the ability to understand and express prosody, both at a discrimination and functional level. Comprising a larger battery of prosodic assessments, we selected three discrimination tasks assessing receptive prosody from the PEPS-C assessment to examine acoustic, linguistic and affective elements of prosody processing. The computerised tasks, run through software designed by Peppe and McCann, were presented to participants via a Toshiba Portege M750-12F laptop and using Sennheiser HD 280 pro headphones. In all tasks, participants were required to select a response from a choice of two presented on the screen (e.g. same/different) by pointing to their choice on the touch screen of the laptop. Choices were automatically recorded and scored via the auto-scoring software included in the program. For each task there were 2 practice items followed by 16 trial items.

In the turn-end type task, assessing the participants' ability to perceive and understand differences in questioning versus declarative intonation, participants were presented with two cartoon figures on the computer screen, one holding a plate with a food item on it and a question mark beside them, the other holding a book with a speech bubble containing the same food item beside them. The former figure represents the person offering the food item in a question format, while the latter represents the person simply saying the word as if they were reading it from a book. Participants were then played a recording of a single word (food item) spoken either interrogatively or declaratively (e.g. "apple?" versus "apple"). Participants were asked to select the picture that matched the spoken form by touching the picture on the screen.

In the affective prosody task, assessing the participants' ability to perceive and understand differences in emotionally intoned single words expressing like or dislike, participants were presented with a picture of a food item whilst being played a recording of a that single food item spoken either in a manner expressing happiness or disgust. The participants were then presented with two cartoon faces on the computer screen, one with a happy face and one with a sad face. Participants were asked to select the face that matched the way the intonation pattern suggested the person speaking felt about the food item e.g. like or dislike.

In the intonation discrimination task, assessing the participants' ability to perceive difference in intonation without linguistic or emotional meaning, participants were presented with a picture of two circles labelled 'same' and a picture of a circle and a square labelled 'different'. Participants were then played a recording of two laryngograph sounds and asked to judge if the two sounds were same or different by pointing to the corresponding picture.

3.2 Results

3.2.1 Group Comparisons

3.2.1.1 MND Participants vs Controls

For groupwise comparisons between patients and controls, t-tests were used. Where data was not normally distributed, as determined using Kolmogorov-Smirnov analysis, Mann-Whitney U tests were used.

3.2.1.1.1 Naming

MND participants performed significantly worse than controls when tested using the Graded Naming Test. However there was no significant difference in performance between patients and controls of overall scores on the Northwestern Naming Test (see Table 3.1 & Figure 3.5).

Variable	MND			Controls			Statistics
	Mean	SD	Range	Mean	SD	Range	
GNT (30)	20.76 (n 21)	5.243	21-28	25.45 (n 22)	2.703	21-29	t (29.621) = 3.663, p = .001*
NW Naming (32)	30.91 (n 23)	1.782	26-32	31.72 (n 25)	0.458	31-32	U = 222.000, z = -1.595, p = .111
NW Naming (Nouns) (16)	15.70 (n 23)	0.635	14-16	16 (n 25)	0	0-0	U = 225.000, z = -2.434, p = .015*
NW Naming (Verbs) (16)	15.22 (n 23)	1.380	11-16	15.72 (n 25)	0.458	15-16	U = 250.500, z = -.936, p = .349

Table 3.1 Comparison of total scores for MND participants & controls on naming measures, followed by noun and verb subscores for Northwestern Naming Test

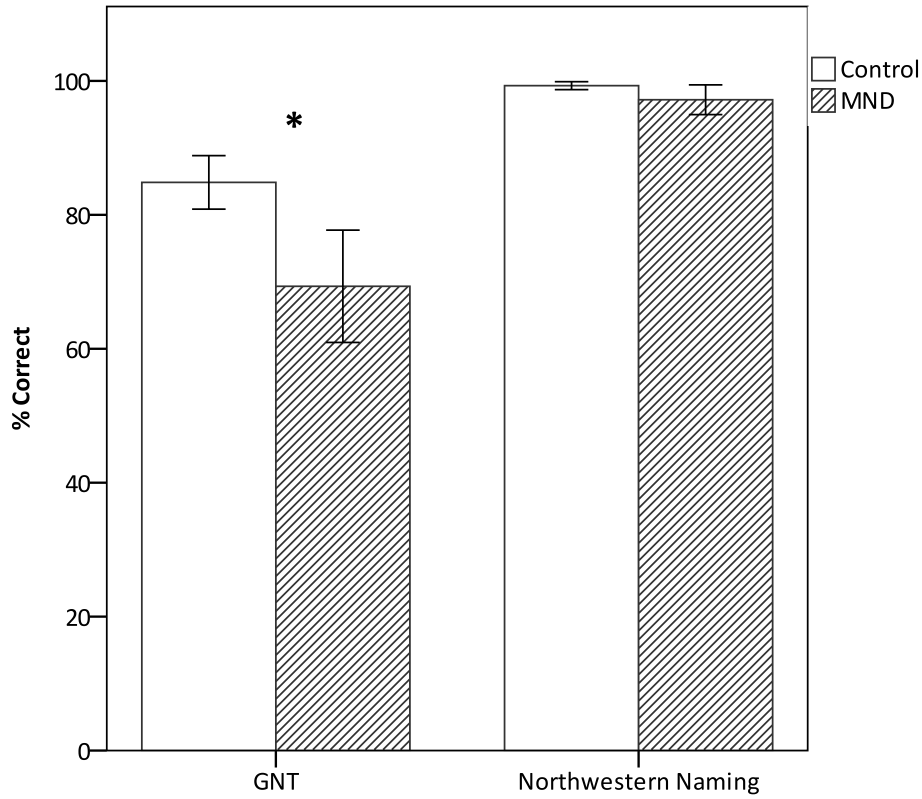


Figure 3.5: Percentage correct on naming tests - * indicates significance (p<.05)

When results on the Northwestern Naming Test were divided into noun and verb naming scores, MND participants were significantly worse naming nouns than controls, yet there was no significant difference between MND participants and controls when naming verbs (see Table 3.1). However this result should be interpreted with caution as control performance was a ceiling for noun naming. Wilcoxon signed ranks test of within group comparison revealed no significant difference between naming of nouns (Mean 15.70; Median 16) and verbs (Mean 15.22, Median 16) in the MND group, however there was a trend towards significance T = 9, p = .054. In the control group, participants were significantly worse at naming verbs (Mean 15.72, Median 16) than nouns (Mean 16, Median 16) T = 0, p = .008.

Further analysis of nouns according to semantic categories revealed that MND participants were significantly worse when naming fruit and vegetables than controls. There was no significant difference between MND participants and controls naming nouns belonging to the animal, tools or clothing category (see Table 3.2).

Variable	MND			Controls			Statistics
	Mean	SD	Range	Mean	SD	Range	
NW Naming Animals % Correct	100	0	0-0	100	0	0-0	U = 287.500, z = .000, p = 1.000
NW Fruit & Veg % Correct	93.48	15.48	50-100	100	0	0-0	U = 237.500, z = -2.153, p = .031*
NW Tools % Correct	98.91	5.213	75-100	100	0	0-0	U = 275.000, z = -1.043, p = .297
NW Clothing % Correct	100	0	0-0	100	0	0-0	U = 287.500, z = .000, p = 1.000

Table 3.2: Comparison of MND patients & controls on percentage of nouns named correctly on the Northwestern Naming Test by semantic category

3.2.1.1.2 Grammatical Comprehension: TROG

MND participant overall scores on the TROG (Mean 36.72; Median 37) were significantly worse than controls (Mean 39.04; Median 39) U = 147.5, z = -3.275, p = 0.001. On analysis of error patterns, MND participants were significantly worse than controls on block K (comparative/absolute), block R (relative clause) and block T (embedded sentence) (see Table 3.3 and Figure 3.6).

Block	MND (n 25)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
K	.24	.436	0-1	.04	.200	0-1	U = 250, z = -2.017, p = .044*
L	.16	.374	0-1	.04	.200	0-1	U = 275, z = -1.400, p = .162
M	.04	.200	0-1	0	0	0-0	U = 300, z = -1.000, p = .317
N	.20	.408	0-1	.08	.277	0-1	U = 275, z = -1.210, p = .226
O	.20	.408	0-1	.04	.200	0-1	U = 262.500, z = -1.723, p = .085
P	.04	.200	0-1	0	0	0-0	U = 300, z = -1.000, p = .317
Q	.08	.277	0-1	.04	.200	0-1	U = 300, z = -.590, p = .556
R	.40	.645	0-2	.04	.200	0-1	U = 224.00, z = -2.571, p = .010*
S	.08	.400	0-2	.08	.277	0-1	U = 301, z = -.542, p = .588
T	1.80	1.414	0-4	.60	.707	0-3	U = 163, z = -3.034, p = .002*

Table 3.3 Comparison of number of errors made by MND patients & controls on TROG, according to block (4 items per block)

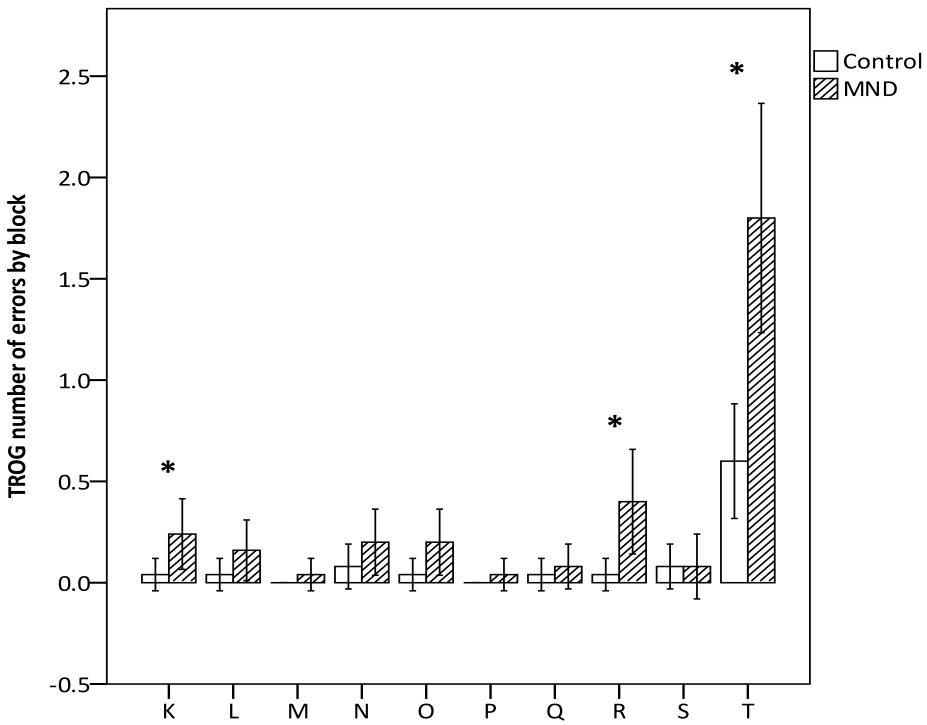


Figure 3.6: Number of errors made by MND participants and controls on TROG by block - * indicates significance (p<.05)

3.2.1.1.3 Reading

3.2.1.1.3.1 Letter String Discrimination

Overall MND participant scores on the letter string discrimination test (Mean 46.64; Median 47) were significantly worse than controls (Mean 47.20; Median 48) ($U = 222$, $z = -1.972$, $p = .049$).

On breakdown of error patterns (see Table 3.4), there was no significant difference between MND participants and controls in the number of errors made where the difference in pairs was a substitution of letters. However, controls were significantly worse than MND participants in perceiving differences between two items when the difference was a transposition of letters (see discussion for explanation of difference in performance).

There was no significant difference between MND participants and controls in the number of errors made perceiving differences between pairs when the pairs were both nonwords, and also when the pairs were both words, however there was a trend towards significantly worse performance by MND participants perceiving differences when items were words ($U = 253.000$, $z = -1.916$, $p = .055$ see Table 3.4). There was also no significant difference between MND participants and controls in the number of false negative errors (i.e. indicating pairs were different when they were the same) for both word and nonword pairs.

On considering the effect of position of the difference in the pair, there was no significant difference between MND participants and controls in the ability to spot differences in the initial, medial or final position.

Variable	MND (n 25)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Sub. Errors (12)	0.12	0.332	0-1	0.16	0.473	0-2	U = 311.000, z = -.052, p = .959
Trans. Errors (12)	0.4	0.645	0-2	0.52	2.4	0-12	U = 240.500, z = -2.005, p = .045*
Word Errors (12)	0.32	1.2	0-6	0.24	0.69	0-3	U = 253.000, z = -1.916, p = .055
Nonword Errors (12)	0.92	1.681	0-7	0.52	1.294	0-6	U = 264.000, z = -1.104, p = .270
Word False Negative Errors (12)	0.12	0.332	0-1	0	0	0	U = 275.000, z = -1.769, p = .077
Nonword False Negative Errors (12)	0.6	1.291	0-5	0.12	0.332	0-1	U = 258.000, z = -1.518, p = .129
Initial Position Errors (8)	0.16	0.374	0-1	0.24	0.831	0-4	U = 302, z = -.338, p = .735
Medial Position Errors (8)	0.16	0.374	0-1	0.24	0.831	0-4	U = 302, z = -.338, p = .735
Final Position Errors (8)	0.2	0.5	0-2	0.2	0.816	0-4	U = 289, z = -.808, p = .419

Table 3.4: Comparison of number of errors, according to subtype, made by MND patients & controls on the Letter Strings Discrimination Test

Wilcoxon signed ranks test of within group analysis of error patterns revealed no significant difference between the MND participants' ability to recognise substitution differences and transposition differences, however there was a trend towards a greater number of errors identifying transposition differences (T = 10, p =.052). The control group however showed no significant difference in their ability to recognise substitution differences and transposition differences (T = 7, p = .891).

Within group analysis of the number of word versus nonword errors revealed that both controls (T = 0, p = .023) and MND participants (T = 10, p = .017) made significantly more errors when the pairs were nonwords than when they were words. However, within group analysis of the number of word versus nonword false negative errors (i.e. identifying pairs as different when they were the same) revealed that while MND participants made significantly more errors with nonword pairs than word pairs ($T = 0$, $p = .014$), control participants showed no significant difference in performance ($T = 0$, $p = .083$).

Friedman tests for within group comparisons of the number of errors made when differences in pairs were in the initial, medial and final positions revealed no significant effect of position on performance for either the MND group ($\chi^2(2) = 0$, $p = 1.00$) or control group ($\chi^2(2) = .500$, $p = .779$).

3.2.1.1.3.2 Spelling Verification Test

Overall MND participant scores on Spelling Verification Test (Mean 69.40; Median 71) were significantly worse than controls (Mean 71.64; Median 72) ($U = 178.5$, $z = -2.985$, $p = 0.003$).

On breakdown of error patterns (see Table 3.5) there was no significant difference between the number of correctly spelled written words and fillers judged as spelled incorrectly (i.e. false negative) by MND participants and controls, however there was a strong trend towards MND participants identifying more correctly spelled words as incorrect than controls ($p = .05$). MND participants did make significantly more errors identifying both phonologically plausible and phonologically implausible nonwords as being correctly spelled, than controls. There was no significant difference between the number of errors made by MND participants and controls when the spoken target was a high predictability – high frequency (HPHF) word. However MND participants made significantly more errors than controls when the spoken target word was a high predictability – low frequency (HPLF), low predictability – high frequency (LPHF) or low predictability – low frequency (LPLF) word.

Variable	MND (n 25)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Correct Word (inc. fillers) (36)	0.64	0.995	0-3	0.24	0.831	0-4	U = 237.000, z = -1.959, p = .050
Similar Word (12)	0.16	0.62	0-3	0.04	0.20	0-1	U = 299.5, z = -.613, p = .540
Phonologically Plausible (12)	1.28	1.99	0-6	0.00	0.00	0	U = 200, z = -3.259, p = .001*
Phonologically Implausible (12)	0.52	0.82	0-3	0.08	0.28	0-1	U = 222, z = -2.432, p = .015*
HPHF (18)	0.640	1.350	0-6	0.640	0.000	0-2	U = 248.5, z = -1.717, p = .086
HPLF (18)	0.640	0.860	0-6	0.120	0.440	0-2	U = 201, z = -2.816, p = .005*
LPHF (18)	0.600	0.957	0-3	0.080	0.277	0-1	U = 231.5, z = -2.253, p = .024*
LPLF (18)	0.760	1.090	0-4	0.000	0.000	0	U = 187.5, z = -3.478, p = .001*

Table 3.5: Comparison of number of errors, according to subtype, made by MND patients & controls on the Spelling Verification Test
HPHF = High Predictability, High Frequency; HPLF = High Predictability, Low Frequency; LPHF = Low Predictability, High Frequency; LPLF = Low Predictability, Low Frequency

Wilcoxon signed ranks test of within group comparison for error patterns revealed MND participants were significantly worse at rejecting phonologically plausible nonword stimuli than phonologically implausible nonword stimuli (T = 5, p = .012). The control group however showed no significant difference in their ability to reject phonologically plausible or phonologically implausible nonword stimuli (T = 0, p = .157).

To assess the effect of predictability/regularity, within group comparison of MND participants' errors on high predictability - high frequency (HPHF) targets against low predictability – high frequency (LPHF) targets was conducted in order to minimise the effect of frequency differences. Wilcoxon signed ranks test revealed no significant difference between errors made with HPHF targets and LPHF targets in the MND participant group (T = 21, p = .852), suggesting no effect of predictability/regularity. There was also no significant difference between errors made with the same targets in the control group (T = 2.5, p =.317), again suggesting no effect of predictability/regularity.

To assess the effect of frequency, within group comparison of MND participant errors on high predictability – high frequency (HPHF) targets against high predictability – low frequency (HPLF) targets was conducted in order to minimise the effect of predictability differences. Wilcoxon signed ranks test revealed no significant between errors made with HPHF targets and HPLF targets in the MND participant group T = 31, p = .516, suggesting no effect of frequency. There was also no significant difference between errors made with the same targets in the control group T = 2, p = .564, again suggesting no effect of frequency.

3.2.1.1.4 Prosody: PEPS – C

There was no significant difference in the performance of MND participants and controls when identifying differences in prosody without phonetic or emotional information (the intonation condition). There was also no significant difference in the performance of MND participants and controls in perception of questioning versus declarative intonation. However MND participants were significantly worse than controls in perceiving differences in affective prosody (see Table 3.6).

Friedman test of within group analysis revealed that there was no significant difference between the scores on perception of affective, intonation and turn-end type prosody made by controls ($\chi^2(2) = 2.141$, p = .343). There was also no significant difference between the scores on perception of affective, intonation and turn-end type prosody made by MND participants ($\chi^2(2) = 4.373$, p = .112).

Variable	MND (n 18)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
PEPS Affect (16)	13.67	2.30	8-16	15.40	0.91	13-16 (3)	U = 106, z = -3.113, p = .002*
PEPS Intonation (16)	14.50	1.43	11-16	14.88	1.17	12-16 (4)	U = 190, z = -.896, p = .370
PEPS Turn-End Type (16)	13.78	3.14	6-16	15.28	1.06	12-16 (4)	U = 174, z = -1.359, p = .174

Table 3.6: Comparison of total scores for MND participants and controls on PEPS-C perception of affective, intonation and turn-end type prosody

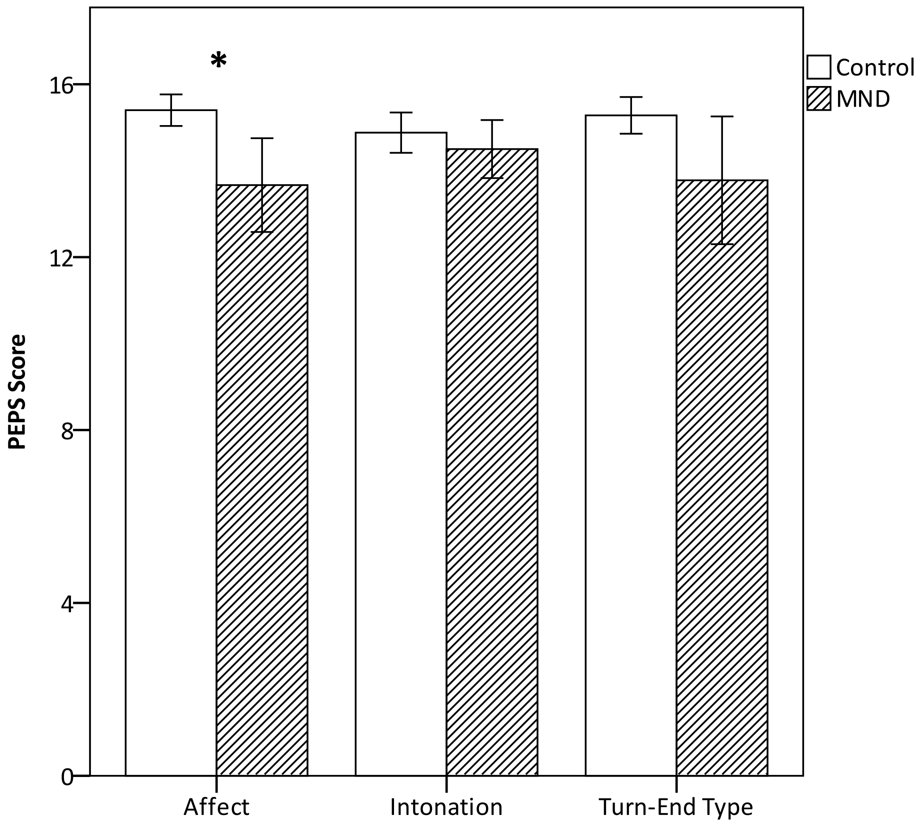


Figure 3.7: Total scores for MND participants and controls when perceiving differences in affect, intonation, and turn-end type prosody - * indicates significance (p<.05)

3.2.1.2 Bulbar Onset vs Non-bulbar Onset

Subdivision of the MND group into bulbar and non-bulbar onset groups revealed the following:

3.2.1.2.1 Naming

There was no significant difference in naming between the bulbar and non-bulbar onset groups on performance using the GNT. However performance on the Northwestern Naming Test was significantly worse in the bulbar onset group than the non-bulbar onset group. When the NNT scores were divided into noun and verb scores it revealed that while there was no significant difference in performance between the bulbar and non-bulbar onset groups on noun naming, the bulbar onset group was significantly worse than the non-bulbar onset group in verb naming (see Table 3.7 and Figure 3.8). This suggests that the significant difference in overall performance between the two onset groups can be attributed to differences in verb naming ability.

Variable	Bulbar Onset			Non-bulbar Onset			Statistics
	Mean	SD	Range	Mean	SD	Range	
GNT (30)	18.82 (n 12)	6.145	7-28	23.22 (n 9)	3.073	19-27	t = -1.996, p = .060
Northwestern Naming (32)	30.45 (n 13)	1.809	26-32	31.89 (n 10)	0.333	31-32	U = 23.500, z = -2.855, p = .004*
NNB Nouns (16)	15.54 (n 13)	0.776	14-16	15.9 (n 10)	0.316	15-16	U = 50.500, z = -1.249, p = .212
NNB Verbs (16)	14.62 (n 13)	1.609	11-16	16 (n 10)	0	0-0	U = 25.000, z = -2.925, p = .003*

Table 3.7: Comparison of total scores for bulbar non-bulbar onset MND participants on naming measures, followed by noun and verb subscores for Northwestern Naming Test

Wilcoxon signed-rank test of within group comparison revealed that those with bulbar onset MND scored significantly lower on the number of verb items named correctly, in comparison to the number of nouns (T = 5, p = .035).

However, there was no significant difference in the number of verb and noun items named correctly by the non-bulbar onset group (T = 0, p =.317).

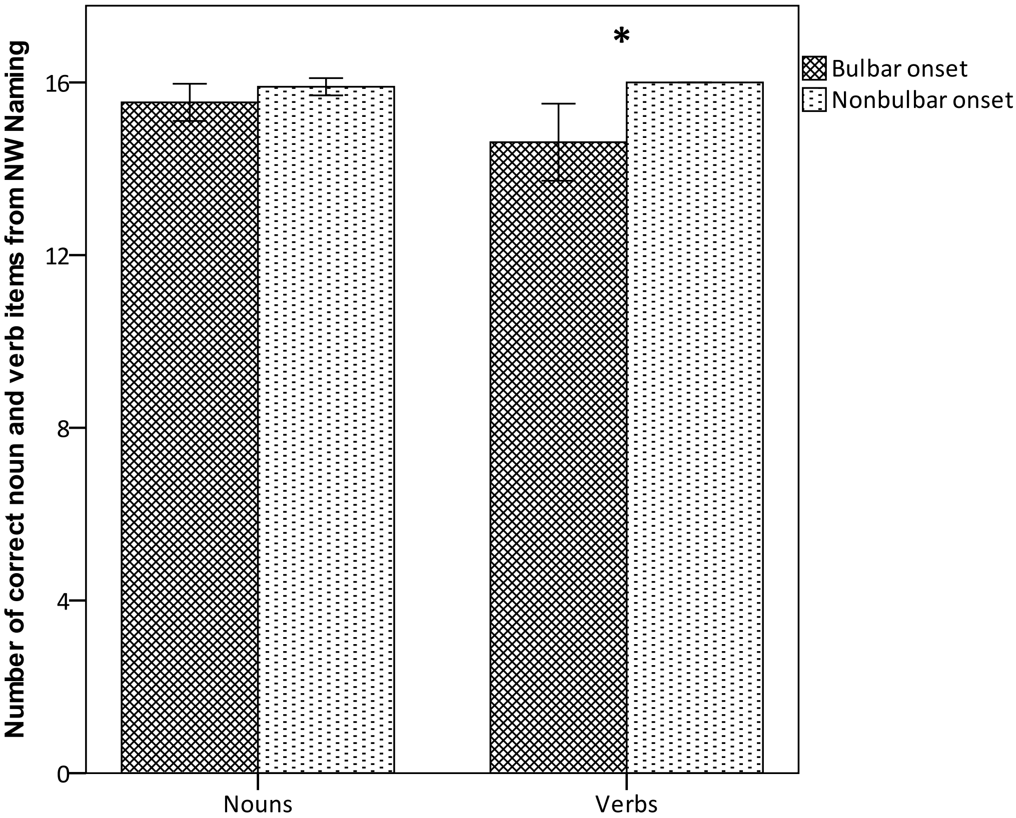


Figure 3.8: Comparison of total scores for bulbar and non-bulbar onset MND participants for noun and verb items named correctly on the Northwestern Naming Test - * indicates significance (p<.05)

3.2.1.2.2 Grammatical Comprehension

There was no significant difference in performance between the bulbar and non-bulbar onset groups on the TROG (see Table 3.8).

Variable	Bulbar Onset			Non-bulbar Onset			Statistics
	Mean	SD	Range	Mean	SD	Range	
TROG (40)	35.93 (n 15)	3.432	28-40	37.90 (n 10)	1.729	35-40	t = -1.889, p =.072

Table 3.8: Comparison of total scores for bulbar and non-bulbar onset MND participants on the TROG

3.2.1.2.3 Reading

There was no significant difference in performance between the bulbar and non-bulbar onset groups on the Letter Strings Discrimination Test (see Table 3.9). There was also no significant difference in performance between the bulbar and non-bulbar onset groups on the Spelling Verification Test.

Variable	Bulbar Onset			Non-bulbar Onset			Statistics
	Mean	SD	Range	Mean	SD	Range	
LS (48)	46.53 (n 15)	2.031	40-48	46.80 (n 10)	2.486	40-48	U = 56.00, z = -1.117, p = .264
SVT (72)	68.67 (n 15)	3.498	62-72	70.50 (n 10)	2.953	64-72	U = 43.500, z = -1.829, p = .067

Table 3.9: Comparison of total scores for bulbar and non-bulbar onset MND participants on the Letter Strings Discrimination and Spelling Verification Tests

3.2.1.2.4 Prosody

There was no significant difference in performance between the bulbar and non-bulbar onset groups on any of the three prosody conditions (see Table 3.10).

Variable	Bulbar Onset (n 12)			Non-bulbar Onset (n 6)			Statistics
	Mean	SD	Range	Mean	SD	Range	
PEPS Affect (16)	13.67	2.674	8-16	13.67	1.506	12-16	U = 30.000, z = -.582, p = .561
PEPS Intonation (16)	14.42	1.621	11-16	14.67	1.033	13-16	U = 34.500, z = -.145, p = .884
PEPS Turn-End Type (16)	13.58	2.778	8-16	14.17	4.021	6-16	U = 25.000, z = .279, p = .279

Table 3.10: Comparison of total scores for bulbar and non-bulbar onset MND participants on perception of affective, intonation and turn-end type (linguistic) prosody

3.2.2 Individual Patient Characteristics

As in chapter 2, the performance of individual MND participants was compared against the control group mean using z-scores. Z-scores were calculated by subtracting the control mean from each individual patient score and dividing by the control group standard deviation (SD). Performance on measures was taken to be impaired where the z-score fell 2 or more below the control mean, that is, a z-score of ≤ -2.

Table 3.11 shows individual scores for MND participants on standard linguistic measurements. Out of all 25 participants only 5 were not impaired on any standard linguistic measure (L120, L121, G97, L146 and L903), of which 2 (L120 and L121) did not complete every assessment, suggesting widespread linguistic impairment across the MND group. Conversely only 1 participant was impaired on 100% of the assessments completed (L901), and only 3 were impaired on all but one of the assessments they completed (L107, L904 and L900).

3.2.2.1 Motor Speech Assessment

Nine participants had mild dysarthria, 5 had moderate dysarthria, 4 had severe dysarthria and 7 were anarthric, communicating via an alternative communication method including handwriting, alphabet chart or text to speech voice output communication aid (VOCA) (e.g. Lightwriter or communication aid app on an iPad). Predominant features included harsh voice quality, slow rate of speech, hypernasality and severely distorted consonants. The dysarthria severity of each participant was rated using the following scale: anarthria = 4; severe dysarthria = 3; moderate dysarthria = 2; mild dysarthria = 1. When this scale was compared to the bulbar subscore of the ALSFRS (see Chapter 2), dysarthria severity was significantly related to lower bulbar ALSFRS subscores, (τ = -.59, p (one-tailed) <.001).

	Onset site	Dysarthria	GNT	NNT	NNT N	NNT V	SVT	LSD	TROG	PEPS A	PEPS I	PEPS T
L120	UL	Mod-severe spastic	DNC									
L125	UL	Mild flaccid										
L161	UL	Mild mixed								DNC	DNC	DNC
G102	UL	Mild mixed								DNC	DNC	DNC
L51	LL	Anarthric										
L46	LL	Anarthric										
L121	LL	Mild flaccid								DNC	DNC	DNC
G91	LL	Mild mixed										
L174	LL	Mild mixed								DNC	DNC	DNC
L176	LL	Mild flaccid										
G97	bulbar	Moderate spastic										
G100	bulbar	Anarthric	DNC									
L107	bulbar	Anarthric	DNC							DNC	DNC	DNC
L54	bulbar	Anarthric										
L146	bulbar	Mild mixed										
L171	bulbar	Severe mixed										
G92	bulbar	Mild mixed										
L165	bulbar	Severe spastic										
L169	bulbar	Anarthric										
G118	bulbar	Moderate mixed										
L902	bulbar	Mild spastic										
L903	bulbar	Moderate mixed										
L904	bulbar	Anarthric										
L901	bulbar	Mild-mod mixed		DNC	DNC	DNC				DNC	DNC	DNC
L900	bulbar	Mod-severe mixed	DNC	DNC	DNC	DNC				DNC	DNC	DNC

Table 3.11: Table of impairment for MND participants on standard linguistic measures
DNC = Did not complete; = ≥2 SD below control mean; = ≥ 3 SD below control mean. GNT = Graded Naming Test; NNT = Northwestern Naming Test (N = Nouns; V = Verbs); SVT = Spelling Verification Test; LSD = Letter Strings Discrimination Test; TROG = Test of Reception of Grammar; PEPS = Profiling Elements of Prosodic Systems (A = Affect; I = Intonation; T = Turn End Type)

Accurate assessment of apraxia of speech proved difficult and only five of the participants were able to complete the apraxia screen without significant influence of physical impairment. For this reason analysis was not conducted on the limited data collected. Those that did complete the assessment showed no evidence of limb, nonverbal oral apraxia or apraxia of speech, and there were no overt signs of such difficulties in any of the MND participants in this study.

3.2.2.2 Naming

Ten of the twenty-one MND participants who completed the GNT performed at least 2SD below the control mean, representing a 47.6% impairment rate. Six of the ten performed ≥2SD below the control mean, while the other 4 performed ≥3SD below the control mean. All 4 who were ≥3SD below the control mean on the GNT belonged to the bulbar onset group (see Table 3.11). Six of the 23 MND participants who completed the NNT (26%) performed ≥3SD below the control mean. All who completed the NNT and were impaired on the GNT were also impaired on the NNT, except for one participant (L169), who only made verb errors on the NNT. As there are no verb items on the GNT, this could suggest a specific verb naming deficit for this particular participant. Interestingly, all those impaired on verb naming were in the bulbar onset group. Also of interest was that of the 8 people impaired on either noun or verb naming , only two were impaired on both noun and verb naming, indicating noun/verb dissociations for the 6 other participants. Of those impaired on noun naming, all errors were from the fruit and vegetable category except one participant (G91) who made an error on one item from the tool category naming ‘mop’ for ‘broom’.

3.2.2.3 Grammatical Comprehension

Thirteen of the 25 MND participants performed at least 2SD below the control mean on the TROG, representing a 52% impairment rate. More participants were impaired on the TROG than any other standard linguistic measure making it the most sensitive measure of linguistic impairment. Three participants scored ≥2SD below the control mean, while the remaining 10 participants were at least 3SD below the control mean (see Table 3.11)

3.2.2.4 Reading

Only two participants (L176 and L901) were impaired on the Letter Strings Discrimination Test. Nine of the 25 MND participants (36%) were impaired on the Spelling Verification Test suggesting that not only is the SVT more sensitive to reading impairments in MND, but that deficits are more likely to be at a more central lexical level than at the level of visual orthographic analysis. Of the 9 participants impaired on the SVT, 6 identified ≥25% of phonologically plausible nonwords as correctly spelled real words (see Table 3.12). This also supports the suggestion that the reading impairment observed in these MND participants may be a more central type dyslexia than a peripheral one.

	Phonologically Plausible Nonwords	Phonologically Implausible Nonwords
L46	50	8.3
L176	25	8.3
L107	16.7	8.3
L54	8.3	0
L165	33.3	8.3
L169	33.3	16.7
L904	0	0
L901	41.7	16.7
L900	41.7	25

Table 3.12 Percentage of phonologically plausible and phonologically implausible nonwords identified as words by those MND participants impaired on the SVT

3.2.2.5 Prosody

Nine of the 18 participants who completed the PEPS (50%) were impaired on the perception of affective prosody. Five participants (27.7%) were impaired on the perception of turn-end type prosody, distinguishing questions from statements. However only one participant (L904) was impaired on discrimination of intonation without linguistic or affective information, suggesting that for most participants, impairment on affective and linguistic prosody was not due to a deficit in auditory analysis but rather in the attribution of meaning to prosody.

3.3 Discussion

3.3.1 Motor Speech

The dysarthria seen in the participants in this study was not only in keeping with the dysarthria reported in the literature, but also reflected the variability of motor speech symptoms throughout disease progression, due to the mixed spastic-flaccid presentation. As an inclusion criteria of this study, all participants had some degree of dysarthria, with 7 of the 25 participants classed as anarthric and reliant on AAC as their main method of communication. The design of the linguistic assessments used in this study allowed for examination of language functioning without influence of dysarthria.

However, this study highlights the difficulty of distinguishing the presence of apraxia of speech when dysarthria or anarthria is the predominant motor speech characteristic. While there were no overt signs of apraxia of speech in any participants, the strong influence of dysarthria and neuromuscular weakness upon performance on the apraxia screening test meant that results could not be accurately reported or analysed. Duffy comments that distinguishing dysarthrias from apraxia of speech is most difficult when attempting to establish if both AOS and dysarthria are present simultaneously (J.R. Duffy, 2005). In order to assist separation of disorders he suggests examining the localization, etiologic, oral mechanism, and speech characteristics of AOS and dysarthria. Duffy comments that assessing for the presence of nonverbal oral apraxia (NVOA), a positive oral mechanism finding in AOS, can be very useful in distinguishing dysarthria from AOS. However, assessing NVOA in people with severe dysarthria poses difficulty. Tasks recommended for assessing NVOA, as used in this study, require good strength and range of movement of the articulator muscles (e.g. puff out your cheeks, lick you lips), which often result in slow, off-target realisations where neuromuscular disturbances occur. In addition, spastic dysarthria, often exhibited as part of a mixed dysarthria presentation in people with MND shares many speech characteristics with AOS, including slow rate, excess and equal stress, monopitch and monoloudness. In addition, other characteristics commonly associated with AOS such as poorly sequenced sequential motion rates (e.g. repetition of /pətəkə/), distorted substitutions and increased errors with increased length may also be affected by neuromuscular features such as poor breath control and reduced tongue movement. Indeed some features particular to mixed spastic flaccid dysarthria such as prolonged intervals, prolonged phonemes, inappropriate silences, vowel distortions and irregular articulatory breakdowns as reported by Darley and colleagues (Darley et al., 1969a; Darley, Aronson, & Brown, 1969b), are also features associated with AOS, but not spastic or flaccid dysarthria in isolation, and it is some of these features which Duffy and colleagues report as evidence for AOS in MND (J. R. Duffy et al., 2007). It is questionable therefore whether AOS is in fact a distinguishing feature of MND, or whether features that have been reported as evidence for AOS could actually be attributed to dysarthria. In addition it is uncertain what percentage of patients with MND are likely to have symptoms of AOS as the patients reported on in Duffy's study were taken from a pool of patients with progressive AOS symptoms between 1995 and 2003, and not specifically an MND population (J.R. Duffy, 2006). When it is considered that the 7 patients reported on in Duffy's study were spread across an 8 year period, it is unsurprising that the MND participants in this study did not demonstrate any signs of AOS. Further research, designed to specifically minimise the impact of dysarthria on assessment performance is required in order to shed more light on this question.

3.3.2 Naming

That impaired performance could be attributed to dysarthria cannot readily be said for MND participant results on the naming tests used in this study. As nonverbal responses, i.e. through writing or communication aid, were accepted, the physical impact of dysarthria upon responses was negated. Furthermore both the error patterns seen within each naming test, and the dissociation between the different naming test performances could not be accounted for by motor speech difficulties. While there was no significant difference between MND participants and controls on overall performance on the Northwestern Naming Test, MND participants were significantly worse than controls on naming using the GNT. This suggests that the GNT is more sensitive to the naming deficits seen in MND, as suggested by Cobble (Cobble, 1998). As the GNT is graded by frequency and the Northwestern Naming Test is not, this could suggest that there may be a frequency effect. Effects of frequency in naming ability have been attributed to semantic deficits (Hodges, Patterson, Oxbury, & Funnell, 1992), access of semantics to the phonological output lexicon (Barry, Morrison, & Ellis, 1997), and the phonological output lexicon itself (Howard, 1995).

While it is difficult to suggest from the results of these assessments what the likely location of impairment is, word class analysis of errors on the Northwestern Naming Test may contribute to the picture of impairment. While there was no significant difference in verb naming between patients and controls, MND participants were significantly worse than controls when naming nouns, specifically fruit and vegetables. However, subdivision of the MND participants into bulbar and non-bulbar onset groups revealed that the bulbar onset participants were significantly worse than the non-bulbar onset participants at naming verbs. This discrepancy in performance patterns could indicate that there are in fact two different language profiles with regards to naming. On testing of the Northwestern Naming Test with a group of primary progressive aphasic patients, Thomson and colleagues found that while agrammatic (or nonfluent) aphasic participants were significantly worse at naming verbs over nouns, those with the semantic variant were worse at naming nouns over verbs (C. K. Thompson et al., 2012). It could be suggested therefore that as MND participants as a group were worse at naming nouns than controls, there may be some impairment at the level of the semantic system, akin to that seen in semantic dementia. However, the within group trend towards greater impairment naming verbs over nouns, and the significantly worse performance naming verbs in the bulbar onset subgroup could indicate an impairment at the lexicon level, or access to it, as suggested in nonfluent primary progressive aphasic patients (Hillis, Tuffiash, & Caramazza, 2002). The within group trend towards greater impairment in naming verbs is also in keeping with previous findings of verb naming deficits in MND (T. Bak & Hodges, 1997; T. H. Bak et al., 2001; Grossman et al., 2008). The fact that the majority of naming tests that have previously been used to detect naming impairments in MND patients, including the GNT and the Boston Naming Test, do not include verbs means that there may be a subset of linguistically impaired individuals, such as participant L169, who are not being detected.

3.3.3 Grammatical Comprehension

The TROG was the most sensitive standard linguistic assessment, with 52% of participants performing at least 2SD below the control mean. This high level of impaired performance is in keeping with reports from the literature (T. H. Bak et al., 2001). Furthermore, the block error pattern is also similar to that reported by Bak and colleagues, with the greatest number of errors being produced in blocks R, relative clauses, and T, embedded sentences. When it is considered that both the sentences in blocks R and T can be read as forms of embedded sentence (block R – right embedded; block T centre embedded), then it easy to see why the pattern of performance in these blocks is similar. However, what is not clear is why for similarly complex sentences such the relative clauses of block N (e.g. the circle in the star is yellow) there was no significant difference in performance between MND participants and controls, while MND participants performed significantly worse than controls understanding the relatively simple sentences in block K (e.g. the knife is longer than the pencil). One argument for this apparently anomalous result could be that as it is the first block presented, the poorer performance could be attributed to participants becoming accustomed to the test administration process. As a flaw of this test, participants were not presented with practice items, so this explanation is possible, particularly when it is considered that there were only 5 errors made in this block by the entire MND group, and 60%

of these errors were on the very first question. However if this is the reason for reduced performance in the first block, there is a question as to why this same pattern was not seen in controls.

3.3.4 Reading

The letter strings discrimination and spelling verification tests used in the study, while not extensive enough to examine all aspects of reading, do provide interesting insights into the written word processing abilities of our MND participants. There was no significant difference in the ability of MND participants and controls to discriminate if strings of letters were the same or different as tested through the letter strings discrimination test. This suggests that the visual orthographic analysis process is intact in our MND participants. However further consideration can be given to this result. One control participant incorrectly identified all pairs where the difference was a transposition of letters as being the same. It is unclear as to the reason for this anomalous result as the participant performed accurately in practice items, and they displayed no impairment on any other test in the study. In addition the test was performed again in the second testing session to ensure participant had understood instructions, yet the pattern of performance remained exactly the same.

Although there was no significant difference between patients and controls in identifying differences in nonword pairs, this may be affected by the anomalous control performance. Within group analysis revealed that both the MND participants and controls had greater difficulty perceiving differences between nonword pairs than word pairs. However within group analysis also revealed that only the MND group made significantly more nonword false errors than word false errors, i.e. identifying pairs as different when they were the same. While decisions to the word pairs need not be made by examining each item letter by letter and can be based on knowledge that items are different words or the same, decisions about nonword pairs cannot be assisted by lexical information. This could suggest that MND participants have greater difficulty when there is lack of lexical/semantic information to support the visual orthographic analysis process and analysis has to be made purely on the basis of orthographic information. However, overall there was no significant difference between patients and controls, and on individual analysis only two participants were impaired on the letter strings discrimination test – these participants will be discussed in greater detail and in relation to their performance on other measures in chapter 5.

The spelling verification test also identified particular difficulty analysing nonwords. MND participants were significantly worse than controls at identifying whether words were spelled correctly or not. To perform this task, participants need to have intact access to the orthographic and phonological input lexicons. Although there was no significant difference between MND participants and controls in the ability to identify correctly spelled words, MND participants were significantly worse than controls at rejecting phonologically plausible nonwords. In addition, within group comparison revealed that MND participants were significantly worse at rejecting phonologically plausible nonwords than phonologically implausible ones. This pattern is suggestive of a deficit at the level of the orthographic input lexicon, and a reliance on the orthographic to phonological processing mechanism. Graham and colleagues identified a markedly poor ability to reject phonologically plausible nonwords, accompanied by a high proportion of phonologically plausible spelling errors in semantic dementia patients (N. L. Graham et al., 2000). They argue that impaired semantic representations impact upon the accurate activation of orthographic representations, and there is a reliance on phonological information via the orthographic to phonological conversion route for lexical decision making tasks. With this hypothesis in mind, it is interesting to note that all but one of the 6 participants who identified ≥25% of phonologically plausible nonwords as correctly spelled real words were also impaired on at least one of the naming measures. However, MND participants were also significantly worse than controls at rejecting phonologically implausible nonwords, suggesting that there may also be some level of phonological impairment impacting on the lexical decision making abilities of some participants. The plausibility of errors will be further considered when examining spelling to dictation performance in chapter 4.

3.3.5 Prosody

The PEPS-C was another particularly sensitive test used in this study. Of particular interest was the dissociation in performance on the three subtests. While there was no significant difference in performance between MND participants and controls in perception of linguistic based prosody, or in the discrimination of intonation patterns without meaning, MND participants were significantly worse at perceiving and understanding affective prosody. These results support the findings of Meier and colleagues (Meier et al., 2010) which they attribute to impaired functioning of the orbitomedial prefrontal cortex. The lack of impairment discriminating non-linguistic intonation patterns suggests that impairment is rooted not in the acoustic features of intonation, but in the ability to infer meaning from prosody. However, unlike the non-fluent primary progressive aphasia patients studied by Rohrer and colleagues (Rohrer et al., 2012), the MND participants, as a group, were not significantly worse than controls discriminating between question and statement prosodic patterns. This suggests that the prosodic impairment seen in the MND participants in this study is not due to a general impairment in the ability to infer meaning from prosody, but in the interaction of prosody with emotional processing and social cognition.

Chapter 4: Experimental Linguistic Assessment

This chapter outlines the experimental linguistic assessments used in this study, focussing on the phonological and orthographic skills of MND participants. As discussed in chapter 1, while writing errors have been reported in MND patients as early as 1893 (Ichikawa, Miller, et al., 2011), dysgraphia has only really been investigated as a linguistic rather than motoric impairment in MND patients in any depth in the last ten years. As dysarthria severity increases and speech intelligibility decreases during disease progression, many patients rely on writing as their main method of communication, and it is at this point that spelling errors are often noticed. Yet errors can often be dismissed as a result of fatigue or fine motor weakness, and this may account for relatively limited research in this area. For example Cobble reported evidence of spelling errors, consisting of missed or repeated letters, in two out of the nine MND patients tested in her study, however she concluded that these errors were “likely to be associated with upper limb weakness affecting motor movements for writing rather than due to a language processing deficit” (Cobble, 1998). However, if we consider the cognitive processes through which a word is written to dictation, it becomes apparent, particularly in the light of increasing evidence of other linguistic impairments, that there is potential for these errors to be attributable to a more central deficit.

4.1 Cognitive neuropsychological model of language processing

Figure 4.1 illustrates the language processing model for single words, based on Patterson and Shewell’s (K. E. Patterson & Shewell, 1987) adaptation of the logogen model. The left hand side of the model relates to spoken to communication, while the right hand side relates to written communication. When a word is spelled to dictation, once it has been processed by peripheral functions of the auditory system it will be broken down into its phonological components through **auditory phonological analysis**. This string of

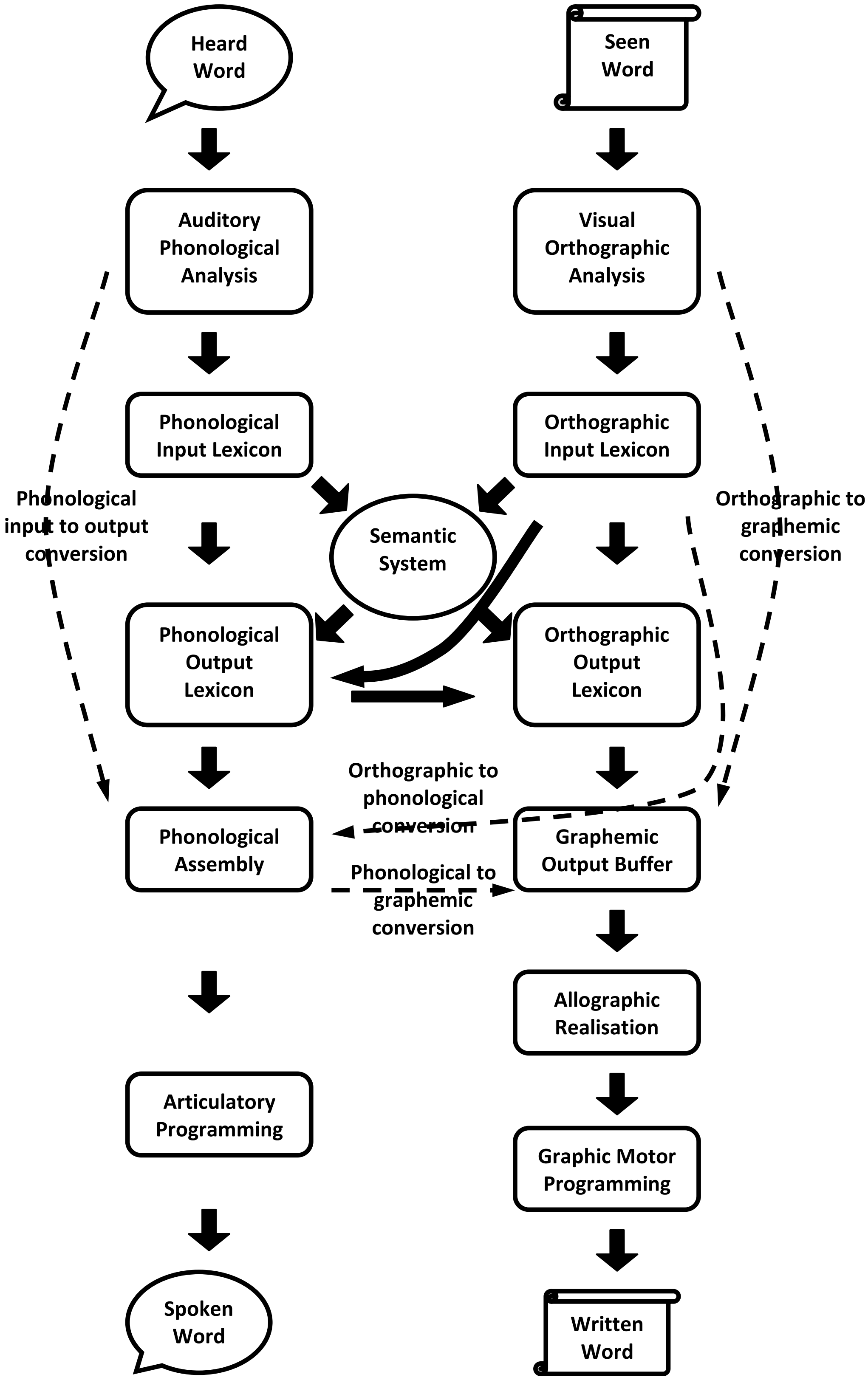


Figure 4.1: Language processing model for single words (K. E. Patterson & Shewell, 1987)

phonological components will then be analysed in the **phonological input lexicon** to determine if they are in fact a word and which word they correspond to. Next this information passes to the **semantic system** where word meaning is activated in response to word recognition. As this is the most central process of the model, an impairment at this level will most often have an impact on both receptive and expressive communication, and across all modalities. From this point, the production of the written word can begin – indeed when words are written spontaneously, they originate straight from the semantic system.

When writing words to dictation, there are three processing routes that can be taken: semantic lexical; sub-lexical; and direct lexical. When using the semantic lexical route, access to the meaning of the word is required from the semantic system, followed by retrieval of the written word from the **orthographic output lexicon**. The semantic lexical route is the usual spelling method and requires the dictated stimuli to be understood as a concept. The sub-lexical route however does not require understanding of the dictated word as it bypasses both the lexical and semantic systems, using the **phonological to graphemic conversion** process instead. Dictated stimuli are processed directly from auditory phonological analysis through **phonological input to output conversion** to **phonological assembly**. This phoneme string is then translated to graphemes and onto the graphemic output buffer. The sub-lexical route is usually that used for spelling unfamiliar or nonwords, but may allow for accurate word spelling to dictation in the presence of an impaired semantic system. The semantic system can also be bypassed using the direct lexical route: the word's phonology is retrieved from the **phonological output lexicon**, which then activates the orthographic form within the orthographic output lexicon. However, as only real words are represented within the phonological and orthographic output lexicons, this route cannot be used for nonwords.

Regardless of the spelling route, all words are then processed via the **graphemic output buffer**. This working memory type component temporarily stores information about the graphemic representation of words until they are transcoded into their output form (i.e. typing, print, cursive). As the graphemic output buffer is a post-lexical component, an impairment at this level should have an effect on all methods of writing, regardless of spelling route (semantic lexical, sub-lexical or direct lexical) or any lexical or semantic variables (i.e. word frequency, imageability, grammatical class, lexicality). These graphemic representations are then mapped into their **allographic realisations**, giving information about the physical form of the letters specified from the orthographic buffer (Margolin, 1984). Finally allographic realisations are translated into the motor patterns required to form the letters and the spelling process is complete. It should be noted however that the model outlined in Figure 4.1 cannot account for oral spelling. Margolin (ibid) proposes that following the graphemic output buffer the system splits in two forming a route for written spelling as previously described and a route for oral spelling, whereby the allographic realisation and graphic motor programming processes are represented by oral counterparts of letter name realisation and articulatory motor programming respectively.

When viewed in these terms, evidence of dysgraphia in people with MND provokes cause for further investigation. To attribute the types of spelling errors reported to date solely to the most peripheral level of the model is to ignore evidence suggesting involvement at more central levels. For example, if dysgraphia in MND patients is merely an issue of upper limb weakness as Cobble suggests (Cobble, 1998), how does this account for the insertion of letters in some target realisations produced by her subjects, thus producing longer words and requiring more physical effort than if the word was spelled correctly? This pattern of extraneous or equal effort spelling errors has also been reported in Italian MND patients with evidence of addition, transposition and substitution of letters (Lucchelli & Papagno, 2005; Zago et al., 2008) while Japanese patients have been documented making morphological errors through the addition of kana components when writing kana letters (Ichikawa, Takahashi, et al., 2008). Furthermore, what do these spelling errors suggest about the integrity of the rest of the language processing system? The interconnection of the lexical and semantic processes required for written and spoken word production could mean that, dependant on the location of the impairment, the errors seen in spelling could also reflect an impairment affecting spoken word production previously masked by dysarthria. The experimental assessments outlined in this chapter aimed to explore the spelling abilities of people with MND and what the results suggest about the integrity and contribution of phonological and orthographic processes to written word production.

4.2 Selection of Materials and Methods

4.2.1 Minimal Pair Discrimination

As one of the aims of this study was to investigate the integrity of phonological processing abilities of our MND participants, assessing receptive as well as expressive skills was important. Not only does such assessment give an idea of overall phonological awareness, but also normal performance enables us to discount any influence of auditory phonological analysis impairment impacting upon other assessments requiring auditory stimuli, particularly spelling to dictation. As auditory phonological analysis is a more peripheral input process, an impairment at this level will have a profound effect on all stages of auditory verbal comprehension (see Figure 4.1). It is this process in the system that identifies acoustic signals as speech sounds, or phonemes, and attaches the first level of linguistic information to the spoken message. A deficit at this level has been referred to as 'word sound deafness' as sounds cannot be distinguished as belonging to words (Franklin, 1989).

Receptive phonological processing has, to the best of our knowledge, never previously been examined in people with MND. While much research has been conducted investigating receptive phonology in the stroke population (Caramazza, Berndt, & Basili, 1983; Franklin, 1989; Miceli, Gainotti, Caltagirone,

& Masullo, 1980), as Patterson and colleagues highlight, the pattern of impairment seen in people with aphasia of a progressive nature does not necessarily mirror that seen in stroke acquired aphasia (K. Patterson, Graham, Lambon Ralph, & Hodges, 2006). Research into the phonological processing skills of with people with progressive aphasia and semantic dementia has produced mixed results. Reilly and colleagues examined the effect of phonological processing skills on single word semantic judgements using a minimal pair judgement task (Reilly, Cross, Troiani, & Grossman, 2007). They found that those with milder semantic deficits performed worse on minimal pair discrimination than those with more severe semantic impairments. They suggest that this paradoxical trend could be as a result of a lexical density interference effects in those with residual lexical-semantic knowledge, while those with more severe semantic deficits have little lexical-semantic knowledge to cause these interference effects upon phonological perception. Another study examining the phonological awareness skills of people with non-fluent progressive aphasia (PNFA) found that while PNFA patients did show evidence of impairment on phoneme segmentation and blending and rhyme judgement tasks, these capacities were far better than those of a comparative stroke acquired non-fluent aphasic group (K. Patterson et al., 2006).

One of the most common tests used to assess the integrity of the auditory phonological analysis system is the minimal pairs discrimination test. This study adapted the word and nonword auditory discrimination minimal pairs tests from the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) (subtests 1 and 2) (Kay et al., 1992).

4.2.1.1 Word Minimal Pairs

In the word version of the assessment participants are presented with two real words and are asked to decide whether the two words are the same or different. The test consisted of 48 pairs in total (42 CVC, 6 CVCV), with 24 ‘same’ pairs and 24 ‘different’ pairs (see Appendix D). ‘Different’ pairs differed selectively by voice, place or manner of articulation distinctive features, and varied according to position of the difference either in the initial, medial (for CVCV words) or final position, or of a metathetic construction (e.g. dog – god). Variations in the position and distinctive features were distributed evenly throughout the test, resulting in 8 pairs of each distinctive feature difference, and 6 pairs of each positional difference. Items were recorded in a professional, isolated recording booth using a Shure SM7 cartoid pattern microphone. Stimuli was recorded by one female from the West coast of Scotland, and one male from the East coast of Scotland using a flat intonation pattern, so as not to give any prosodic cues about differences between items.

The recorded stimuli were inserted into a Powerpoint presentation with one pair of words per slide, represented on the screen by two speaker symbols and programmed to play with a 1 second interval between words. The order in which the pairs were presented was randomised when programming, however this order then remained identical for each participant. Pairs were alternately presented by the male and female voice, however the voice remained the same within a pair. The Powerpoint presentation was played via a Toshiba Portege M750-12F laptop, using Sennheiser HD 280 pro headphones and at a volume that was clear for the participant, in order to try and eliminate influence of background noise and achieve maximum clarity of item presentation.

Participants were presented with 3 practice items before moving on to the test items to ensure instructions had been understood. Participants were asked to respond either orally by saying 'same' or 'different', or by indicating to the words 'same' and 'different' on a board. The task did not require any verbal output, and indications as to judgements could be facilitated through the researcher if hand function was impaired, thus making the test easy to conduct with MND participants.

4.2.1.2 Nonword Minimal Pairs

In order to fully test the integrity of the auditory phonological analysis process, a nonword version of the minimal pairs assessment was also administered. As words are normally processed through the lexical-semantic route, weaknesses in the auditory phonological analysis process may be aided through intact lexical-semantic knowledge. This could result in misleading performance on word minimal pair discrimination, reflecting integrated lexical-semantic and phonological processing, rather than solely phonological analysis. As nonwords cannot be supported by lexical or semantic information, the nonword minimal pairs task, particularly in comparison to performance on the word version, could provide additional, more targeted information about phonological processing.

Programmed and presented in an identical format to the word minimal pairs assessment, the nonword version comprised 48 pairs (42 CVC, 6 CVCV), with 24 'same' pairs and 24 'different' pairs (see Appendix D). Again 'different' pairs varied selectively by voice, place or manner of articulation distinctive features, and varied according to position of the difference either in the initial, medial (for CVCV words) or final position, or of a metathetic construction (e.g. deg – ged). Variations in the position and distinctive features were distributed evenly throughout the test, matching with the word minimal pairs and resulting in 8 pairs of each distinctive feature difference, and 6 pairs of each positional difference.

4.2.2 Word Spelling

Another key aim of this study was to investigate the nature of spelling errors in people with MND and what they can tell us about language processing deficits in this population. While increasing evidence emerges of spelling errors produced by people with MND, little systematic research has been conducted to investigate the nature of these errors. A few clinical observations of written spelling errors exist (see chapter 1 and (Ichikawa et al., 2012) for review), predominantly from Japan, where dissociated impairment between kana and kanji letters have been reported (Ichikawa et al., 2010; Ichikawa, Miller, et al., 2011). As kana letters have a strict phoneme to grapheme relationship, and kanji letters convey meaning but with varying pronunciation, respective parallels can be drawn between phonologically mediated regular spellings and lexical-semantically mediated irregular spellings in alphabetic languages. Cases of both patients who produce errors in writing kana but not kanji (Ichikawa, Takahashi, et al., 2008) and those who produce errors writing kanji but not kana (Iroi et al., 2002) have been described, however the former is more commonly reported in MND patients. This could suggest that the spelling errors produced by people with MND could reflect a deficit in phonological processing, or in the conversion of phonemes to graphemes. Furthermore, it has been suggested that this dissociation of greater kana errors over kanji could also partly correspond to the verb-noun dissociation seen in some English speaking MND patients (Ichikawa et al., 2012).

Additional reports of spelling errors produced by people with MND in alphabetical languages suggest that there may be impairment at a more peripheral stage in the writing process. One of the earliest mentions of spelling errors in MND documented evidence of transposition, insertion and deletion of letters (Ferguson & Boller, 1977b). More recent studies have supported these findings, suggesting that this may indicate an impairment in the graphemic or phonological output buffer (Lucchelli & Papagno, 2005; Zago et al., 2008). Zago and colleagues (2008) and Lucchelli and Papagno (2005) suggest that written production is dependent on the subvocal articulatory rehearsal mechanism in the graphemic buffer, storing sequences of graphemes until production. They propose that as articulation is impaired in MND patients, this disrupts the ability to rehearse and then produce the correct string of graphemes causing errors characteristic of a graphemic buffer deficit such as omission, transposition and deletion of letters, word length effects, serial position effects and impairment across the output modalities (Caramazza & Miceli, 1990).

However if the spelling impairments seen in MND patients are attributable to the graphemic buffer, we would expect performance to be unaffected by variables such as frequency, regularity and word class. Therefore a graphemic buffer impairment could not account for the kana-kanji dissociation seen in Japanese MND patients. Furthermore other studies examining subvocal rehearsal in people with dysarthria have concluded that phonological coding and subvocal rehearsal can operate in the face of impaired articulation (A. D. Baddeley & Wilson, 1985; D. V. Bishop & Robson, 1989). Thus further examination into spelling impairment in MND is required in order to examine the prevalence and nature of these errors and what they can suggest about language impairment in this population.

Methods

To do this a novel spelling to dictation test was designed, examining the effects of word class, word length and subvocal rehearsal on spelling performance. 36 word items were selected from the CELEX English lexical database (Baayen, Piepenbrock, & Guilikers, 1995) via the University of Edinburgh qcel database retrieval program. Eighteen nouns and eighteen verbs were selected, with items varying in word length: 12 four letter words, 12 seven letter words and 12 ten letter words. Items were selected for their direct phoneme to grapheme relationship, thus controlling for regularity. Items were also matched as closely as possible for frequency according to the wordform COBUILD frequency per million recorded in the CELEX database. Items were split between three presentation conditions: immediate, delayed and delayed with articulatory suppression (described below) (see Appendix E). There was no significant difference in frequency for words between the immediate (mean CobMln 15.67), delayed (mean CobMln 14.33) and delayed with articulatory suppression conditions (mean CobMln 11.92) (χ^2 (2) = .038, p = .981). There was also no significant difference in frequency for 4 letter (mean CobMln 9.75), 7 letter (mean CobMln 15.25) and 10 letter (mean CobMln 10.75) words (χ^2 (2) = 3.548, p = .170). However nouns (mean CobMln 21.50) were significantly higher in frequency than verbs (mean CobMln 2.33) (U = 14.000, z = -4.713, p = .000).

Items were recorded by the same two Scottish English speakers and using the same recording methods described in the minimal pairs assessment. The recorded stimuli were inserted into a Powerpoint presentation with one word per slide, represented on the screen by a speaker symbol. The Powerpoint presentation was played via a Toshiba Portege M750-12F laptop, using Sennheiser HD 280 pro headphones and at a volume that was clear for the participant, in order to try and eliminate influence of background noise and achieve maximum clarity of item presentation. Items were alternately presented by the male and female voices, starting with 4 letter items and increasing to the 10 letter items.

The items were divided between three different presentation conditions: immediate, delayed and delayed with articulatory suppression. Each condition contained four 4 letter items, four 7 letter items and four 10 letter items (12 items in total), split equally between nouns and verbs, and presented in the same order to each participant. Each condition was preceded with three practice items. In the immediate condition participants were instructed to write each word immediately after hearing it. In the delayed condition participants were presented with the word item but instructed to wait until the next slide telling them to 'spell' appeared. This slide was programmed to appear after a 15 second delay, during which time participants were instructed to silently repeat the word over, thus using the phonological loop to preserve items until written. The delayed with articulatory suppression condition was programmed to run following the same procedure as the delayed condition, except during the 15 second delay participants were asked to quietly repeat the word 'the' over until the 'spell' slide appeared. In doing this participants were prevented from rehearsing the items and disrupting the phonological loop (Neath, 2000). It would be expected that if the spelling impairment was as a result of a deficit in the graphemic output buffer, and articulatory rehearsal is required to hold and manipulate information in this buffer, MND participants would perform best in the immediate condition, but with little difference in performance between the delayed and delayed with articulatory suppression conditions. Furthermore, it would also be expected that in the delayed with articulatory suppression condition control participants would perform similar to MND participants in the delayed condition, as reported by Luchelli and Papagno (2005).

Spellings were marked as either correct or incorrect, the latter labelled as misspelled words (MSW). Where MSW were deemed to be as a likely result of hearing error they were classed as 'correct'. Such MSW were all real words and classified on the basis of responses that were MSW differing by only one distinctive feature (e.g. 'drab' for 'grab') or where final plural 's' was omitted from the target, and that the same MSW had also been produced by control participants. Using these criteria 13 MSW produced by MND participants and 12 MSW produced by controls across all three conditions were discounted from error analysis and classed as correct. MSW were also categorised as 'orthographically plausible' or 'orthographically implausible' errors based on existent English orthography patterns (Rollings, 2004). Non responses (produced by one patient L901) were grouped into the orthographically implausible category. These categorisations were made by the researcher, a speech and language therapist, and also by two other raters; one another speech and language therapist, the other from a non-clinical background, educated to a postgraduate level. There was complete agreement between all three raters for categorisation of 93% of the MSW. Where there was a discrepancy in orthographic plausibility categorisation between the three raters, the majority decision was taken.

4.2.3 Nonword Repetition and Spelling

In order to distinguish phonological processing from lexical processing, a third experimental test was employed. Nonword repetition and spelling tests are frequently used to test the integrity of the phonological input to output conversion process employed in the sublexical repetition and spelling routes. As nonwords do not have lexical or semantic representations, they cannot be processed via the lexical route and therefore rely solely on phonology, and can therefore help dissociate between lexical-semantic and phonological word production deficits.

Originally designed as a nonword repetition test, this assessment was alternatively employed as a nonword spelling test with those participants whose dysarthria prevented them from repeating. Although nonword spelling and nonword repetition use different output processes, both use the same input process and both require intact phonological input to output conversion. The original aim of this assessment, as a repetition test, was to examine whether the phonological dysgraphia suggested by the reports of a selective deficit writing kana letters (Ichikawa, Takahashi, et al., 2008) and poor nonword spelling in PNFA patients (Sepelyak et al., 2011) could also be reflected in the nonword repetition skills of our MND participants. In doing this, results could suggest whether the reported phonological deficits also exist in spoken language, or whether they were more likely to be attributable to the phoneme to grapheme conversion process specific to writing.

Methods

Following the same format of the word spelling to dictation test, 36 items of varying phoneme length (12 four phoneme nonwords, 12 seven phoneme nonwords and 12 ten phoneme nonwords) were created, based on constructions retrieved from the ARC Nonword Database (Rastle, Harrington, & Coltheart, 2002) (see Appendix F). Items were recorded by the same two Scottish English speakers and using the same recording methods described in the minimal pairs and word spelling assessments. Items were presented with the same format and equipment used in the word spelling test, with items alternately presented by the male and female voices, starting with 4 phoneme items and increasing to the 10 phoneme items.

Again, items were divided between the three different presentation conditions used in the word spelling test: immediate, delayed and delayed with articulatory suppression. Each condition contained four 4 phoneme items, four 7 phoneme items and four 10 phoneme items (12 items in total), presented in the same order to each participant. Each condition was preceded with three practice items. In the immediate condition participants were instructed to repeat each nonword immediately after hearing it. In the delayed condition participants were presented with the nonword item but instructed to wait until the next slide telling them to 'repeat' appeared. This slide was programmed to appear after a 15 second delay, during which time participants were instructed to silently repeat the nonword over, thus using the phonological loop to preserve items until repeated. The delayed with articulatory suppression condition was programmed to run following the same procedure as the delayed condition, except during the 15 second delay participants were asked to quietly repeat the word "the" over until the 'repeat' slide appeared. In doing this participants were prevented from rehearsing the items and disrupting the phonological loop. In using the same three presentation conditions as used in the word spelling assessment, comparisons can be made about the role of the phonological loop in the rehearsal of the word and nonword items, as there is evidence to suggest that word items can also be refreshed via lexical-semantic representations, something which is unavailable to nonwords and thus more susceptible to decay and disruption (Romani, McAlpine, Olson, Tsouknida, & Martin, 2005)

Repeated responses were transcribed phonemically in real time using the International Phonetic Alphabet (IPA) and marked as correct or incorrect. Where repetitions were distorted by dysarthria (e.g. nasal emissions, frication of plosives) these were transcribed as the attempted phoneme. Repetitions were also recorded via microphone using Audacity (version 1.3) recording and editing software, to enable repetitions to be reviewed if necessary. When the assessment was conducted as a nonword spelling test, the test was administered in the same way, only participants were instructed to spell the nonwords as accurately as they could based on how it sounded. Spellings were marked as either correct or incorrect, on the basis of orthographic plausibility according to existent English orthography patterns (Rollings, 2004).

4.3 Results

4.3.1 Group Comparisons

4.3.1.1 MND Participants vs Controls

For groupwise comparisons between patients and controls, t-tests were used. Where data was not normally distributed, as determined using Kolmogorov-Smirnov analysis, Mann-Whitney U tests were used.

4.3.1.1.1 Minimal Pair Discrimination

There was no significant difference between MND participants and controls in the ability to discriminate between both word and nonword minimal pairs (see Table 4.1).

Variable	MND (n 24)			Control (n 25)			Statistics
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**	
Word Minimal Pairs (48)	47.04	1.429	42-48	47.44	0.651	46-48	U = 273.5, z = -.584, p = .559
Nonword Minimal Pairs (48)	47.33	1.239	44-48	47.44	1.121	44-48	U = 293, z = -.169, p = .865

Table 4.1: Comparison of total scores for MND participants and controls on word and nonword minimal pairs

4.3.1.1.2 Word spelling

All 25 participants completed the word spelling test, however only 18 were able to complete all three conditions, as 7 were too severely dysarthric to complete the delayed with articulatory suppression condition. When considering effects and differences of condition, it is important to bear in mind that while stimuli was matched for word length, class and frequency, as the items were not exactly the same in each condition, only tentative conclusions about differences in performance between conditions can be drawn.

4.3.1.1.2.2 Participants who completed all three conditions

MND participants performed significantly worse than controls across all three spelling conditions: immediate, delayed and delayed with articulatory suppression (see Table 4.2 and Figure 4.2).

Variable	MND (n 18)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate Spelling (12)	9.440	3.072	1-12	11.400	0.707	10-12	U = 116.000, z = -2.826, p = .005*
Delayed Spelling (12)	9.940	3.058	2-12	11.760	0.436	11-12	U = 145.500, z = -2.310, p = .021*
Delayed Spelling with Suppression (12)	10.060	2.754	2-12	11.600	0.645	10-12	U = 138.500, z = -2.363, p = .018*

Table 4.2: Comparison of total scores for MND participants who completed all three conditions and controls on immediate, delayed and delayed with suppression word spelling

Effect of condition: Friedman test of within group comparison of performance across the three spelling conditions revealed that the performance of the control participants did not differ significantly across the three conditions: immediate, delayed, delayed with suppression (χ^2 (2) = 3.309, p = .191). Similarly there was no significant difference in performance across the three conditions in the MND participant group (χ^2 (2) = 3.825, p = .148).

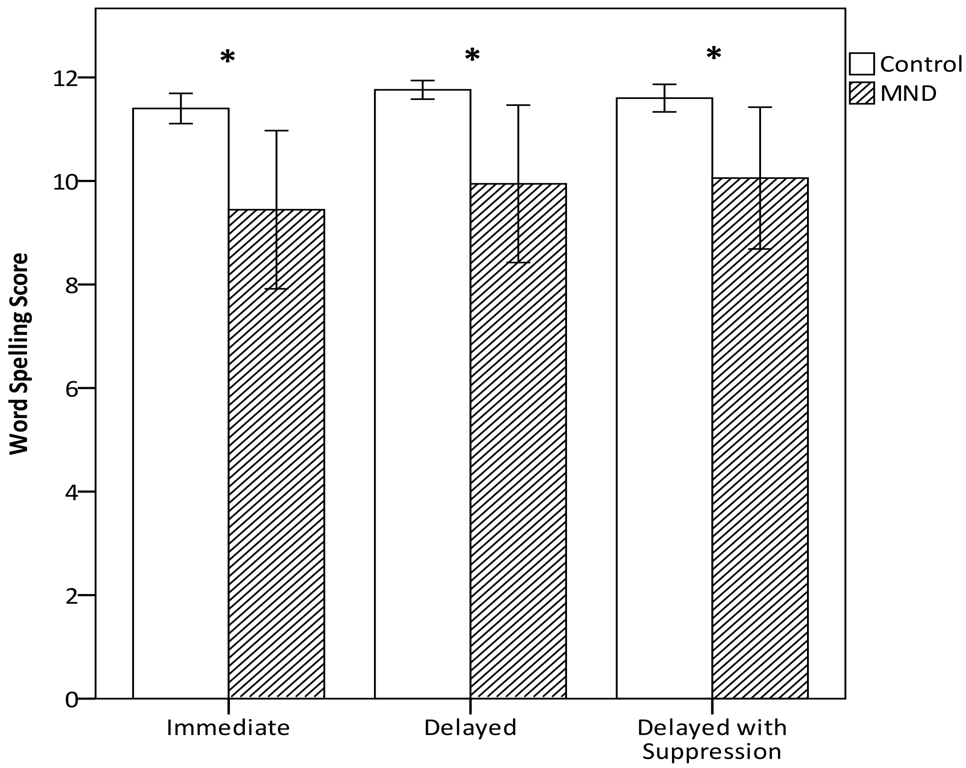


Figure 4.2: Number of words spelled correctly by MND participants who completed all three conditions and controls- * indicates significance (p<.05)

Effect of word length: On analysis of misspelled word (MSW) patterns according to the number of letters in the target (see Table 4.3 and Figure 4.3), MND participants produced significantly more MSW than controls for words of all three lengths in the immediate condition. In the delayed spelling condition, MND participants were significantly worse than controls at spelling 4 and 10 letter words, however there was no significant difference between groups for 7 letter words. It is important to note however that the significant difference in performance between groups for 4 letter words in the immediate and delayed conditions may be as a result of the ceiling performance of controls. In the delayed with articulatory suppression spelling condition, MND participants were significantly worse than controls when spelling words 10 letters long, however there was no significant difference between groups when spelling the shorter words (4 and 7 letters).

Condition	MND (n 18)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate							
4 Letters	.28	.752	0-3	0	0	0-0	U = 187.500, z = -2.090, p = .037*
7 Letters	1.22	1.309	0-4	.24	.436	0-1	U = 114.000 z = -3.102, p = .002*
10 Letters	1.06	1.349	0-4	.16	.374	0-1	U = 128,000 z = -2.894 p = .004*
Delayed							
4 Letters	.28	.752	0-3	0	0	0-0	U = 187.500 z = -2.090 p = .037*
7 Letters	.72	1.179	0-4	.20	.408	0-1	U = 175.000 z = -1.568 p = .117
10 Letters	1.06	1.434	0-4	.04	.200	0-1	U = 131.000, z = -3.256, p = .001*
Delayed with Suppression							
4 Letters	.11	.471	0-2	0	0	0-0	U = 212.500, z = -1.179, p = .239
7 Letters	.56	1.097	0-4	.20	.408	0-1	U = 200.000, z = -.835, p = .404
10 Letters	1.28	1.447	0-4	.04	.200	0-1	U = 93.500, z = -4.104, p = .000*

Table 4.3: Comparison of MND participants who completed all three conditions and controls on the number of word spelling MSW produced in each condition by word length of the targets (maximum 4)

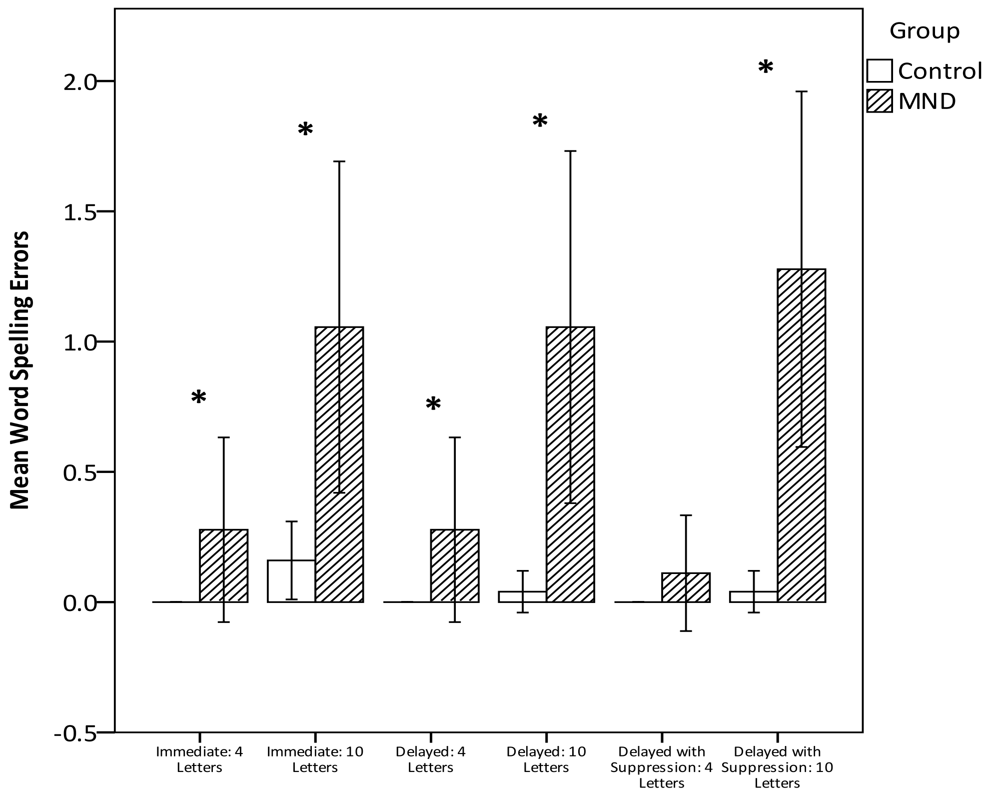


Figure 4.3: Number of short (4 letters) and long (10 letters) word spelling MSW produced by MND participants and controls across the three conditions (maximum 4) - * indicates significance (p<.05)

Wilcoxon tests of within group comparison for word length effects revealed that in the immediate condition both the control group (T = .00, p = .046) and the MND group (T = .00, p = .006) produced significantly more MSW when spelling long words (10 letters) than short words (4 letters). However, in the delayed condition, while MND participants were again significantly worse at spelling long word than short words (T = .00, p = .010), there was no significant difference in the number of short and long words spelled incorrectly by controls (T = .00, p = .317). The same pattern was shown in the delayed with articulatory suppression condition, where MND participants were significantly worse at spelling long words than short (T = .00, p = .003) while there was no significant difference for controls (T = .00, p =.317). While this difference in result pattern in the immediate condition could be seen as an effect of condition, as there was no overall difference in performance across the conditions, it may also be due to different stimuli being used. It is also worth noting that the difference in control group performance between spelling of short and long words is only just at the level of significance (p = .046).

Overlap with target: In order to examine whether MSW produced by MND participants were more inaccurate than those produced by controls, differences in MSW were analysed according to their overlap with the target words. MSW were scored according to the number of letters and the number of *correct* letters within each MSW. These scores were then entered into the following formula to calculate the overlap score for each MSW:

$$\frac{\text{Number of correct letters in MSW x 2}}{\text{Number of letters in target + Number of letters in MSW}}$$

Correct spellings were given a score of 1, and all scores were combined for each condition, giving a total overlap score for each condition. On analysis of misspelled word (MSW) patterns according overlap with target scores (see Table 4.4 and Figure 4.4), MND participants had a significantly lower overlap with target score than controls when spelling words in all three conditions.

Variable	MND (n 18)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate Spelling (12)	11.526	0.877	8.64-12	11.961	0.070	11.76-12	U = 100.000, z = -3.280, p = .001*
Delayed Spelling (12)	11.442	1.091	7.68-12	11.964	0.073	11.71-12	U = 148.500, z = -2.214, p = .027*
Delayed Spelling with Suppression (12)	11.469	1.275	6.59-12	11.956	0.081	11.65-12	U = 137.500, z = -2.344, p = .019*

Table 4.4: Comparison of overlap with target total scores for MND participants who completed all three conditions and controls on immediate, delayed and delayed with suppression word spelling

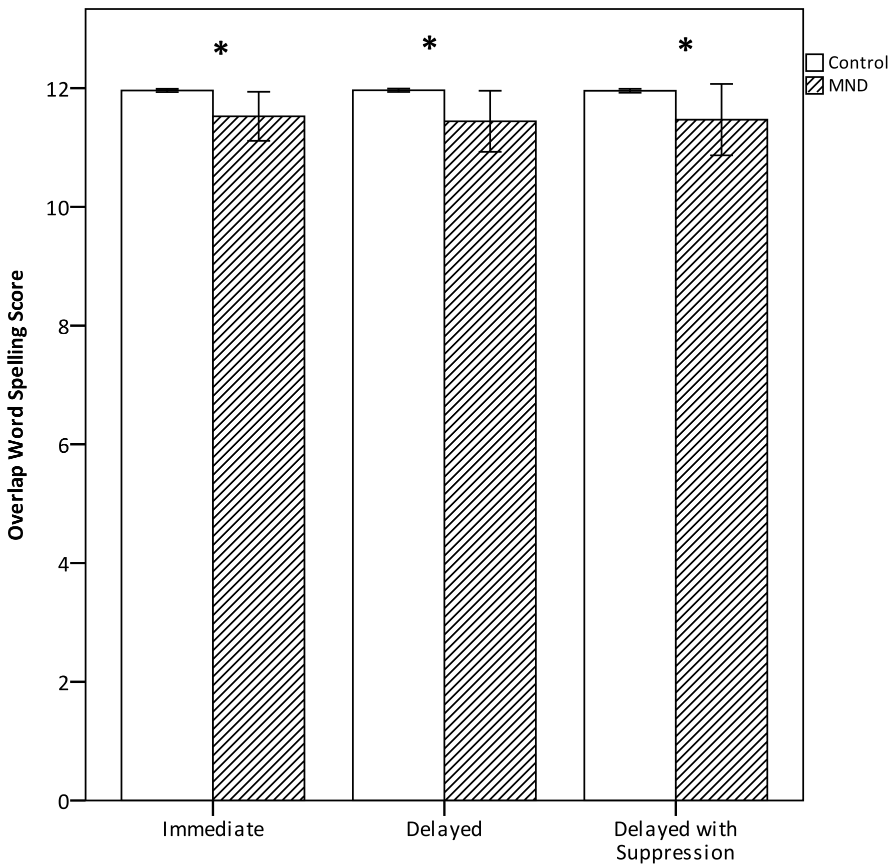


Figure 4.4: Overlap with target word spelling scores for MND participants who completed all three conditions and controls- * indicates significance (p<.05)

Friedman test of within group comparison of performance across the three spelling conditions for overlap of MSWs to target revealed that the performance of the control participants did not differ significantly across the three conditions: immediate, delayed, delayed with suppression (χ^2 (2) = .593, p = .744). Similarly there was no significant difference in performance across the three conditions in the MND participant group (χ^2 (2) = .857, p = .651).

In addition, the overlap score was analysed in terms of length of target words. As longer words present a greater number of opportunities for errors to occur, using the overlap score allows for the examination of the proportion of correct letters rather than the number of correct whole words, and is a more sensitive measure of word length effects. Using this analysis, MND participants had a significantly lower overlap score with target words of all three lengths than controls in the immediate spelling condition. In the delayed spelling condition, MND participants had a significantly lower overlap score with target words of 4 and 10 letter words than controls, however there was no significant difference between groups for 7 letter words. In the delayed with articulatory suppression spelling condition, MND participants had a significantly lower overlap score with target words of 7 and letter words than controls (see Table 4.5 and Figure 4.5).

Condition	MND (n 18)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate							
4 Letters	3.89	.289	2.86-4	4	0	4-4	U = 187.500, z = -2.090, p = .037*
7 Letters	3.81	.349	2.81-4	3.98	.037	3.86-4	U = 129.500 z = -2.692, p = .007*
10 Letters	3.82	.311	2.81-4	3.98	.050	3.80-4	U = 118.000 z = -3.105 p = .002*
Delayed							
4 Letters	3.85	.405	2.55-4	4	0	4-4	U = 187.500 z = -2.090 p = .037*
7 Letters	3.867	.271	2.96-4	3.969	.072	3.71-4	U = 176.500 z = -1.511 p = .131
10 Letters	3.730	.496	2.17-4	3.996	.022	3.89-4	U = 131.000, z = -3.254, p = .001*
Delayed with Suppression							
4 Letters	3.910	.386	2.36-4	4	0	4-4	U = 212.500, z = -1.179, p = .239
7 Letters	3.858	.435	2.15-4	3.986	.070	3.65-4	U = 200.000, z = -2.125, p = .034*
10 Letters	3.702	.504	2.07-4	3.970	.050	3.85-4	U = 128.000, z = -2.631, p = .009*

Table 4.5: Comparison of overlap with target scores produced in each condition by word length of the targets (maximum 4) for MND participants who completed all three conditions and controls

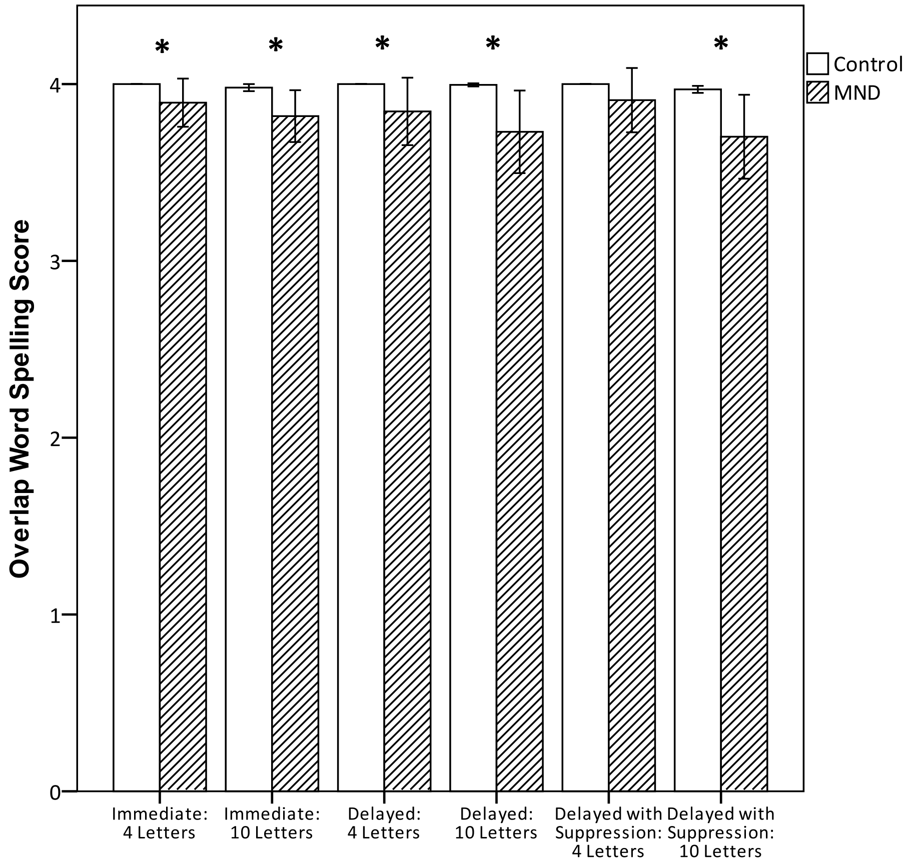


Figure 4.5: Overlap with target word spelling scores according to word length produced by MND participants and controls across the three conditions (maximum 4) - * indicates significance (p<.05)

Wilcoxon test of within group comparison for word length effects based on overlap of MSWs with targets revealed that in the immediate condition MND participants (T = 10.00, p = .040) were significantly worse at spelling long words (10 letters) than short (4 letters), however there was no significant difference in the performance of controls spelling short or long words (T = .00, p = .059). In the delayed condition, there was no significant difference in the performance of MND participants (T = 7.00, p = .123) or control participants (T = .00, p = .317) spelling short or long words. In the delayed with articulatory suppression condition however, both the control group (T = .00, p = .011) and the MND group (T = .00, p = .003) were significantly worse at spelling long words than short.

Effect of word class: As there was no overall significant effect of condition and word class should not be affected by condition, the results for noun and verb MSW were collapsed across the three conditions. MND participants produced significantly more MSW than controls spelling both nouns and verbs (see Table 4.6 and Figure 4.6).

Condition	MND (n 18)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Noun	3.61	4.654	0-17	.52	.823	0-3	U = 99.000, z = -3.308, p = .001*
Verb	2.94	4.207	0-14	.52	.653	0-2	U = 114.000, z = -2.908, p = .004*

Table 4.6: Comparison of MND participants who completed all three conditions and controls on the number of noun and verb MSW collapsed across the three conditions (maximum 18)

Wilcoxon test of within group comparison for word class effects revealed that there was no significant difference in the number of nouns and verbs spelled correctly by both controls (T = 37.50, p = .902) and MND participants (T = 39.00, p = .217).

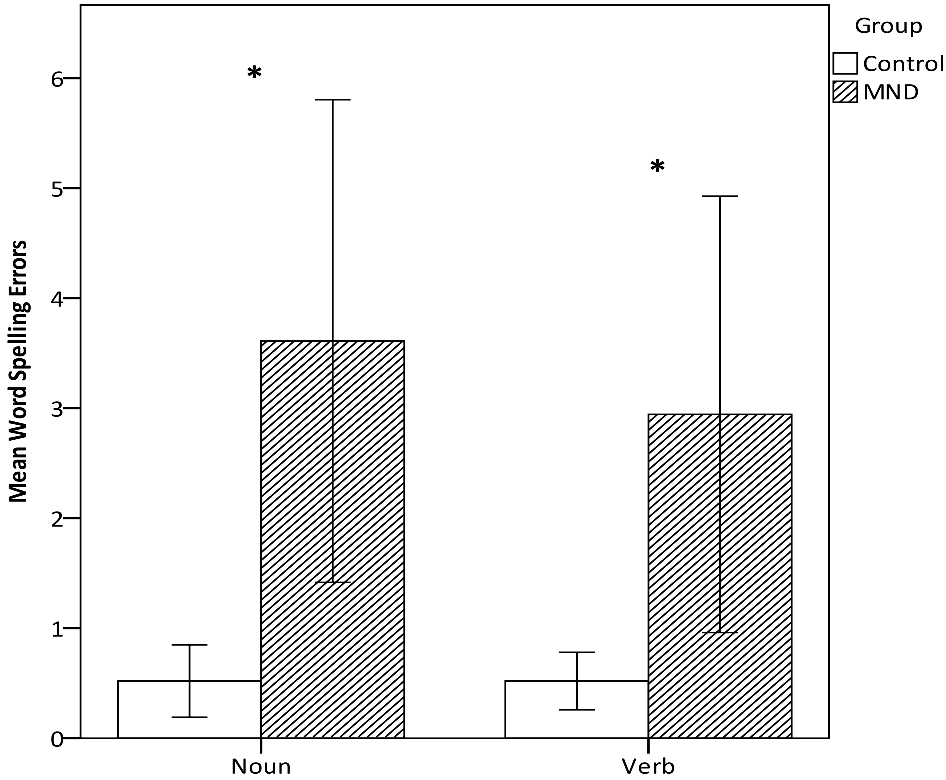


Figure 4.6: Number of noun and verb word MSW produced by MND participants and controls collapsed across the three conditions (maximum 18) - * indicates significance (p<.05)

Plausibility of MSW: In the immediate condition, there was no significant difference in the number of orthographically plausible MSW produced by MND participants and controls, however MND participants produced significantly more orthographically implausible MSW than controls. In the delayed condition, again there was no significant difference in the number of orthographically plausible MSW produced by MND participants and controls, however MND participants produced significantly more orthographically implausible MSW than controls. In the delayed with suppression condition MND participants produced significantly more orthographically plausible and implausible MSW than controls (see Table 4.7 and Figure 4.7).

Condition	MND (n 18)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate							
Plausible	.78	.878	0-3	.36	.569	0-2	U = 164.500, z = -1.698, p = .089
Implausible	1.78	3.246	0-11	.04	.200	0-1	U = 143.500 z = -2.956, p = .003*
Delayed							
Plausible	.44	.616	0-2	.16	.374	0-1	U = 171.500 z = -1.736 P = .083
Implausible	1.61	2.873	0-10	.08	.277	0-1	U = 149.500 z = -2.615 p = .009*
Delayed with Suppression							
Plausible	.67	.840	0-2	.16	.374	0-1	U = 153.000, z = -2.254, p = .024*
Implausible	1.28	2.630	0-10	.08	.277	0-1	U = 164.000, z = -2.214, p = .027*

Table 4.7: Comparison of MND participants who completed all three conditions and controls on the number of orthographically plausible and implausible MSW produced

Wilcoxon test of within group comparison revealed that in the immediate condition, controls produced significantly more plausible MSW than implausible (T = .00, p = .011), however there was no significant difference in the number of plausible and implausible MSW produced by MND participants (T = 42.50, p = .525). In the delayed condition, there was no significant difference in the number of plausible and implausible MSW produced by both controls (T = 7.00, p = .414) and MND participants (T = 4.00, p = .089). This was also the pattern in the delayed with suppression condition where there was no significant difference in the number of plausible and implausible MSW produced by controls (T = 7.00, p = .414) and MND participants (T = 27.00, p = .588).

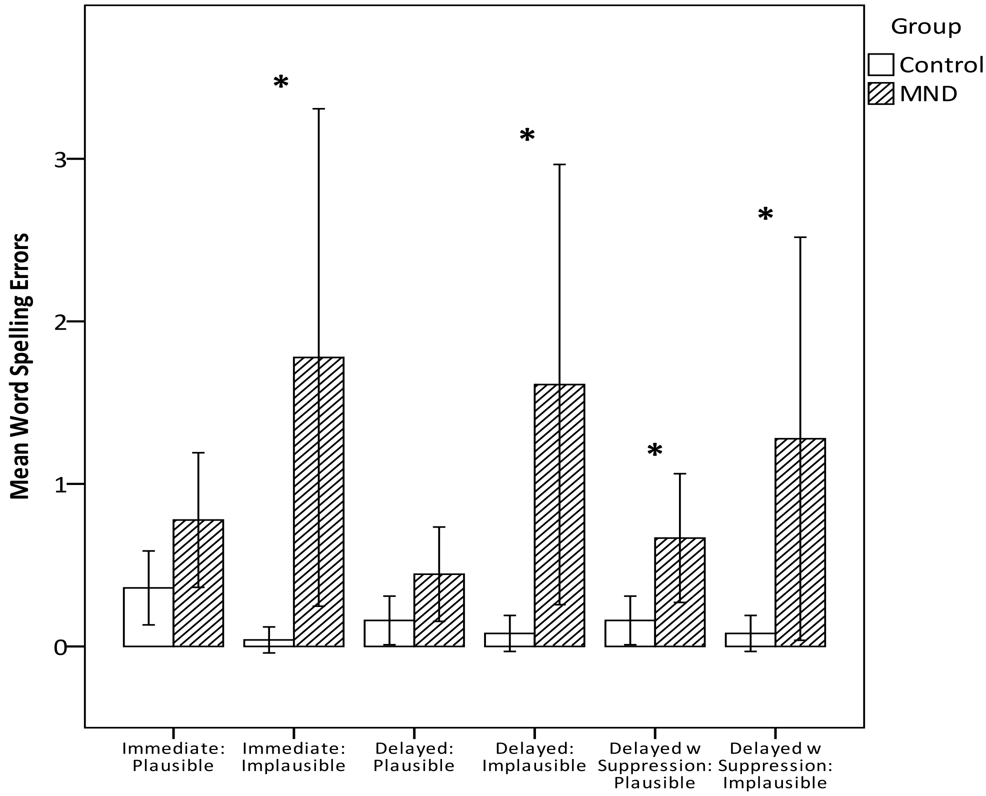


Figure 4.7: Number of orthographically plausible and implausible MSW produced by MND participants and controls across the three conditions - * indicates significance (p<.05)

4.3.1.1.2.2 All participants who completed immediate and delayed conditions

All 25 MND participants were able to complete the immediate and delayed spelling conditions. When the scores of all MND participants are analysed, the results show that MND participants performed significantly worse overall than controls in both the immediate and delayed conditions (see Table 4.8 and Figure 4.8).

Variable	MND (n 25)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate Spelling (12)	9.72	2.821	1-12	11.40	.707	10-12	U = 177.000, z = -2.766, p = .006*
Delayed Spelling (12)	9.80	2.799	2-12	11.76	.436	11-12	U = 154.500, z = -3.399, p = .001*

Table 4.8: Comparison of total scores for all MND participants and controls on immediate and delayed word spelling

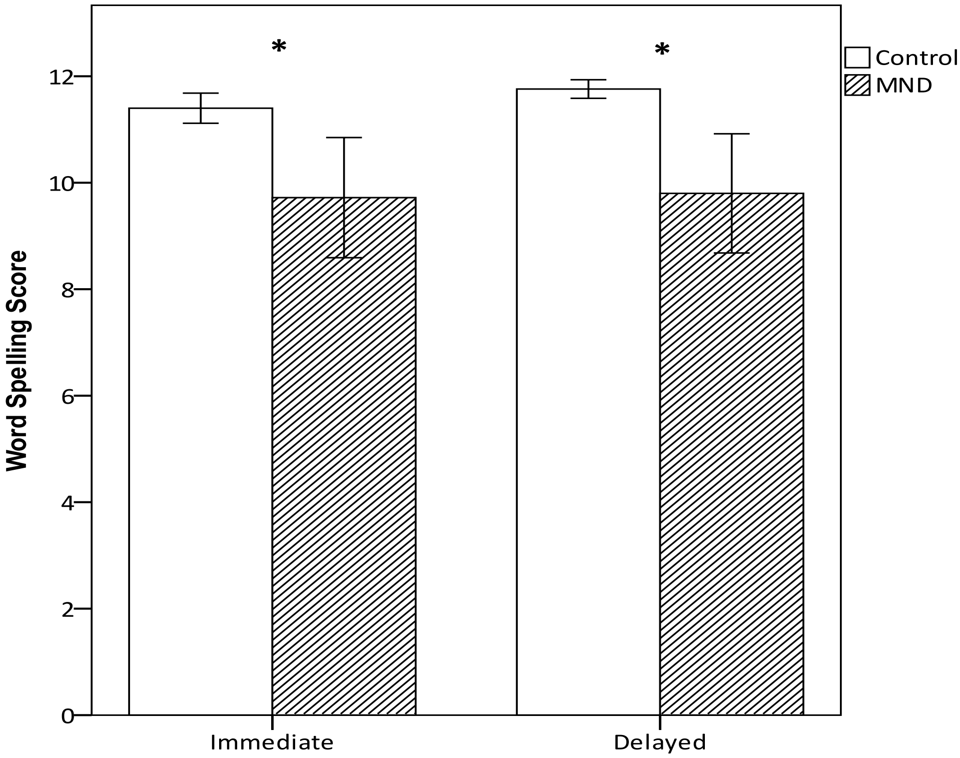


Figure 4.8: Number of words spelled correctly by all MND and control participants in the immediate and delayed conditions - * indicates significance (p<.05)

Effect of condition: Wilcoxon test of within group comparison of performance across the two spelling conditions revealed that the performance of the MND participant group did not differ significantly between the two conditions ($T = 106.50$, $p = .745$). Control group performed significantly worse in the immediate than in the delayed spelling condition ($T = 15.00$, $p = .048$), however as this difference is at borderline significance, this effect may be due to the use of different stimuli in each condition.

Effect of word length: On analysis of error patterns according to the number of letters in the target (see Table 4.9 and Figure 4.9), MND participants produced significantly more MSW than controls for words of all three lengths in the immediate condition. In the delayed spelling condition, MND participants again produced significantly more MSW than controls for words of all three lengths.

Condition	MND (n 25)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate							
4 Letters	.28	.678	0-3	0	0	0-0	U = 250.000, z = -2.331, p = .020*
7 Letters	1.08	1.256	0-4	.24	.436	0-1	U = 182.000 z = -2.871, p = .004*
10 Letters	1.00	1.225	0-4	.16	.374	0-1	U = 175.500 z = -3.124 p = .002*
Delayed							
4 Letters	.40	.764	0-3	0	0	0-0	U = 225.000 z = -2.818 p = .005*
7 Letters	.84	1.214	0-4	.20	.408	0-1	U = 215.000 z = -2.269 p = .023*
10 Letters	.96	1.274	0-4	.04	.200	0-1	U = 171.500, z = -3.554, p = .000*

Table 4.9: Comparison of all MND participants and controls on the number of MSW produced in the immediate and delayed conditions by word length of the targets (maximum 4)

Wilcoxon test of within group comparison for word length effects revealed that in the immediate condition both MND participants (T = .00, p = .001) and controls (T = .00, p = .046) were significantly worse at spelling long words (10 letters) than short (4 letters), although again the significance in the control group was borderline, perhaps reflecting the difference in stimuli. In the delayed condition, MND participants were again significantly worse at spelling long words than short words (T = 15.00, p = .028), however there was no significant difference in the performance of controls spelling short or long words (T = .00, p = .317).

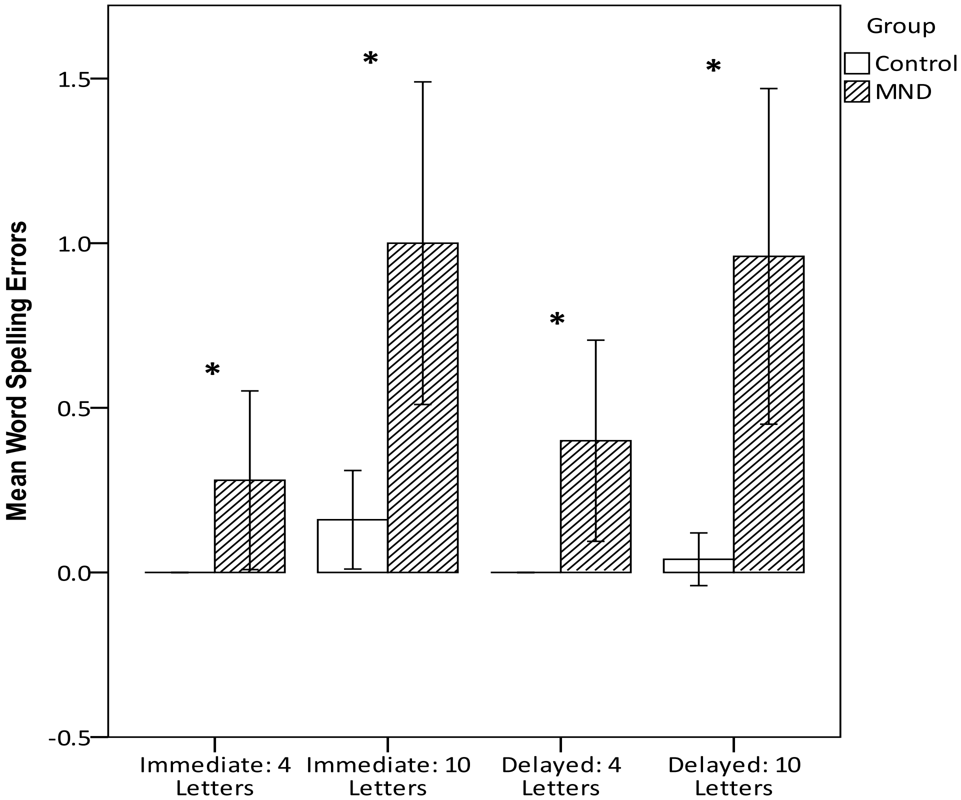


Figure 4.9: Number of short (4 letters) and long (10 letters) MSW produced by all MND participants and controls in the immediate and delayed conditions (maximum 4) - * indicates significance (p<.05)

Overlap with target: On analysis of misspelled word (MSW) patterns according overlap with target scores (see Table 4.10 and Figure 4.10), MND participants had a significantly lower overlap with target score than controls when spelling words in both the immediate and delayed conditions.

Variable	MND (n 25)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate Spelling (12)	11.580	.797	8.64-12	11.961	.070	11.76-12	U = 149.000, z = -3.346, p = .001*
Delayed Spelling (12)	11.440	.961	7.68-12	11.964	.073	11.71-12	U = 157.000, z = -3.323, p = .001*

Table 4.10: Comparison of overlap with target total scores for all MND and controls on immediate and delayed word spelling

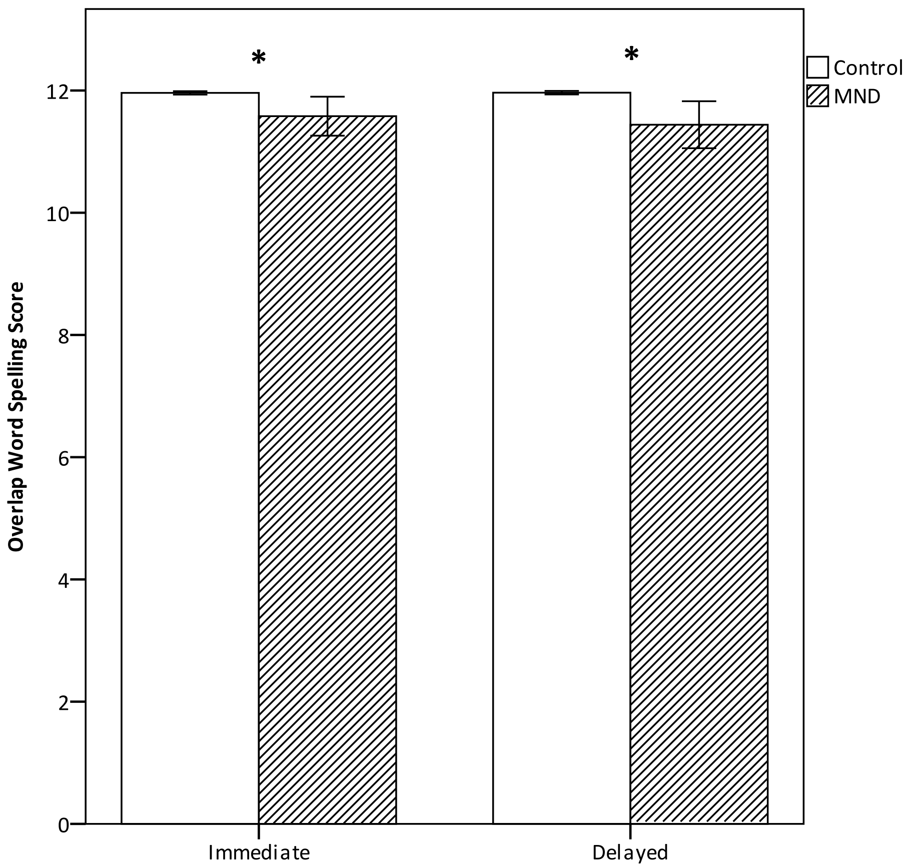


Figure 4.10 Overlap with target word spelling scores for all MND and control participants in the immediate and delayed conditions - * indicates significance (p<.05)

Wilcoxon test of within group comparison of performance across the two spelling conditions for overlap of MSWs to target revealed that the performance of the control participants did not differ significantly between the two conditions (T = 37.50, p = .906). Similarly there was no significant difference in performance between the two conditions in the MND participant group (T = 92.50, p = .166).

Analysis of the overlap score in terms of length of target words revealed that MND participants had a significantly lower overlap score than controls with target words of all three lengths than controls in both the immediate and delayed spelling conditions (see Table 4.11 and Figure 4.11).

Condition	MND (n 25)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate							
4 Letters	3.914	.250	2.86-4	4	0	4-4	U = 262.500, z = -2.062, p = .039*
7 Letters	3.823	.338	2.81-4	3.981	.037	3.86-4	U = 198.500 z = -2.526, p = .012*
10 Letters	3.842	.276	2.81-4	3.980	.050	3.80-4	U = 170.500 z = -3.169 p = .002*
Delayed							
4 Letters	3.835	.355	2.55-4	4	0	4-4	U = 225.000 z = -2.814 p = .005*
7 Letters	3.823	.302	2.94-4	3.970	.072	3.71-4	U = 211.500 z = -2.323 p = .020*
10 Letters	3.782	.430	2.17-4	3.995	.022	3.89-4	U = 172.000, z = -3.535, p = .000*

Table 4.11: Comparison of overlap with target scores produced in the immediate and delayed condition by word length of the targets (maximum 4) for all MND participants and controls

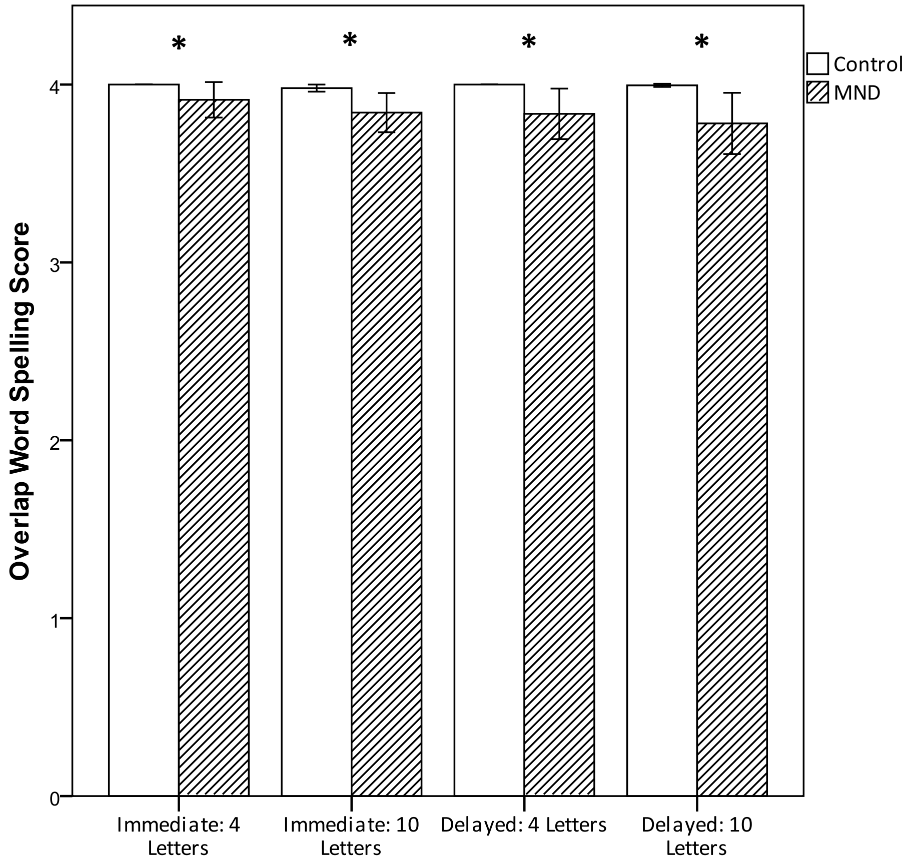


Figure 4.11: Overlap with target word spelling scores according to word length produced by all MND participants and controls in the immediate and delayed conditions (maximum 4) - * indicates significance (p<.05)

Wilcoxon test of within group comparison for word length effects based on overlap of MSWs with targets revealed that in the immediate condition MND participants (T = 14.00, p = .009) were significantly worse at spelling long words (10 letters) than short (4 letters), however there was no significant difference in the performance of controls spelling short or long words (T = .00, p = .059). In the delayed condition, there was no significant difference in the performance of MND participants (T = 38.00, p = .363) or control participants (T = .00, p = .317) spelling short or long words.

Effect of word class: The results for noun and verb MSW were collapsed across the immediate and delayed conditions. MND participants produced significantly more MSW than controls spelling both nouns and verbs (see Table 4.12 and Figure 4.12).

Condition	MND (n 25)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Noun	2.60	3.069	0-12	.44	.768	0-3	U = 142.500, z = -3.515, p = .000*
Verb	1.88	2.603	0-9	.36	.569	0-2	U = 170.500, z = -2.995, p = .003*

Table 4.12: Comparison of all MND participants and controls on the number of noun and verb MSW collapsed across the immediate and delayed conditions (maximum 12)

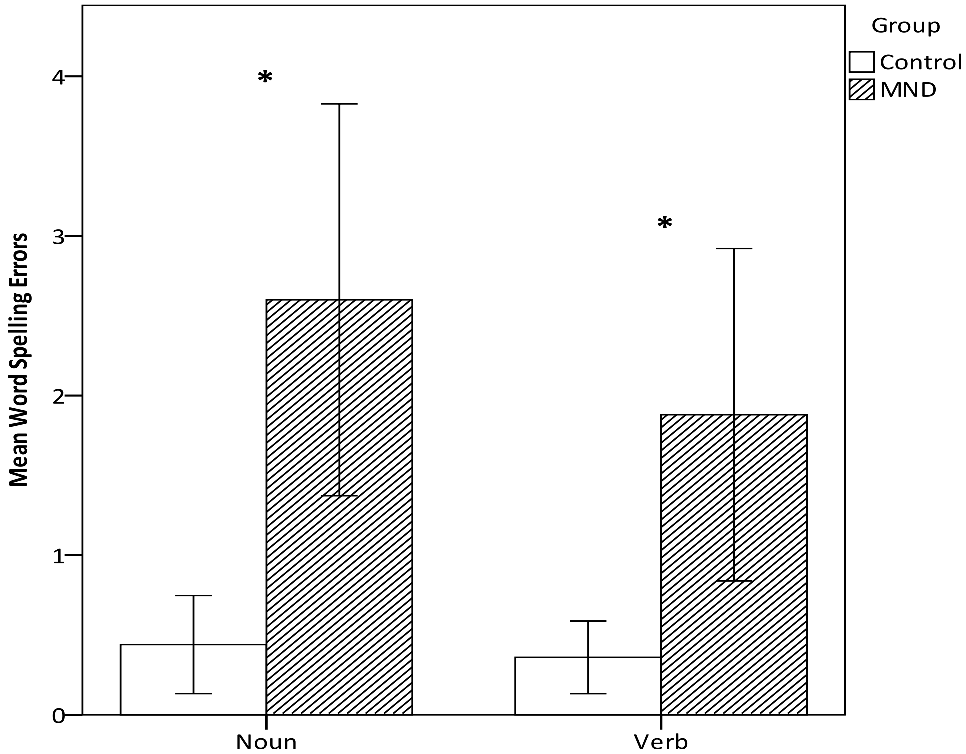


Figure 4.12: Number of noun and verb MSW produced by all MND participants and controls collapsed across the immediate and delayed conditions (maximum 12) - * indicates significance (p<.05)

Wilcoxon within group comparison revealed that when MSW were collapsed across the immediate and delayed conditions, there was no significant difference in the number of nouns and verbs spelled correctly by controls (T = 30.00, p .776). MND participants however produced significantly more MSW spelling nouns than verbs (T = 36.00, p = .048).

Plausibility of MSW: In the immediate condition MND participants produced significantly more orthographically plausible and implausible MSW than controls. In the delayed condition there was no significant difference in the number of orthographically plausible MSW produced by controls and MND participants, although there was a trend towards significance. MND participants did however make significantly more orthographically implausible MSW than controls in the delayed condition (see Table 4.13 and Figure 4.13).

Condition	MND (n 25)			Controls (n 25)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate							
Plausible	.88	.927	0-3	.36	.569	0-2	U = 211.500, z = -2.187, p = .029*
Implausible	1.40	2.858	0-11	.04	.200	0-1	U = 221.500 z = -2.636, p = .008*
Delayed							
Plausible	.52	.770	0-3	.16	.374	0-1	U = 233.500 z = -1.958 P = .050
Implausible	1.68	2.529	0-10	.08	.277	0-1	U = 166.000 z = -3.512 p = .000*

Table 4.13: Comparison of MND participants who completed the immediate and delayed conditions and controls on the number of orthographically plausible and implausible MSW produced

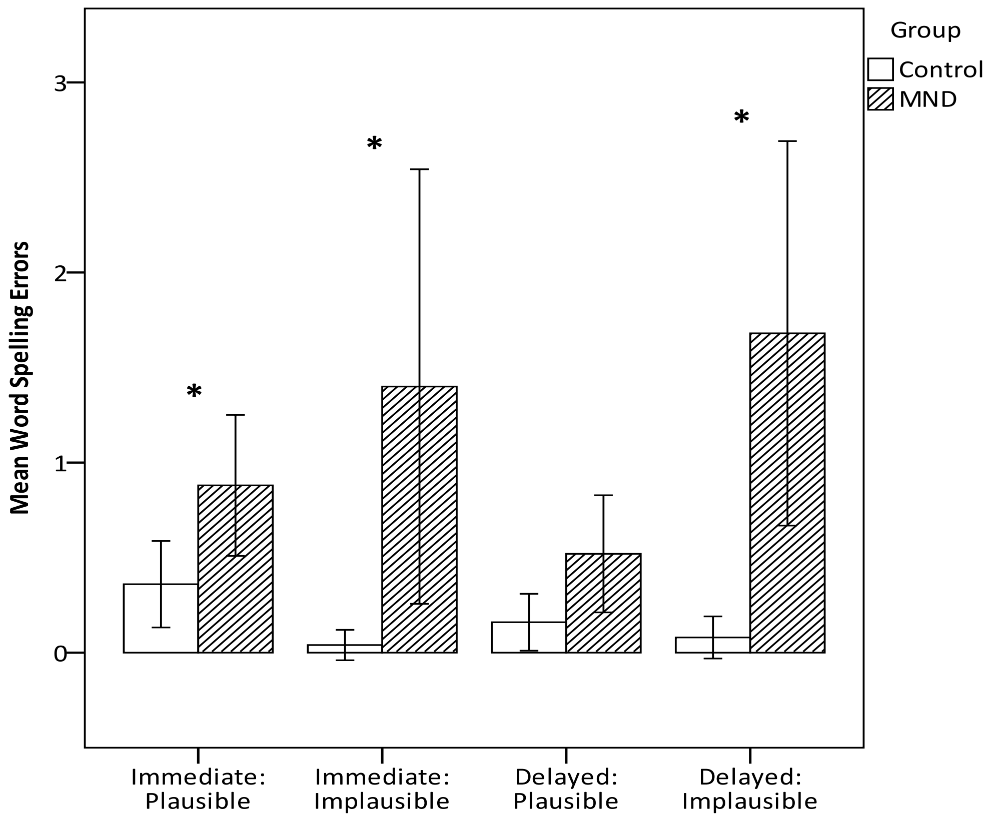


Figure 4.13: Number of orthographically plausible and implausible MSW produced by all MND participants and controls across the immediate and delayed conditions - * indicates significance (p<.05)

Wilcoxon within group comparison revealed that in immediate condition controls produced significantly more plausible MSW than implausible (T = .00, p = .011), while for MND participants there was no significant difference in the number of plausible and implausible MSW (T = 84.50, p = .945). In the delayed condition there was no significant difference in the number of plausible and implausible MSW produced by controls (T = 7.00, p = .414), while MND participants produced significantly more implausible MSW than plausible (T = 12.00, p =.017).

4.3.1.1.2.3 Length of MSW in comparison to target

In order to help ascertain whether MSW could be attributed to motor weakness or fatigue, as suggested by Cobble (1998) the lengths of MSW were compared to the targets. For all those participants who produced MSW across all conditions completed, the percentage of their MSW that were shorter, the same length and longer than the target was calculated. If MSW produced by MND participants were predominantly shorter than the target, it could be suggested that MSW may be attributable to physical weakness or fatigue. However, there was no significant difference between MND participants and controls in the percentage of MSW that were shorter than the target. In addition, there was no significant difference between MND participants and controls in the percentage of MSW that were the same length and longer than the target word (see Table 4.14).

Variable	MND (n 25)			Controls (n 16)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Percentage Shorter	20.53	30.641	0-100	17.19	35.022	0-100	U = 164.500, z = -1.080, p = .280
Percentage Same	53.26	35.84	0-100	40.63	41.708	0-100	U = 167.000, z = -.902, p = .367
Percentage Longer	26.21	30.771	0-100	42.19	44.459	0-100	U = 169.500, z = -.850, p = .395
Percentage Same + Longer	79.47	30.64	0-100	82.81	35.022	0-100	U = 158.500, z = -1.242, p = .214

Table 4.14: Percentage of MSW shorter, the same length and longer than the target word for those who produced MSW across all conditions completed

4.3.1.1.2.4 Summary of Findings

MND patients were significantly worse than controls in all three presentation conditions, however there was no effect of condition on performance. Errors increased with word length, and overlap of MSW with targets was significantly lower with longer words than short. There was no effect of word class. MND patients produced significantly more orthographically implausible MSW than controls in all three conditions.

4.3.1.1.3 Nonword Repetition

Only 9 of the 25 MND participants had speech which was intelligible enough to complete the nonword repetition tests. MND participants were significantly worse at repeating nonwords than controls in the immediate condition, however there was no significant difference in performance between groups in the delayed condition. In the delayed repetition with suppression of articulatory rehearsal, MND participants again performed significantly worse than controls as group (see Table 4.15 and Figure 4.14).

Condition	MND (n 9)			Control (n 24)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate (12)	8.11	1.537	5-10	9.29	1.922	4-12	U = 58.500, z = -2.038, p = .042*
Delayed (12)	6.78	2.333	3-10	7.83	2.496	2-12	t = 1.100, p = .280
Delayed with Suppression (12)	5.44	3.167	1-9	8.04	2.742	0-11	U = 50.500, z = -2.354, p = .019*

Table 4.15: Comparison of total scores for MND participants and controls on immediate, delayed and delayed with suppression nonword repetition

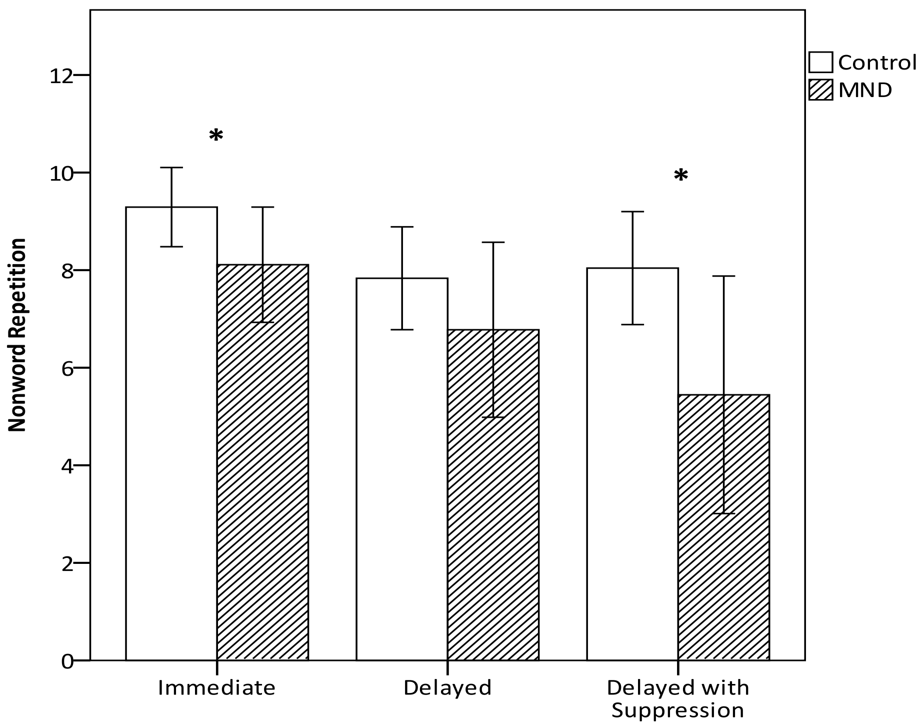


Figure 4.14: Number of nonwords repeated correctly by MND participants and controls in the immediate, delayed and delayed with suppression conditions - * indicates significance (p<.05)

Effect of condition: Friedman test of within group comparison of performance across the three repetition conditions revealed no significant effect of condition on performance for either the MND group (χ^2 (2) = 4.595, p = .100) or control group (χ^2 (2) = 3.935, p = .140). However, while the stimuli used in all three conditions was matched for phoneme length, as different items were used in each condition, conclusions drawn about the effect of condition can only be tentative (see discussion).

Effect of word length: On analysis of misrepeated nonword (MRNW) patterns according to the number of phonemes in the target (see Table 4.16 and Figure 4.15), in the immediate condition there was no significant difference between the MND participant group and the control group for the number of MRNW produced when targets were 4, 7 or 10 phonemes in length. There was also no significant difference in the number of MRNW produced in the delayed repetition condition when targets were 4, 7 or 10 phonemes in length. However in the delayed with articulatory suppression condition MND participants produced significantly more MRNW when repeating nonwords of 4 phonemes than controls. There was no significant difference between MND participants and controls in the number of MRNW produced when targets were 7 phonemes in length in this condition, however MND participants produced significantly more MRNW than controls when targets were 10 phonemes in length.

Wilcoxon tests of within group comparison for word length effects revealed that in the immediate condition the control group produced significantly more MRNW when repeating long nonwords (10 phonemes) than short nonwords (4 phonemes) (T = .00, p = .000). MND participants also produced significantly more MRNW when repeating long nonwords than short nonwords in the immediate condition (T = .00, p = .026). In the delayed condition the control group produced significantly more MRNW repeating long nonword than short nonwords (T = .00, p =.000). MND participants also produced significantly more MRNW repeating long nonwords than short nonwords in the delayed condition (T =2.00, p =.014). In the delayed with articulatory suppression condition the control group produced significantly more MRNW repeating long nonwords than short nonwords (T = 26.00, p =.008). However there was no significant difference in the number of MRNW produced by MND participants when repeating long or short nonwords in the delayed with articulatory suppression condition (T = 5.00, p = .121).

Condition	MND (n 9)			Controls (n 24)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate							
4 Phonemes	.67	.707	0-2	.38	.647	0-2	U = 81.000, z = -1.285, p = .199
7 Phonemes	1.11	.782	0-2	.63	1.013	0-4	U = 66.500, z = -1.833, p = .067
10 Phonemes	2.00	1.000	0-3	1.71	.908	0-3	U = 86.500, z = -.914, p = .361
Delayed							
4 Phonemes	.89	.782	0-2	.58	.830	0-3	U = 81.000, z = -1.201, p = .230
7 Phonemes	1.78	1.093	0-3	1.08	1.213	0-4	U = 67.500, z = -1.707, p = .088
10 Phonemes	2.56	1.130	1-4	2.46	1.141	0-4	U = 104.500, z = -.147, p = .883
Delayed with Suppression							
4 Phonemes	1.89	1.054	0-3	.83	1.007	0-4	U = 48.500, z = -2.515, p = .012*
7 Phonemes	1.89	1.691	0-4	1.42	1.100	0-4	U = 95.000, z = -.545, p = .586
10 Phonemes	2.78	1.202	1-4	1.67	1.308	0-4	U = 58.500, z = -2.063, p = .039*

Table 4.16: Comparison of MND participants and controls on the number of MRNW produced in each condition by phoneme length of the targets (maximum 4)

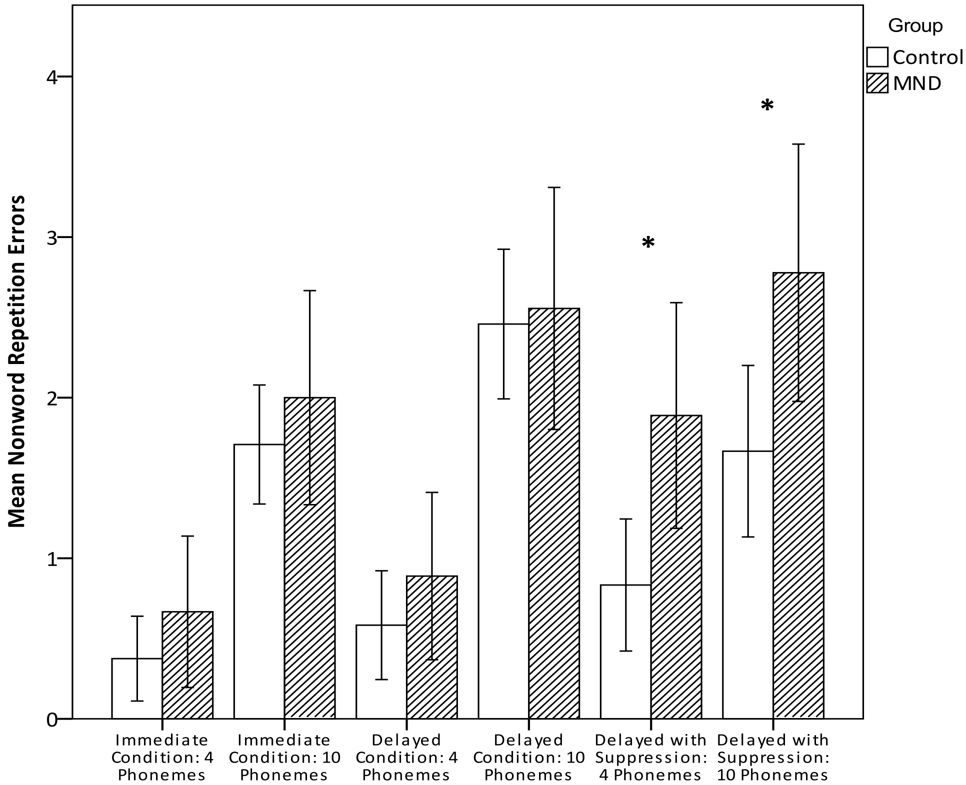


Figure 4.15: Number of 4 and 10 phoneme MRNW produced by MND participants and controls across the three conditions (maximum 4) - * indicates significance (p<.05)

4.3.1.1.4 Nonword Spelling

Those who were unable to complete the nonword repetition test due to severe dysarthria were given the test as a nonword spelling test. If participants who had completed the nonword repetition were willing, they also completed the nonword repetition test as a nonword spelling test in a separate session, which was at least one week later, to avoid retest effects. Of the 16 MND participants who completed the nonword spelling test, only 8 were able to complete all three conditions due to the articulation requirement of the articulatory suppression condition. These patients will be firstly analysed separately.

4.3.1.1.4.1 Participants who completed all three conditions

There was no significant difference in performance between those MND participants who completed all three conditions and controls in the immediate condition. However in the delayed and delayed with articulatory suppression conditions the MND participants were significantly worse at spelling nonwords than controls (see Table 4.17 and Figure 4.16).

Condition	MND (n 8)			Control (n 22)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate (12)	6.88	3.137	1-9	8.95	1.397	6-11	U = 48.500, z = -1.895, p = .058
Delayed (12)	5	2.33	1-8	7.64	1.941	4-11	t = 3.123, p = .004*
Delayed with Suppression (12)	5.25	2.375	2-8	8.14	1.91	3-11	U = 27.500, z = -2.878, p = .004*

Table 4.17: Comparison of total scores for MND participants who completed all three conditions and controls on immediate, delayed and delayed with suppression nonword spelling

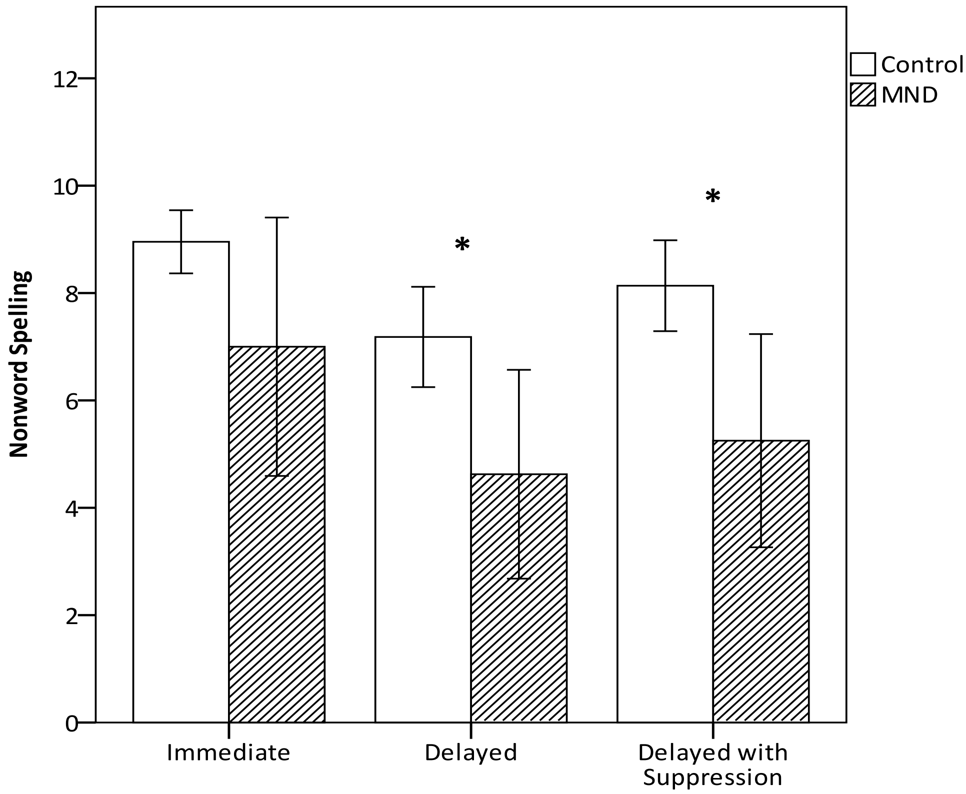


Figure 4.16: Number of nonwords spelled correctly by MND participants who completed all three conditions - * indicates significance (p<.05)

Effect of condition: Friedman test of within group comparison of performance across the three spelling conditions revealed that the performance of control participants did differ significantly across the three conditions (χ^2 (2) = 9.100, p = .011). Wilcoxon tests were used to follow up this finding. A Bonferroni correction was applied and so all effects are reported at a p ≤0.0167 level of significance. Scores were significantly higher in the immediate condition than the delayed condition (T = 27.50, p = .003), but scores did not differ significantly between the immediate and delayed with suppression conditions (T = 55.50, p = .060), or between the delayed and delayed with suppression conditions, T = 57.50, p = .216. The scores of the MND participants who completed all three conditions did not significantly differ across the three conditions: immediate, delayed, delayed with suppression, however there was a strong trend towards significance (χ^2 (2) = 6.000, p = .050).

Effect of word length: On analysis of misspelled nonword (MSNW) patterns according to the number of phonemes in the target (see Table 4.18 and Figure 4.17), the MND participants produced significantly more MSNW than controls when spelling 4 phoneme nonwords in the immediate condition, however there was no significant difference between the groups in the number of MSNW produced when spelling 7 and 10 phoneme nonwords in this condition. In the delayed condition MND participants produced significantly more MSNW than controls when spelling nonwords 4 and 7 phonemes in length, however there was no significant difference between the groups in the number of MSNW produced when spelling 10 phoneme nonwords in the second condition. MND participants produced significantly more MSNW than controls when spelling nonwords of all three lengths when in the delayed with articulatory suppression condition.

Condition	MND (n 8)			Controls (n 22)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate							
4 Phonemes	1.38	.916	0-3	.55	.596	0-2	U = 41.50, z = -2.388, p = .017*
7 Phonemes	1.25	1.581	0-4	.59	.854	0-3	U = 70.500, z = -.915, p = .360
10 Phonemes	2.25	.886	1-4	1.91	1.019	0-4	U = 69.500, z = -.926, p = .354
Delayed							
4 Phonemes	1.13	1.126	0-3	.32	.477	0-1	U = 50.500, z = -2.021, p = .043*
7 Phonemes	2.38	1.061	1-4	1.14	.941	0-3	U = 35.000, z = -2.582, p = .010*
10 Phonemes	3.50	.756	2-4	2.91	1.269	0-4	U = 66.500, z = -1.087, p = .277
Delayed with Suppression							
4 Phonemes	1.38	.916	0-3	.41	.734	0-2	U = 35.000, z = -2.776, p = .005*
7 Phonemes	2.38	1.061	1-4	1.32	1.086	0-4	U = 42.500, z = -2.213 p = .027*
10 Phonemes	3.00	1.069	1-4	2.14	.990	1-4	U = 48.000, z = -1.974, p = .048*

Table 4.18: Comparison of MND participants who completed all three conditions and controls on the number of MSNW produced in each condition by phoneme length of the targets (maximum 4)

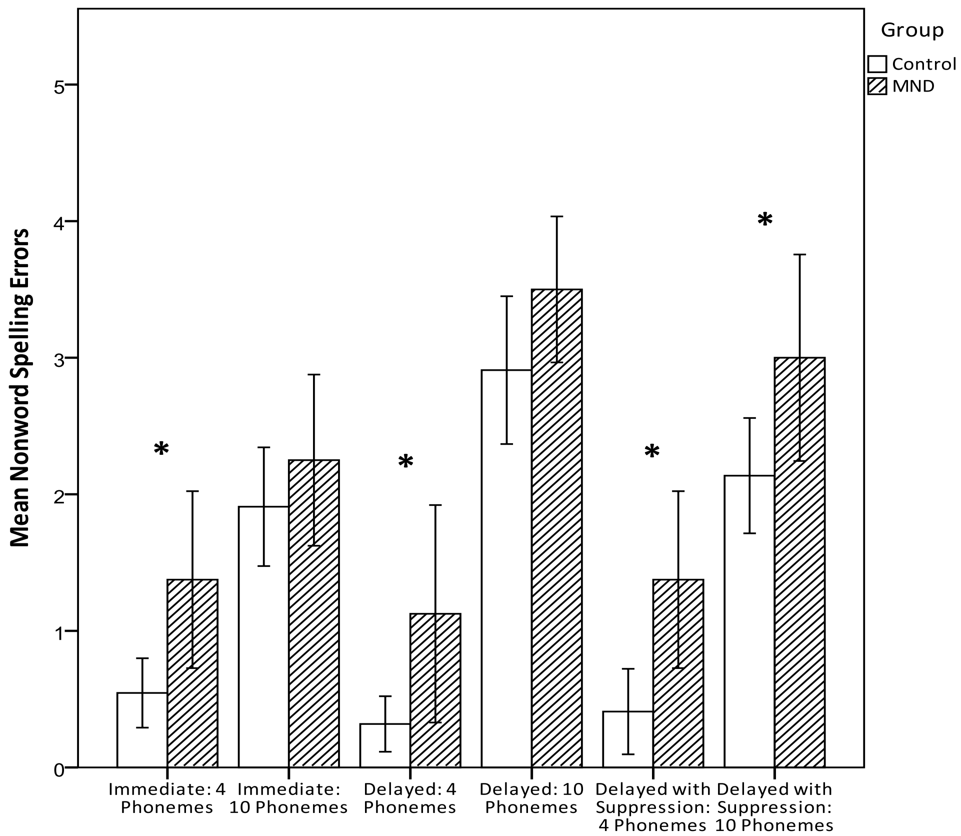


Figure 4.17: Number of 4 and 10 phoneme MSNW produced by MND participants and controls across the three conditions (maximum 4) - * indicates significance (p<.05)

Wilcoxon tests of within group comparison for word length effects revealed that in the immediate condition the control group produced significantly more MSNW when spelling long nonwords (10 phonemes) than short nonwords (4 phonemes) (T = 4.50, p = .000). MND participants also produced significantly more MSNW when spelling long nonwords than short nonwords in the immediate condition (T = .00, p = .034). In the delayed condition the control group produced significantly more MSNW spelling long nonword than short nonwords (T = .00, p =.000). MND participants also produced significantly more MSNW spelling long nonwords than short nonwords in the delayed condition (T =.00, p =.011). In the delayed with articulatory suppression condition the control group produced significantly more MSNW spelling long nonwords than short nonwords (T = 4.00, p =.000). MND participants also produced significantly more MSNW spelling long nonwords than short nonwords in the delayed with articulatory suppression condition (T = .00, p = .026).

4.3.1.1.4.2 All participants who completed immediate and delayed conditions

When the scores of all MND participants who completed the immediate and delayed conditions were analysed, MND participants performed significantly worse than controls on nonword spelling in both the immediate and delayed conditions (see Table 4.19 and Figure 4.18).

Condition	MND (n 16)			Control (n 22)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate (12)	6.00	3.246	1-10	8.95	1.397	6-11	U = 76.500, z = -2.987, p = .003*
Delayed (12)	4.94	2.407	1-11	7.64	1.941	4-11	U = 61.500, z = -3.417 p = .001*

Table 4.19: Comparison of total scores for all MND participants who completed and controls on immediate and delayed nonword spelling

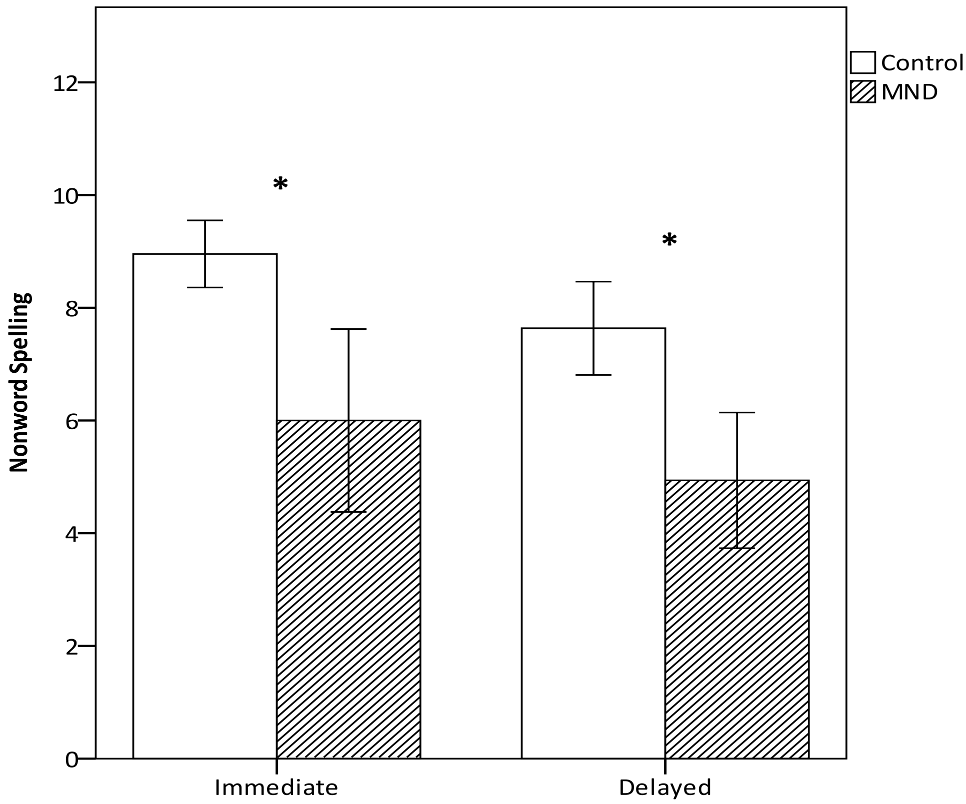


Figure 4.18: Number of nonwords spelled correctly by all MND participants who completed the immediate and delayed conditions- * indicates significance (p<.05)

Effect of condition: Wilcoxon tests of within group comparison of performance on the immediate and delayed conditions revealed that control participants were significantly worse at spelling nonwords in the delayed condition than the immediate condition (T = 27.50, p = .003). However there was no significant difference in performance of nonword spelling between the immediate and delayed conditions for all the MND participants who completed these conditions (T = 27.50, p = .062).

Effect of word length: On analysis of MSNW patterns according to the number of phonemes in the target (see Table 4.20 and Figure 4.19), the MND participants produced significantly more MSNW than controls when spelling 4 and 7 phoneme nonwords in the immediate condition, however there was no significant difference between the groups in the number of MSNW produced when spelling 10 phoneme nonwords in this condition, although there was a trend towards significance. In the delayed condition MND participants produced significantly more MSNW than controls when spelling nonwords 4 and 7 phonemes in length, however there was no significant difference between the groups in the number of MSNW produced when spelling 10 phoneme nonwords in the second condition.

Wilcoxon test of within group comparison for word length effects revealed that in the immediate condition both the control group (T = 4.50, p = .000) and MND participants (T = .00, p = .001) produced significantly more MSNW when spelling long nonwords (10 phonemes) than short nonwords (4 phonemes). In the delayed condition again both the control group (T = .00 p = .000) and MND participants (T = .00, p = .000) produced significantly more MSNW spelling long nonword than short nonwords.

Condition	MND (n 16)			Controls (n 22)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate							
4 Phonemes	1.56	1.094	0-3	.55	.596	0-2	U = 81.500, z = -2.969, p = .003*
7 Phonemes	1.75	1.483	0-4	.59	.854	0-3	U = 97.500, z = -2.474, p = .013*
10 Phonemes	2.56	.964	1-4	1.91	1.019	0-4	U = 114.000, z = -1.955, p = .051
Delayed							
4 Phonemes	1.19	.911	0-3	.32	.477	0-1	U = 79.000, z = -3.142, p = .002*
7 Phonemes	2.44	1.094	0-4	1.14	.941	0-3	U = 67.000, z = -3.318, p = .001*
10 Phonemes	3.44	.796	1-4	2.91	1.269	0-4	U = 136.00, z = -1.291, p = .197

Table 4.20: Comparison of all MND participants who completed the immediate and delayed conditions and controls on the number of MSNW produced in each condition by phoneme length of the targets (maximum 4)

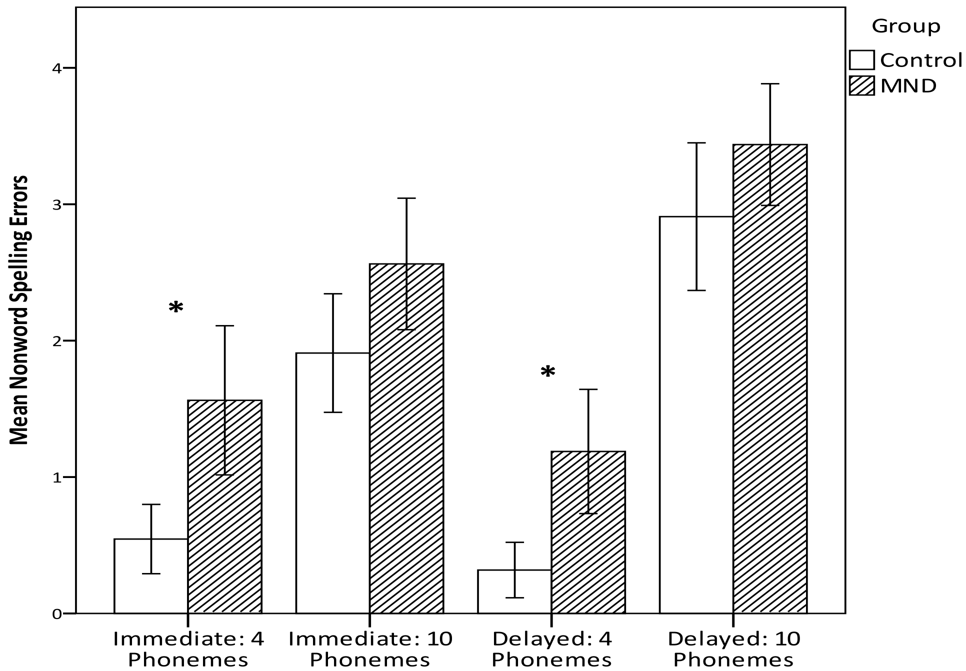


Figure 4.19: Number of 4 and 10 phoneme MSNW produced by all MND participants who completed the immediate and delayed conditions and controls across the three conditions (maximum 4) - * indicates significance (p<.05)

4.3.1.1.4.3 Summary of Findings: MND participants performed significantly worse than controls in all three nonword spelling conditions, however there was no effect of condition on performance. Both patients and controls made significantly more MSNW when spelling long nonwords over short.

4.3.1.2 Bulbar Onset vs Non-bulbar Onset

Subdivision of the MND group into bulbar and non-bulbar onset groups revealed the following:

4.3.1.2.1 Minimal Pair Discrimination

There was no significant difference between bulbar and non-bulbar onset participants in the ability to discriminate both word and nonword minimal pairs (see Table 4.21).

Variable	Bulbar Onset (n 14)			Non-bulbar Onset (n 10)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Word Minimal Pairs (48)	47.00	1.109	45-48	47.10	1.853	42-48	U = 57.500, z = -.804, p = .421
Nonword Minimal Pairs (48)	47.36	1.277	44-48	47.30	1.252	44-48	U = 63.500, z = -.456, p = .648

Table 4.21: Comparison of total scores for bulbar and non-bulbar onset MND participants on word and nonword minimal pairs

4.3.1.2.2 Word spelling

Ten bulbar onset and eight non-bulbar onset participants completed all three conditions of the word spelling test. There was no significant difference in performance between the bulbar and non-bulbar onset participants in all three conditions (see Table 4.22).

Variable	Bulbar Onset (n 10)			Non-bulbar Onset (n 8)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate Spelling (12)	9.20	3.327	1-12	9.75	2.915	3-12	U = 35.500, z = -.407, p = .684
Delayed Spelling (12)	9.40	3.307	2-12	10.63	2.774	4-12	U = 29.000, z = -1.045, p = .296
Delayed Spelling with Suppression (12)	9.60	3.239	2-12	10.63	2.066	6-12	U = 32.000, z = -.738, p = .460

Table 4.22: Comparison of total scores for bulbar and non-bulbar onset MND participants who completed all three conditions on immediate, delayed and delayed with suppression word spelling

When the scores of all MND participants who completed the immediate and delayed conditions are analysed (15 bulbar and 10 non-bulbar onset), again there was no significant difference in performance between bulbar and non-bulbar onset participants in the immediate and delayed conditions (Table 4.23).

Variable	Bulbar Onset (n 15)			Non-bulbar Onset (n 10)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate Spelling (12)	9.47	2.973	1-12	10.10	2.685	3-12	U = 63.500, z = -.654, p = .513
Delayed Spelling (12)	9.20	2.933	2-12	10.70	2.452	4-12	U = 46.000, z = -1.656, p = .098

Table 4.23: Comparison of total scores for bulbar and non-bulbar onset MND participants who completed the immediate and delayed word spelling conditions

4.3.1.2.3 Nonword Repetition

Four bulbar and five non-bulbar onset participants completed the nonword repetition test. There was no significant difference in performance between bulbar and non-bulbar onset participants in all 3 conditions (see Table 4.24).

Condition	Bulbar Onset (n 4)			Non-bulbar Onset (n 5)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate (12)	8.50	1.291	7-10	7.80	1.789	5-10	t = .654 p = .534
Delayed (12)	6.75	.500	6-7	6.80	3.271	3-10	U = 9.500, z = -.129, p = .898
Delayed with Suppression (12)	7.00	2.828	3-9	4.20	3.114	1-8	t = 1.394, p =.206

Table 4.24: Comparison of total scores for bulbar and non-bulbar onset MND participants on immediate, delayed and delayed with suppression nonword repetition

4.3.1.2.4 Nonword Spelling

Five bulbar onset and three non-bulbar onset participants completed all three conditions of the nonword spelling test. There was no significant difference in performance between bulbar and non-bulbar onset MND participants in all three conditions (see Table 4.25).

Condition	Bulbar Onset (n 5)			Non-bulbar Onset (n 3)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Immediate (12)	6.20	3.899	1-9	8.00	1.000	7-9	U = 7.500, z = .000, p = 1.000
Delayed (12)	4.80	2.864	1-8	5.33	1.528	4-7	t = -.292, p = .780
Delayed with Suppression (12)	5.20	2.775	2-8	5.33	2.083	3-7	t = -.071, p = .946

Table 4.25: Comparison of total scores for bulbar and non-bulbar onset MND participants who completed all three conditions on immediate, delayed and delayed with suppression nonword spelling

When the scores of all MND participants who completed the immediate and delayed conditions are analysed (11 bulbar and 5 non-bulbar onset), again there was no significant difference in performance between bulbar and non-bulbar onset participants in the immediate and delayed conditions (see Table 4.26).

Condition	Bulbar Onset (n 11)			Non-bulbar Onset (n 5)			Statistics
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**	
Immediate (12)	5.36	3.668	1-10	7.40	1.517	5-9	t = -1.570, p = .139
Delayed (12)	4.82	2.857	1-11	5.20	1.095	4-7	U = 20.000, z = -.870 p = .384

Table 4.26: Comparison of total scores for bulbar and non-bulbar onset MND participants who completed the immediate and delayed nonword spelling conditions

4.3.2 Individual Patient Characteristics

As in previous chapters, the performance of individual MND participants was compared against the control group mean using z-scores. Z-scores were calculated by subtracting the control mean from each individual patient score and dividing by the control group standard deviation (SD). Performance on measures was taken to be impaired where the z-score fell 2 or more below the control mean, that is, a z-score of ≤ -2.

Table 4.27 (next page) shows individual scores for MND participants on the experimental linguistic measurements. Of the 25 participants, 10 were not impaired on any experimental linguistic measure completed (L120, L161, L51, L121, G91, G97, L146, G92, G118 and L903). Only participants L171 and L901 were impaired on all of the experimental linguistic assessments completed, however participant L171 had a WHO category 'slight' hearing impairment within range of speech perception impact (see chapter 2), which may have impacted upon performance in these tests. In addition participant L901 only completed the three word spelling conditions therefore interpretations about performance across these linguistic measures cannot be accurately made for this participant.

	Onset site	Word Spelling C1	Word Spelling C2	Word Spelling C3	Nonword Spelling C1	Nonword Spelling C2	Nonword Spelling C3	Nonword Rep C1	Nonword Rep C2	Nonword Rep C3	Word Min Pairs	Nonword Min Pairs
L120	UL				DNC	DNC	DNC	DNC	DNC	DNC		
L161	UL				DNC	DNC	DNC					
L51	LL			DNC			DNC	DNC	DNC	DNC		
L46	LL			DNC	▨		DNC	DNC	DNC	DNC		
L121	LL							DNC	DNC	DNC		
G91	LL											
L903	bulbar										▨	
G118	bulbar				DNC	DNC	DNC	DNC	DNC	DNC		
G97	bulbar				DNC	DNC	DNC					
L146	bulbar						DNC			DNC		
G92	bulbar											
G100	bulbar			DNC	▨		DNC	DNC	DNC	DNC		▨
L125	UL			▨	DNC	DNC	DNC	▨				
L174	LL		■		DNC	DNC	DNC			▨		
L176	LL	■	■	■	DNC	DNC	DNC			▨	■	■
L107	bulbar		■	DNC	■	▨	DNC	DNC	DNC	DNC	▨	
L54	bulbar		■	DNC		■	DNC	DNC	DNC	DNC		
L171	bulbar	■	■	■	■	■	▨	DNC	DNC	DNC	■	■
L165	bulbar	■	■	■	■	▨	■	DNC	DNC	DNC	▨	
L169	bulbar		■	DNC	■	▨	DNC	DNC	DNC	DNC	▨	
L902	bulbar		■	▨								
L904	bulbar	■	■	DNC	■	▨	DNC	DNC	DNC	DNC		
L901	bulbar	■	■	■	DNC	DNC	DNC	DNC	DNC	DNC	DNC	DNC
L900	bulbar	■	■		DNC	DNC	DNC	DNC	DNC	DNC	▨	

Table 4.27: Table of Impairment for MND participants on the experimental linguistic measures; DNC = Did Not Complete; ▨ = ≥2 SD below control mean; ■ = ≥ 3 SD below control mean C1 = Immediate; C2 = Delayed; C3 =Delayed with Suppression; Rep = Repetition.

This distribution of impaired performance suggests several things. Firstly, as 40% of participants were not impaired on any experimental linguistic assessment, these linguistic impairments are not prevalent across the group as a whole. Following on from this, as this percentage is higher than the 20% who were not impaired on any standard linguistic assessment (see chapter 3), this suggests that these tests tap into a more specific set of linguistic skills, and thus reveal more specific linguistic impairment than standard linguistic measures. Thirdly, that those who were impaired on some experimental linguistic measures were not impaired across all measures, and that this pattern was not consistent across all impaired participants, suggests that there may be multiple forms of linguistic impairment evident in our participants.

4.3.2.1 Minimal Pairs

Of the 24 participants who completed the word minimal pairs assessment, 7 performed at least 2SD below the control mean, representing a 29% impairment rate, of which 2 participants (L176 and L171) performed ≥3SD below the control mean. Only 3 of the 24 participants performed at least 2SD below the control mean on the nonword minimal pairs assessment, representing a 13% impairment rate. The two participants who performed ≥3SD below the control mean on the word minimal pairs assessment also performed ≥3SD below the control mean on the nonword minimal pairs assessment. Participant G100 was the only participant who was impaired on nonword minimal pairs, but not on word minimal pairs. Conversely participants L107, L165, L169, L903 and L900 were impaired on the word minimal pairs assessment, but not the nonword version. This may suggest some influence of lexicality upon performancefor these participants.

4.3.2.2 Word Spelling

Of the 25 participants who completed the immediate word spelling, 7 performed ≥3SD below the control mean, representing a 28% impairment rate.

In the delayed condition 11 participants performed ≥3SD below the control mean, representing a 44% impairment rate. Only 18 of the 25 participants completed the delayed with articulatory suppression condition, of whom 7 performed at least 2 SD below the control mean, representing a 39% impairment rate. Of the 7 impaired on the final condition, 4 (L176, L171, L165 and L901) performed ≥3SD below the control mean, all of whom also performed ≥3SD below the control mean on both the immediate and delayed conditions. Participant L904 was the only other participant to perform ≥3SD below the control mean on all conditions completed, having not completed the delayed with articulatory suppression condition. Of these 5 participants who had 100% impairment across all word spelling conditions completed, 3 (L171, L165 and L904) completed the nonword spelling test and were again impaired on all nonword spelling conditions completed. This suggests that the spelling impairment seen in these participants is due to a deficit in a process common to both word and nonword spelling and therefore at a post-lexical level, although the possibility exists of multiple orthographic deficits of both the lexical and sublexical spelling routes.

4.3.2.3 Nonword Repetition & Spelling

Only 10 of the 25 MND participants completed the nonword repetition test. Of these 10, only one participant (L125) was impaired on the immediate condition, while a further two participants (L174 and L176) were impaired on the delayed with articulatory suppression condition.

Sixteen participants completed the immediate and delayed conditions of the nonword spelling assessment, while only 8 of these participants were able to complete all three conditions. In the immediate condition, 7 participants performed at least 2SD below the control mean, while 5 of these scores (L107, L171, L165, L169 and L904) performed ≥3SD below the control mean. In the delayed condition, 6 participants performed at least 2SD below the control mean, of which 2 performed ≥3SD below the control mean and 5 (L107, L171, L165, L169 and L904) were those participants who were also ≥3SD below the control mean in the immediate condition. Three of the 8 participants who completed the delayed with articulatory suppression performed at least 2SD below the control mean, of whom 2 (L171 ad L165) were also impaired on the immediate and delayed nonword spelling conditions.

Only 5 of the 25 MND participants completed both the nonword repetition and nonword spelling assessments. None of these participants (G91, L146, G92, L902 and L903) were impaired on any condition on either test. This indicates that the phonological input to output conversion and phonological assembly processes common to both the repetition and spelling tests are intact in these participants, in addition to the graphemic output processes required for the nonword spelling task alone. However as the participants who were impaired on the nonword spelling test were unable to perform the nonword repetition test, it is difficult to draw conclusions as to whether this impairment is phonological or orthographic in nature.

4.4 Discussion

4.4.1 Phonological processing

4.4.1.1 Minimal Pairs

Although there was no significant difference between MND participants and control groups in both word and nonword minimal pairs assessments, interesting observations can be made from individual patterns of performance. That some participants were impaired on word and not nonword minimal pairs, and that there were a greater number of participants impaired on word minimal pairs than nonword suggests that there may be an effect of lexicality upon performance of some individuals. As nonword minimal pair discrimination is not aided by additional information from the phonological input lexicon, this is a purer test of auditory phonological analysis. However, in the same way that word minimal pair discrimination can be assisted by intact lexical knowledge, it could be suggested that impaired lexical knowledge may be a hindrance. This is supported by findings in semantic dementia patients, whereby those with mild semantic impairment performed worse in minimal pair discrimination than those with more severe semantic impairments (Reilly et al., 2007). In addition this pattern of lexical interference on phonological processing performance has been shown in stroke aphasia patients, with better rhyme judgements for nonwords over real words (Kalinyak-Fliszar, Kohen, & Martin, 2006).

The two participants who were impaired on both word and nonword minimal pairs both performed well below the control mean for both tests, which could suggest two things: either these participants displayed a genuine impairment at the level of auditory phonological analysis or as both participants have suspected hearing impairments (see chapter 2), their performance was affected by an acoustic and not linguistic variable. However, the overall lack of significant difference between groups in both word and nonword minimal pair assessments suggests not only that there is not a general phonological analysis deficit, but also the integrity of the auditory phonological analysis system is intact and that this cannot be responsible for spelling errors on the spelling to dictation test.

4.4.1.2 Nonword Repetition

Unfortunately only limited conclusions can be drawn about the integrity of phonological input to output processes, and the relationship between written and spoken deficits in MND from performance on the nonword repetition test due to limited numbers. Only nine of the 25 MND participants were able to complete the nonword repetition test. While this assessment may have been able to provide further information about the likely locus of spelling impairment and the integrity of phonological processes, it was not really suitable for use with the participants in this study due to the dysarthria severity of many of the participants. However, future research examing nonword repetition performance comparison to word and nonword spelling performance in MND patients with little to no dysarthria may produce useful insights.

4.4.2 Spelling

That MND participants were significantly worse than controls in all three conditions of word spelling to dictation is in keeping with both case reports (Ferguson & Boller, 1977b; Ferrer et al., 1991; Ichikawa, Koyama, et al., 2008; Ichikawa, Takahashi, et al., 2008; Lucchelli & Papagno, 2005) and more recent group studies (Taylor et al., 2013; Zago et al., 2008) reporting evidence of spelling impairment in MND patients. However, previous studies have done little to explore the nature of these spelling deficits. The results presented from this experimental spelling to dictation test begin to shed some light on the likely locus of spelling impairment observed in a subgroup of MND patients.

In considering the effect of presentation condition on the spelling performance, it was surprising that there was no within group difference for either the control or MND group. The original hypothesis was that both MND participants and controls would perform best in the immediate condition, with controls showing a gradual decline in performance with each subsequent condition, but that MND participants would show little difference in performance between the delayed and delayed with articulatory suppression condition. This hypothesis was born out of the suggestion by Lucchelli and Papagno's (2005) study that spelling errors seen in the MND case reported there may be attributable to a deficit in subvocal rehearsal, and that similar error patterns were observed in controls when spelling under articulatory suppression. From the results of this study it could be suggested that as the delayed with articulatory suppression condition is no more difficult for both controls and MND participants than the immediate condition, subvocal rehearsal is not being employed in this task. Rather, it could be suggested that lexical representations are being refreshed via the orthographic output lexicon. In a study examining articulatory rehearsal and suppression in serial spoken recall of words and nonwords, Romani and colleagues have suggested that, in the presence of suppression and disrupted phonological retention, alternative lexical-semantic representations are used to recall words (Romani et al., 2005). Furthermore, it has been questioned whether an output buffer and the associated rehearsal mechanism is even required in the production of single words due to the continued activation of phonemes within familiar words through permanent links to the lexicon (Romani, Galluzzi, & Olson, 2011).

However, as nonwords do not have lexical-semantic representations from which support can be drawn, there is a greater reliance on output buffer performance in nonword spelling, MND participants performed significantly worse than controls in all three nonword spelling conditions, and nonword spelling performance was worse than word spelling for both MND participants and controls. However, within group comparison revealed that while controls were significantly worse at spelling nonwords in the delayed condition than the immediate condition, there was no significant difference in performance between the two conditions for the MND participants. This suggests that the delayed condition was no more difficult for MND participants than the immediate condition and could support the presence of a graphemic buffer impairment. In addition, the presence of a word length effect, in both nonword and word spelling is in keeping with a graphemic buffer deficit.

The lack of word class effect in word spelling for both the control and MND groups is noteworthy for several reasons. While items were matched as closely as possible for frequency when designing the test, verb items were significantly less frequent than noun items. This was a flaw in the test that future assessment should take into consideration, as a frequency effect could wrongly be interpreted as an effect of another variable, such as word class in this case. Reports of greater errors in verb naming and comprehension over noun would predict more MSW when writing verbs than nouns (T. Bak & Hodges, 1997; T. H. Bak et al., 2001). With verbs items in this spelling to dictation assessment being lower frequency than noun items, this may have also predicted more MSW with verbs over nouns. However as there was no effect of word class, or frequency for that matter, this could suggest that the spelling to dictation is not being conducted via the semantic system, but rather a lexical or sublexical route. Alternatively, this may also support the hypothesis that the dysgraphia observed in MND patients is at the level of the graphemic output buffer, as traditionally a deficit at this level, being post lexical, should not be affected by lexical variables such as word class and frequency (Caramazza et al., 1987). However, other researchers have questioned the detachment of the graphemic buffer from lexical influences, thus the influence of word class and frequency in graphemic buffer disorders is still a matter for debate (Sage & Ellis, 2004).

However, not all MND participants displayed evidence of dysgraphia and it is difficult to draw conclusions about the likely locus of the spelling impairment seen in those who were impaired on measures of spelling when performing analyses of whole group performance against controls. A review of the overall pattern of linguistic impairment, in addition to a more qualitative examination of error patterns may help to identify the nature of spelling deficits in impaired participants and the possible correlates with impairments reported in progressive aphasia. It is for this reason that chapter 5 synthesises MND group performance across the battery, and examines individual case studies of some of the most impaired participants.

Chapter 5: Synthesis

This chapter aims to consolidate the findings from the medical, neuropsychological, standard linguistic and experimental linguistic measures to examine the overall profile of language impairment seen in MND patients in this study.

5.1 Group comparison across all measures: Linguistically Impaired vs Non Linguistically Impaired MND participants

In order to examine the overall pattern of impairment across the MND participants, the nonword repetition, nonword spelling and word spelling tests were collapsed across the immediate and delayed conditions to form one composite score. As there was no significant effect of condition for any of the three assessments (see chapter 4), and as a number of participants were unable to perform the delayed with articulatory suppression condition in the nonword and word spelling tests due, combining the immediate and delayed conditions allows for maximum data to be analysed. The composite word spelling scores for individual MND participants were converted to z-scores (see Table 5.8). Those participants with composite word spelling z-scores that were ≥ 3SD below the control mean were categorised as 'linguistically impaired'. Eleven participants were classed as 'linguistically impaired' (LI), while 14 were classed as 'non linguistically impaired' (NLI). This represents a 44% linguistic impairment rate within the MND group as a whole, which is consistent with the 43% impairment rate on a composite language measure reported in recent study by Taylor and colleagues (Taylor et al., 2013). Participants in the LI group, according to this composite word spelling impairment categorisation, were also impaired on a significantly higher percentage of tests than the non-linguistically impaired participants (see Table 5.1). This suggests that spelling impairment is a salient marker of a more general linguistic impairment.

Variable	MND Linguistically Impaired (n 11)			MND Non Linguistically Impaired (n 14)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Percentage Tests Impaired	56.94	21.906	19.05-100	10.35	10.632	0-38.89	U = 2.500, z = -4.085, p = .000*

Table 5.1: Comparison of LI and NLI MND participants on the percentage of tests impaired on across the entire battery

5.1.1 General and Health Demographic Measurements

Analyses of background measurements from the MND LI and NLI groups revealed no significant difference between the two groups in terms of age, sex and years of education (see Table 5.2). Additionally there was no significant difference between the two groups on measures of disease duration and overall disease severity (as measured through the ALS-FRS). This suggests that differences in performance on linguistic measures between the two groups cannot be attributable to differences in overall disease progression. Furthermore there was no significant difference in performance between the two groups on measures of anxiety and depression (as measured through the Hospital Anxiety and Depression Scale (HADS)) and levels of daytime sleepiness (as measured through the Epworth Sleepiness Scale (ESS)) – an indicator of respiratory insufficiency, which, as discussed in chapter 2, has been shown to impact upon cognitive functioning (Newsom-Davis et al., 2001). This is also supported by the lack of significant difference between the two groups on the respiratory subscore of the ALS-FRS).

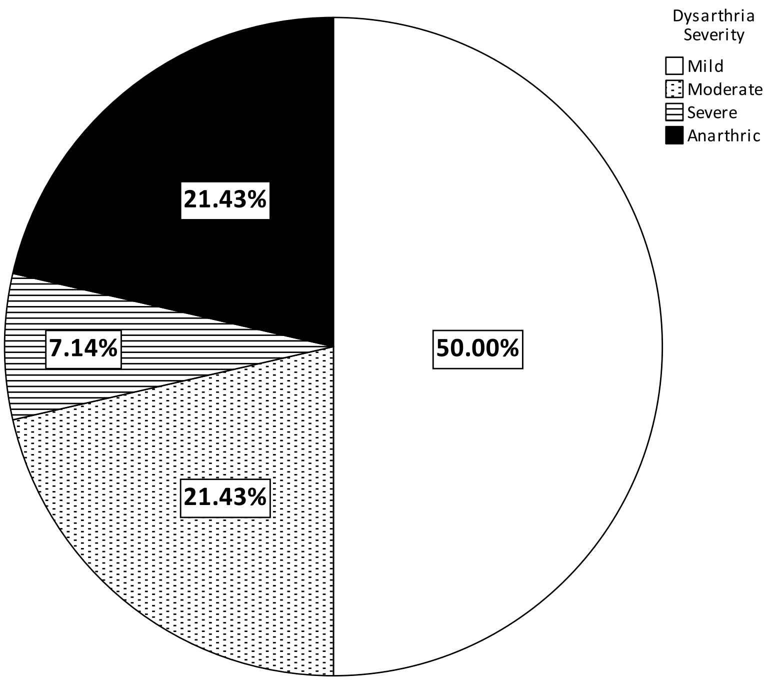
When the Computerised Frenchay Dysarthria Assessment (CFDA) dysarthria severity measures were grouped in to mild-moderate and severe-anarthric categories, there was no significant difference between LI and NLI groups in terms of dysarthria severity (see Table 5.2). This was also echoed through the lack of significant difference between the two groups on the bulbar score of the

ALS-FRS. However, while there was no significant difference in the dysarthria severity between the LI and NLI, over 63% of the participants in the LI group

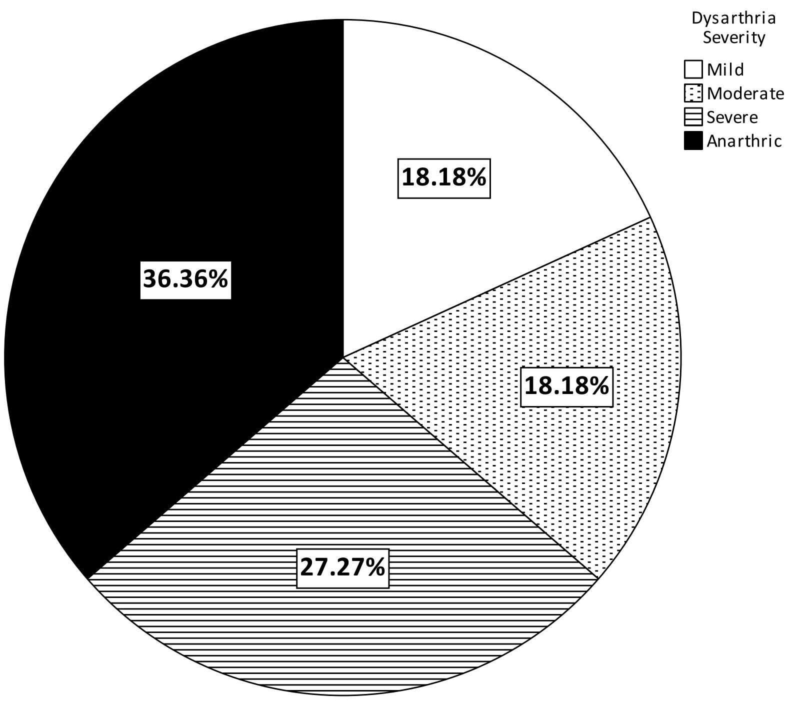
Variable	MND Linguistically Impaired (n 11)			MND Non Linguistic Impaired (n 14)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Age	60.55	12.127	40-77	61.64	8.741	47-79	t = .263, p = .795
Sex	6 M; 5 F	-	-	3 M; 11 F	-	-	χ^2 (1) = 2.932, p = .087
Education (years)	11.36	2.976	10-20	11.64	1.946	10-16	U = 53.000, z = -1.385, p = .166
Onset	9 B; 2 NB	-	-	6 B; 8 NB	-	-	χ^2 (1) = 3.896, p = .048*
Disease Duration (months)	15.73	8.284	7-36	29.36	32.498	7-108	U = 56.500, z = -1.124, p = .261
Dysarthria Severity	4 M-M; 7 S-A	-	-	10 M-M; 4 S-A	-	-	χ^2 (1) = 3.074, p = .080
ALS FRS	30.73	6.589	18-39	32.57	9.701	18-45	t = .539, p = .595
ALS FRS Bulbar	5.82	3.628	1-11	7.14	3.278	0-10	U = 58.500, z = -1.022, p = .307
ALSFRS Respiratory	11.18	1.168	8-12	10.64	1.823	6-12	U = 67.500, z = -.558, p = .577
HADS A	4.78 (n 9)	2.279	2-10	5.21	4.117	1-13	t = .326, p = .747
HADS D	5.33 (n 9)	4.093	1-13	2.57	2.065	0-7	t = -1.877, p = .088
ESS	6.09	5.186	0-16	5.50	3.917	0-11	t = -.325, p = .748

Table 5.2: Comparison of LI and NLI MND participants on background and medical measures
ALS-FRS = ALS Functional Rating Scale; HADS = Hospital Anxiety and Depression Scale (A = Anxiety; D = Depression); ESS = Epworth Sleepiness Scale

had either severe dysarthria or anarthria (see Figure 5.1 next page), and there were also significantly more bulbar onset participants in the LI group than the in NLI group (see Table 5.2). Thus while there may not be a significant



Non Linguistically Impaired



Linguistically Impaired

Figure 5.1: Percentage of NLI (Top) and LI (Bottom) MND participants according to Dysarthria Severity

relationship between dysarthria severity and linguistic impairment, this finding makes two critical points. Firstly the communication difficulties are not solely attributable to dysarthria in all MND patients. Secondly there is high proportion of MND patients for whom severe dysarthria or anarthria may not only be a significant speech difficulty, but may also be masking other linguistic impairment.

5.1.2 Genetic considerations: C9ORF72 mutation

While this study is not primarily concerned with the genetic or pathological changes associated with linguistic and cognitive change in MND, the last two years have seen major advancements concerning our understanding of the genetic relationship between MND and FTLD. In 2011, the hexanucleotide GGGGCC repeat expansion of the C9ORF72 gene was identified as being present in families with a history of MND and/or FTLD (DeJesus-Hernandez et al., 2011; Renton et al., 2011). As Snowden and colleagues highlight, this discovery raises a number of questions about the clinical phenotype of such patients (Snowden et al., 2012). Particularly relevant this study is the question that as MND has previously been associated with the PNFA (Caselli et al., 1993; Catani et al., 2004; Doran et al., 1995) and SD (Kim et al., 2009; Ostberg & Bogdanovic, 2011) variants of Primary Progressive Aphasia (PPA), a form of FTLD, can the C9ORF72 mutation provide more information about the existence of language impairment in some MND patients and not others?

As part of the Scottish Motor Neurone Disease Register, Audit, Research and Trials (SMART) project currently being conducted at the University of Edinburgh, blood samples were obtained from a number of participants who gave consent to be involved in the DNA bank arm of the project. Eight of these had their samples screened for the C9ORF72 mutation, using the method described by Renton and colleagues (Renton et al., 2011). Under the guidelines of the ethics approval for the SMART project, the researcher of this study was blind to the identities of those from whom bloods samples had been obtained and tested. Two lists containing the names of participants who were in the LI and NLI groups were given to the researcher of the register study, identified to them as group A (LI) and group B (NLI).

Of the participants in group A, the LI group, 3 of the 11 had given blood samples for analysis, of which none were identified as having the C9ORF72 mutation. Of the participants in group B, the NLI group, blood samples had been obtained from 5 of the 14, of which one participant was identified as having the C9ORF72 mutation. While only tentative conclusions can be drawn from these results due to the limited number of blood samples obtained from participants, it could be suggested that the C9ORF72 mutation is not associated with language impairment in MND. Indeed, research into the clinical characteristics of those with the C9ORF72 mutation suggests that the strongest association is with behavioural variant FTLD (B. F. Boeve et al., 2012; Chio et al., 2012; Snowden et al., 2012). Furthermore, there is little association between the mutation and language impairment in the literature, with an absence of cases presenting with SD or PNFA in several studies (B. F. Boeve et al., 2012; Byrne et al., 2012; Chio et al., 2012).

5.1.3 Neuropsychological Background Assessment

Between group analyses of performance on measures of working memory revealed that there was no significant difference in performance on forward digit span, forward spatial span and reverse spatial span tasks (see Table 5.3 and Figure 5.2). However, the LI group were significantly worse than the NLI group on the reverse digit span task.

Variable	MND Linguistically Impaired (n 11)			MND Non Linguistically Impaired (n 14)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Forward digit span	6.00 (n 7)	1.000	5-7	6.85 (n 13)	0.801	5-8	U = 24.500, z = -1.834, p =.067
Reverse digit span	3.86 (n 7)	0.690	3-5	5.69 (n 13)	1.109	4-7	U = 9.500, z = -2.963, p = .003*
Forward spatial span	5.00 (n 7)	1.414	3-7	5.69 (n 13)	1.251	4-8	t = 1.129, p = .274
Reverse spatial span	4.43 (n 7)	1.272	3-6	5.15 (n 13)	1.144	3-7	t = 1.302, p = .209
VFI Written Unconstrained	16.6790 (n 10)	30.978	2.28-103.00	2.5507 (n 14)	1.715	.57-6.90	U = 21.000, z = -2.870, p =.004*
VFI Written Constrained	49.5290 (n 10)	38.158	11.63-116.00	9.6771 (n 14)	7.761	1.95-34.30	U = 4.000, z = -3.865, p = .000*
VFI Spoken Unconstrained	15.9240 (n 5)	23.815	4.09-58.50	3.7991 (n 11)	1.160	2.44-6.50	U = 5.500, z = -2.494, p = .013*
VFI Spoken Unconstrained	16.0920 (n 5)	7.846	9.33-29.00	7.5809 (n 11)	3.606	3.67-14.00	t = -3.043, p =.009*

Table 5.3: Comparison of LI and NLI MND participants on background neuropsychological measures

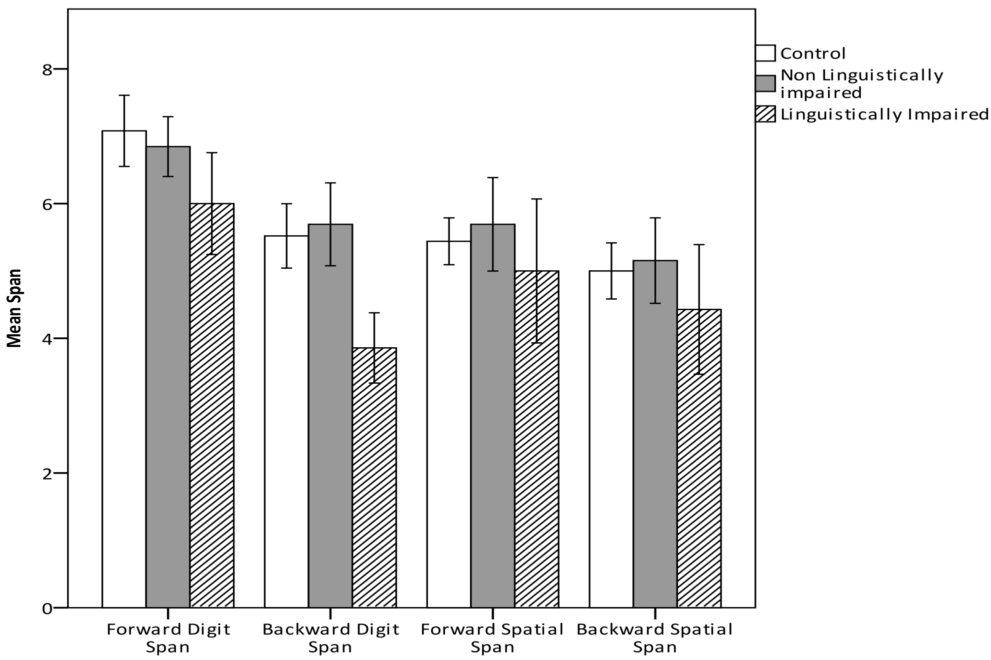


Figure 5.2: Mean digit and spatial spans for control, MND NLI and MND LI participants

Regarding executive functioning, the LI group were significantly worse than the NLI group on all verbal fluency measures, both constrained and unconstrained, written and spoken (see Table 5.3 and Figure 5.3). However, whether these verbal fluency scores purely reflect an executive dysfunction is a matter of debate. As the test also comprises a strong linguistic component it could be argued that this pattern of performance is heavily influenced by the presence of linguistic impairment.

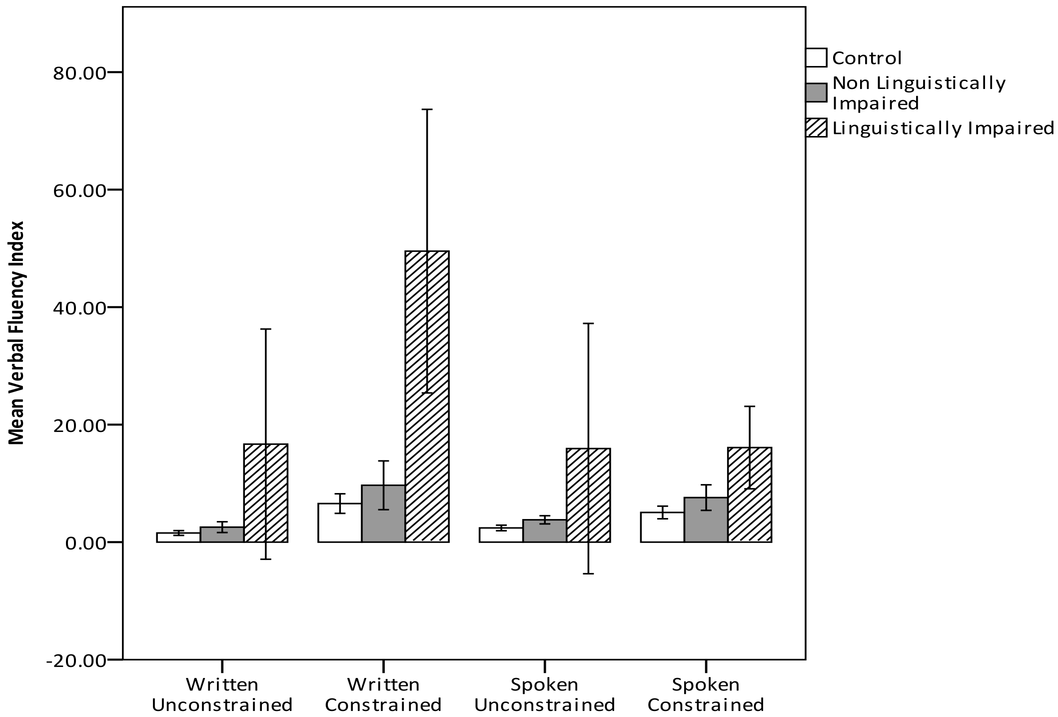


Figure 5.3: Mean verbal fluency indices for control, MND NLI and MND LI participants

When comparing the performance of the NLI group on the verbal fluency measures against controls, there was no significant difference between the groups on the written unconstrained, written constrained or spoken unconstrained variations. However, in the spoken constrained condition, NLI MND participants (mean 7.581, SD 3.609) performed significantly worse than controls (mean 5.050, SD 2.638) ($t = 3.658$, $p = .009$). This difference is most likely attributable to the impaired performance of two participants within the NLI group, one of whom (G91 – see Table 5.8) was not impaired on any other measure except spoken unconstrained verbal fluency. This suggests that while linguistic deficits may contribute to impaired verbal fluency performance, it cannot account for all impaired performances.

5.1.4 Standard Linguistic Assessment

Between group analyses of performance on standard linguistic measures revealed that the LI group were significantly worse on both measures of naming ability: the Graded Naming Test (GNT) and Northwestern Naming Test (NNT) (see Table 5.4 and Figure 5.4). When the NNT was broken down into noun and verb items, participants in the LI group were significantly worse than those in the NLI group at naming both nouns and verbs. Wilcoxon within group comparison revealed that there was no significant difference between the number of noun and verb naming errors produced by both LI participants ($T = 4.00$, $p = .086$), and NLI participants ($T = 1.50$, $p = .414$).

MND LI participants were also significantly worse than non impaired participants in comprehending syntactically complex sentences, as measured through the Test of Reception of Grammar (TROG) (see Table 5.4 and Figure 5.4). In addition MND LI participants were significantly worse than non impaired participants on the two measures of reading skills: Letter String Discrimination test (LS) and the Spelling Verification Test (SVT) (see Table 5.4 and Figure 5.4).

Variable	MND Linguistically Impaired (n 11)			MND Non Linguistically Impaired (n 14)			Statistics
	Mean	SD	Range	Mean	SD	Range	
GNT (30)	16.44 (n 9)	4.613	7-21	24.00 (n 12)	2.796	19-28	t = 4.666, p = .000*
NNT (32)	29.67 (n 9)	1.959	26-32	31.71 (n 14)	0.611	30-32	U = 22.000, z = -2.865, p = .004*
NNT Nouns (16)	15.33 (n 9)	0.866	14-16	15.93 (n 14)	0.267	15-16	U = 38.500, z = -2.143, p = .032*
NNT Verbs (16)	14.33 (n 9)	1.803	11-16	15.79 (n 14)	0.579	14-16	U = 28.000, z = -2.600, p = .009*
TROG (40)	34.82 (n 11)	3.401	28-40	38.21 (n 14)	1.477	35-40	t = 3.369, p = .003*
LSD (48)	45.55 (n 11)	2.876	40-48	47.50 (n 14)	0.760	46-48	U = 35.000, z = -2.438, p = .015*
SVT (72)	67.09 (n 11)	3.239	62-72	71.21 (n 14)	2.155	64-72	U = 12.500, z = -3.697, p = .000*
PEPS Affect (16)	12.57 (n 7)	3.101	8-16	14.36 (n 11)	1.362	13-16	U = 25.000, z = -1.266, p = .206
PEPS Intonation (16)	13.86 (n 7)	1.773	11-16	14.91 (n 11)	1.044	13-16	t = 1.595, p = .130
PEPS Turn-end type (16)	11.88 (n 8)	3.871	6-16	15.3 (n 10)	1.059	13-16	U = 18.500, z = -2.006, p = .045*

Table 5.4: Comparison of total scores for LI and NLI MND participants on standard linguistic measures
GNT = Graded Naming Test; NNT = Northwestern Naming Test; TROG = Test of Reception of Grammar; LSD = Letter String Discrimination; SVT = Spelling Verification Test; PEPS = Profiling Elements of Prosodic Systems

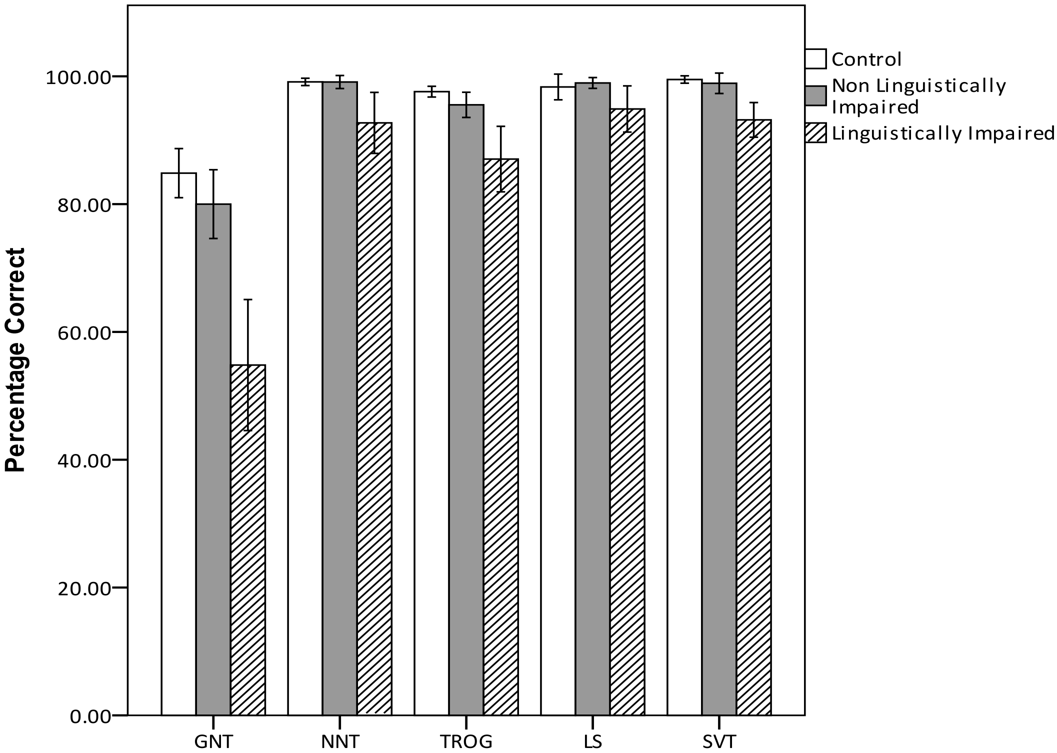


Figure 5.4: Percentage of items correct across standard linguistic measures for controls, MND NLI and MND LI. GNT = Graded Naming Test; NNT = Northwestern Naming Test; TROG = Test of Reception of Grammar; LS = Letter Strings Discrimination; SVT = Spelling Verification Test

On further examination of the errors made on the SVT according to stimuli type (see Table 5.5), the MND LI participants were significantly less accurate than the MND NLI participants at rejecting both phonologically plausible and phonologically implausible nonwords as correct spellings. Wilcoxon within group analysis revealed that while there was no significant difference in the percentage of phonologically plausible and implausible nonwords correctly rejected by NLI participants (T = .00, p = .180), LI participants correctly rejected significantly fewer phonologically plausible nonwords than implausible (T = 4.00, p = .028). In addition, they were also significantly less accurate at identifying correctly spelled real words.

On analysis of the effect of frequency and predictability (regularity), the MND LI participants were significantly worse than MND NLI participants across all variations of frequency and predictability, suggesting no relationship between these variables and impaired performance of MND LI participants on the SVT.

Variable	MND Linguistically Impaired (n 11)			MND Non Linguistically Impaired (n 14)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Correct Word (inc. fillers)	96.46	3.3056	91.70-100	99.60	1.0168	97.20-100	U = 34.000, z = -2.750, p = .006*
Similar Word	96.97	7.7012	75-100	100	0	100-100	U = 63.000, z = -1.628, p = .103
Phonologically Plausible	80.30	16.3653	58.30-100	96.43	13.3631	50-100	U = 30.500, z = -2.965, p = .003*
Phonologically Implausible	90.92	7.8737	75-100	99.41	2.2183	91.70-100	U = 25.000, z = -3.344, p = .001*
HPHF	92.91	9.9574	66.70-100	99.21	2.9666	88.90-100	U = 35.000, z = -2.791, p = .005*
HPLF	93.42	5.4538	83.30-100	98.80	2.3846	94.40-100	U = 31.500, z = -2.782, p = .005*
LPHF	94.45	5.5500	88.90-100	98.41	4.5971	83.30-100	U = 46.500, z = -2.028, p = .043*
LPLF	91.41	6.2540	77.80-100	99.21	2.9666	88.90-100	U = 20.500, z = -3.526, p = .000*

Table 5.5: Comparison of MND NLI and MND LI Participants performance on the SVT showing percentage correct according to stimuli type

Regarding the ability to perceive prosodic differences, as measured using the Profiling Elements of Prosodic Systems (PEPS), comparison of the NLI and LI groups revealed an interesting pattern of impairment. While there was no significant difference between the NLI and LI group in the ability to perceive affective and delexicalised intonation patterns, participants in the LI group were significantly worse than the NLI participants in the perception of linguistic, turn-end type prosody (see Table 5.4 and Figure 5.5). However, as a group as a whole, MND participants were significantly worse than controls in the affective condition (see chapter 3). This suggests that there may be a gradient or spreading pattern of impairment between the LI and NLI in the ability to perceive linguistic and affective prosody. It could be argued that as interpretation of affective prosody requires both intact linguistic skills and social cognition, this is a more difficult task than the question-statement interpretation of the linguistic subtest. Thus while LI participants were impaired on both the linguistic and affective subtests, NLI participants showed a milder prosodic deficit through impaired performance on the affect subtest alone.

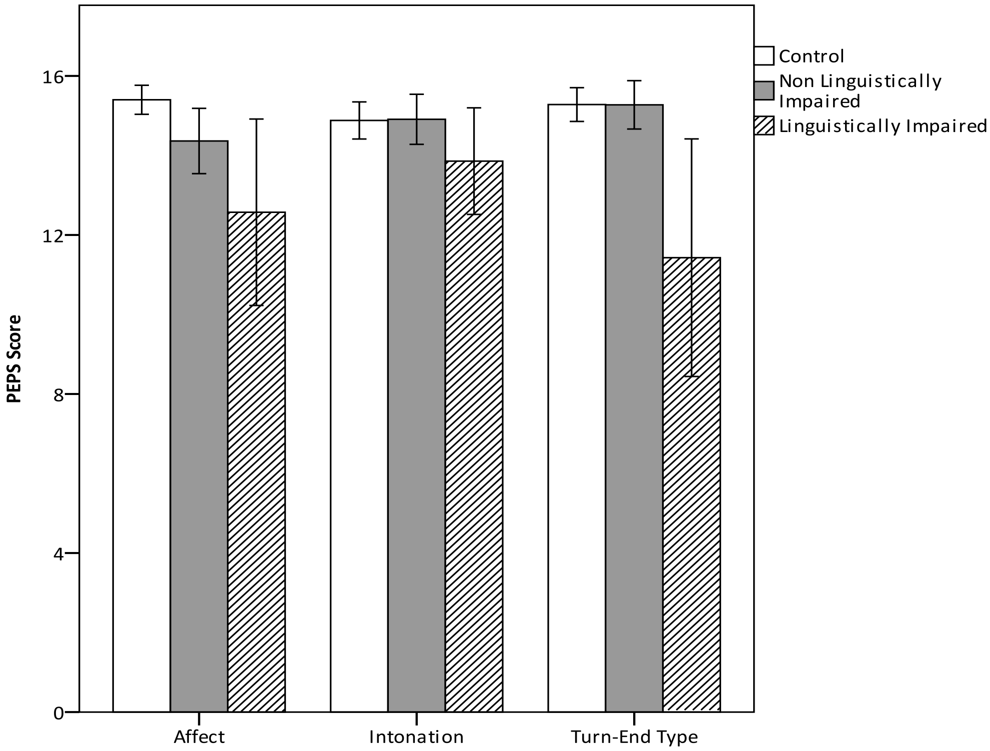


Figure 5.5: Number of items correct when perceiving differences in affect, intonation and turn-end type prosody by control, MND NLI and MND LI participants

5.1.5 Experimental Linguistic Assessment

Comparison of performance on the experimental linguistic assessments revealed no significant difference between the MND NLI and LI participants on phoneme discrimination in both the word and nonword minimal pair assessments, however there was a trend toward significance in the word version of the test (see Table 5.6 and Figure 5.6).

Variable	MND Linguistically Impaired (n 11)			MND Non Linguistically Impaired (n 14)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Word Minimal Pairs (48)	46.30 (n 10)	1.889	42-48	47.57 (n 14)	0.646	46-48	U = 40.000, z = -1.930, p = .054
Nonword Minimal Pairs (48)	46.90 (n 10)	1.595	44-48	47.64 (n 14)	0.842	45-48	U = 48.500, z = -1.510, p = .131
Nonword Repetition Composite (24)	12.50 (n 2)	.707	12-13	15.88 (n 8)	3.357	8-18	U = 2.000, z = -1.591, p = .112
Nonword Spelling Composite (24)	8.25 (n 8)	5.392	4-16	13.63 (n 8)	3.926	9-21	U = 15.500, z = -1.742, p = .082
Word Spelling Composite (24)	15.27	5.968	3-20	22.86	.663	22-24	U = .000, z = -4.303, p = .000*

Table 5.6: Comparison of total scores for LI and NLI MND participants on experimental linguistic measures

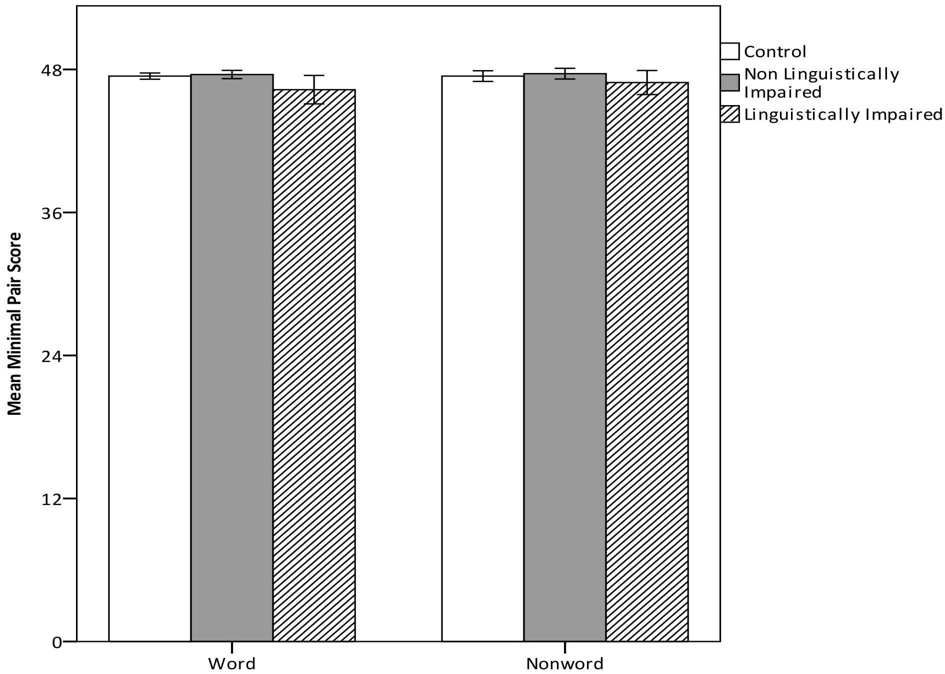


Figure 5.6: Number of items correct on word and nonword minimal pair discrimination for control, MND NLI and MND LI participants

There was no significant difference between MND NLI and LI participants on the nonword repetition and nonword spelling composite scores (see Table 5.6 and Figure 5.7). Furthermore Wilcoxon within group comparison of word and nonword spelling composite scores revealed that both the LI (T = .00, p = .012) and NLI (T = .00, p = .012) groups were significantly worse at spelling nonwords than words. That these participants were impaired on word spelling, but with no significance difference in performance on nonword measures to NLI participants, and a comparative within group difference in performance between word and nonword spelling to NLI participants, it could be suggested that the locus of deficit for the LI group is at a lexical and not sublexical phonological conversion level. However, these results should be interpreted with caution. Three participants who were impaired on word spelling did not complete the nonword spelling test, so their results cannot be included in this group analysis. Furthermore, due to the influence of dysarthria, only two participants from the LI group were able to complete the nonword repetition test. Thus to examine the possible locus of impairment further, individual patient analysis is needed.

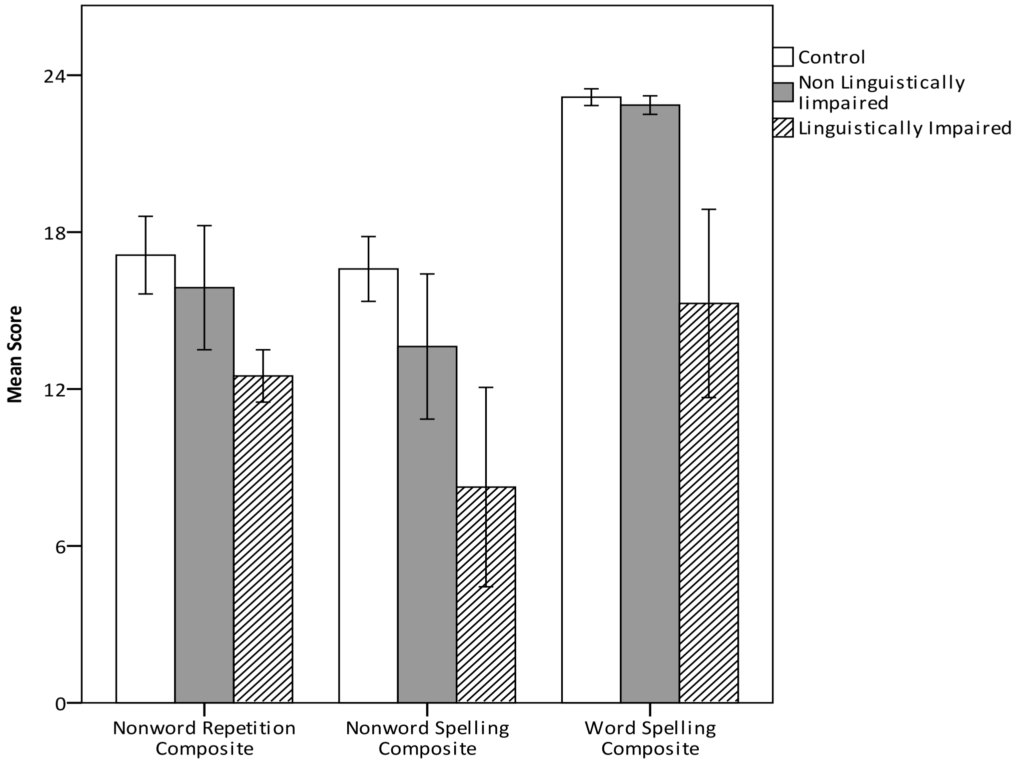


Figure 5.7: Number of items correct on nonword repetition, nonword spelling and word spelling composite measures for control, MND NLI and MND LI participants

5.1.5.1 Word Spelling Composite - Overlap Score

On analysis of MSW patterns according overlap with target scores calculated using the formula described in chapter 4 (see page 112), MND LI participants had a significantly lower overlap with target score than NLI participants for the word spelling composite measure (see Table 5.7).

Variable	MND Linguistically Impaired (n 11)			MND Non Linguistically Impaired (n 14)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Word Spelling Composite Overlap Score (24)	21.94	2.211	16.32-23.69	23.87	0.108	23.66-24.00	t = 2.901 p = .016*

Table 5.7: Comparison of overlap with target total scores for MND LI participants and MND NLI participants on composite word spelling

Analysis of the overlap score in terms of length of target words revealed that MND LI participants had a significantly lower overlap score than NLI participants with target words of all three lengths than controls in word spelling composite measure (see Table 5.8 and Figure 5.8).

Variable	MND Linguistically Impaired (n 11)			MND Non Linguistically Impaired (n 14)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Word Spelling Composite Overlap 4 Letters (8)	7.46	0.807	5.41-8.00	7.98	0.089	7.67-8.00	U = 32.500, z = -2.943, p = .003*
Word Spelling Composite Overlap 7 Letters (8)	7.27	0.786	5.93-7.93	7.95	0.069	7.79-8.00	U = 9.000, z = -3.778, p = .000*
Word Spelling Composite Overlap 10 Letters (8)	7.21	0.898	4.98-7.90	7.95	0.062	7.80-8.00	U = 4.000, z = -4.057, p = .000*

Table 5.8: Comparison of overlap with target scores produced in the collapsed immediate and delayed word spelling according to word length of the targets (maximum 8) for MND LI and NLI participants

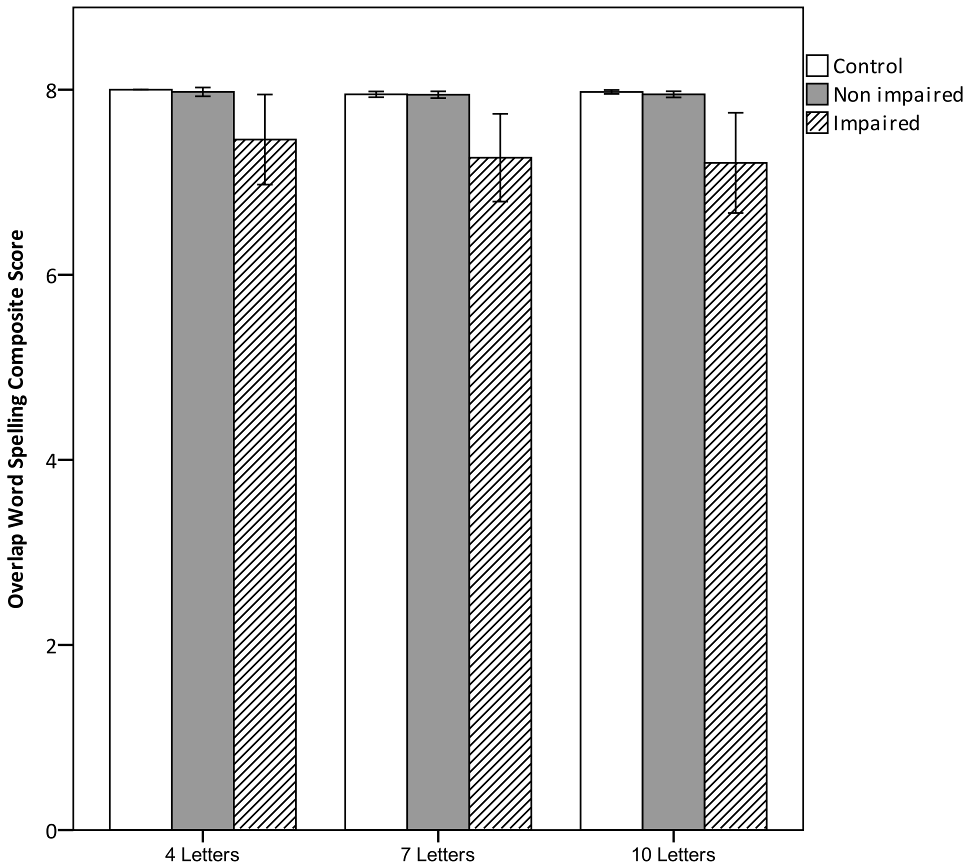


Figure 5.8: Overlap with target word spelling composite scores according to word length for control, MND NLI and MND LI (maximum 8)

5.1.5.2 Word Spelling Composite - Word Class

Analysis of the number of noun and verb MSW for the word spelling composite revealed that MND LI participants produced significantly more MSW than NLI participants spelling both nouns and verbs (see Table 5.9).

Variable	MND Linguistically Impaired (n 11)			MND Non Linguistically Impaired (n 14)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Word Spelling Composite Noun MSW	5.18	3.027	2-12	.57	0.514	0-1	U = .000, z = -4.321, p = .000*
Word Spelling Composite Verb MSW	3.55	3.236	0-9	.57	0.514	0-1	U = 22.000, z = -3.127, p = .002*

Table 5.9: Comparison of the number of noun and verb misspelled words (MSW) produced by MND NLI and LI participants in the word spelling composite

5.1.5.3 Word Spelling Composite – Plausibility of MSW

Analysis of the number of orthographically plausible and orthographically implausible misspelled words (MSW) produced in the word spelling composite score revealed that the LI group produced significantly more orthographically plausible and implausible MSW than the NLI group (see Table 5.10).

Variable	MND Linguistically Impaired (n 11)			MND Non Linguistically Impaired (n 14)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Plausible MSW	2.09	1.758	0-6	.71	0.726	0-2	U = 37.000, z = -2.319, p = .020*
Implausible MSW	6.64	6.470	0-21	.43	0.646	0-2	U = 12.500, z = -3.665, p = .000*

Table 5.10: Comparison of the number of orthographically plausible and implausible misspelled words (MSW) produced by MND NLI and LI participants in the word spelling composite

Wilcoxon within group comparison revealed that while in the NLI group there was no significant difference between the number of plausible and implausible MSW produced by participants (T = 13.50, p = .248), in the LI group there was a trend towards significantly more orthographically implausible than plausible MSW ($T = 11.50$, $p = .055$).

The number of orthographically implausible MSW produced in the word spelling composite was significantly correlated to the percentage of tests across the entire battery that participants were impaired on (see Table 5.11) ($r_s = .74$, $p = .000$). However the number of orthographically plausible MSW produced in the word spelling composite was also significantly correlated to the percentage of tests participants were impaired on, though to a lesser degree ($r_s = .46$, $p = .021$).

Table 5.11 shows the percentage MSW rate and percentage of orthographically plausible and implausible MSW produced by all MND participants. All participants in the LI group had a percentage MSW rate >15%. 73% of participants in the LI group produced a greater percentage of implausible MSW than plausible, while only 21% of participants in the NLI group produced a greater percentage of implausible MSW than plausible.

Participant	Linguistically Impaired?	No. of MSW	Percentage MSW rate	Percentage Plausible	Percentage Implausible
L120	No	1	2.78	100	0
L161	No	1	2.78	100	0
L903	No	1	2.78	100	0
G97	No	1	2.78	100	0
L121	No	1	2.78	100	0
L146	No	1	2.78	0	100
G92	No	1	2.78	100	0
*G100	No	1	4.17	0	100
*L51	No	1	4.17	0	100
G118	No	2	5.56	100	0
G91	No	2	5.56	100	0
*L46	No	2	8.33	100	0
L174	No	2	5.56	50	50
L125	No	4	11.11	50	50
*L107	Yes	4	16.67	25	75
G102	Yes	6	16.67	100	0
*L54	Yes	4	16.67	75	25
*L169	Yes	4	16.67	25	75
L900	Yes	7	19.44	14.29	85.71
L902	Yes	7	19.44	42.86	57.14
L171	Yes	10	27.78	50	50
L165	Yes	17	47.22	23.53	76.47
*L904	Yes	13	54.17	46.15	53.85
L176	Yes	23	63.89	8.7	91.3
L901	Yes	31	86.11	0	100

Table 5.11: Percentage of Plausible and Implausible MSW produced by MND participants. * indicates those having only completed the immediate and delayed conditions

5.1.5.4 Word Spelling Composite - Serial positions of errors

In order to examine whether the MSW produced by the MND participants in the LI group were likely to be as a result of an impairment at the level of the orthographic output buffer, as suggested by previous reports of spelling impairments in MND (Zago et al., 2008), serial position analysis of errors within MSW was conducted.

Wing and Baddeley (Wing & Baddeley, 1980) identified a higher proportion of errors occurring in the medial position of words than at the beginning or end when the graphemic buffer was placed under stress in healthy adults. They postulated this serial position effect was as a result of interference between neighbouring items in the buffer, and that as medial letters have the most neighbours, they are most vulnerable to degradation. This pattern results in a characteristic bow-shaped curve when plotted on a graph. As the length of the target stimuli varied, a binning procedure used by Wing & Baddeley and Caramazza and colleagues (Caramazza et al., 1987), and expanded by Kan and colleagues (Kan, Biran, Thompson-Schill, & Chatterjee, 2006) was employed to normalise the distribution of letters (see Table 5.12).

Word length (letters)	**Letter Position**									
	1st	**2nd**	**3rd**	**4th**	**5th**	**6th**	**7th**	**8th**	**9th**	**10th**
4	A	C	C	E	N/A	N/A	N/A	N/A	N/A	N/A
7	A	B	B	C	D	D	E	N/A	N/A	N/A
10	A	A	B	B	C	C	D	D	E	E

Table 5.12: Binning procedure used in the serial position analysis

MSW were analysed on a letter by letter basis in terms of their relative position to the target. A minimal error rule was applied whereby, in the case of deletion or insertion errors, subsequent letters could be considered correct, for example the deletion error ‘admister’ for administer would be considered correct for positions A, A, B, B, D, D, E & E, with errors only occurring in the two C positions. When MSW were analysed in this manner, the observed serial position effect for errors produced by the LI group is roughly consistent with that expected of a graphemic buffer deficit, however there are more errors in the final position of MSW than in the traditional bow-shaped curve (see Figure 5.9).

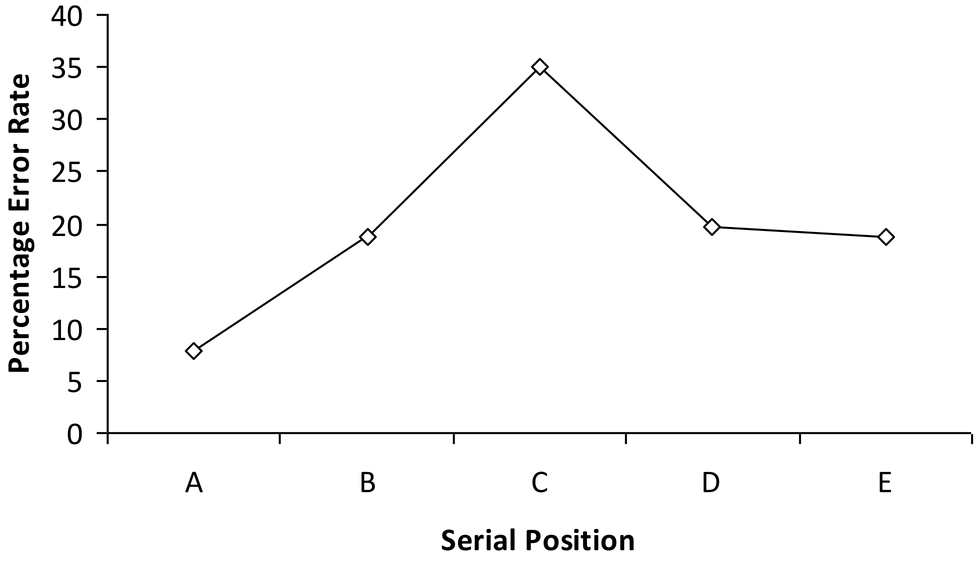


Figure 5.9: Percentage of errors in each serial position for MSW produced by MND LI participants in the composite word spelling

5.1.5.5 Nonword Spelling Composite – Nonword length

Analysis of the number of misspelled nonwords (MSNW) in the nonword spelling composite score in terms of length of target words revealed that MND LI participants made significantly more errors spelling short nonwords (4 phonemes) than NLI participants, however there was no significant difference in performance between the two groups when spelling nonwords of 7 and 10 phonemes in length (see Table 5.13 and Figure 5.10).

Variable	MND Linguistically Impaired (n 8)			MND Non Linguistically Impaired (n 8)			Statistics
	Mean	SD	Range	Mean	SD	Range	
Composite NWS 4 Phonemes (8)	3.63	1.768	1-5	1.88	1.356	0-3	U = 13.000, z = -2.049, p = .040*
Composite NWS 7 Phonemes (8)	5.25	2.252	2-7	3.13	2.100	0-6	t = -1.952, p = .071
Composite NWS 10 Phonemes (8)	6.63	1.598	4-8	5.38	1.408	3-7	U = 17.500, z = -1.553, p = .120

Table 5.13: Comparison of number of MSNW produced in the composite nonword spelling according to length of the targets (maximum 8) for MND LI and NLI participants

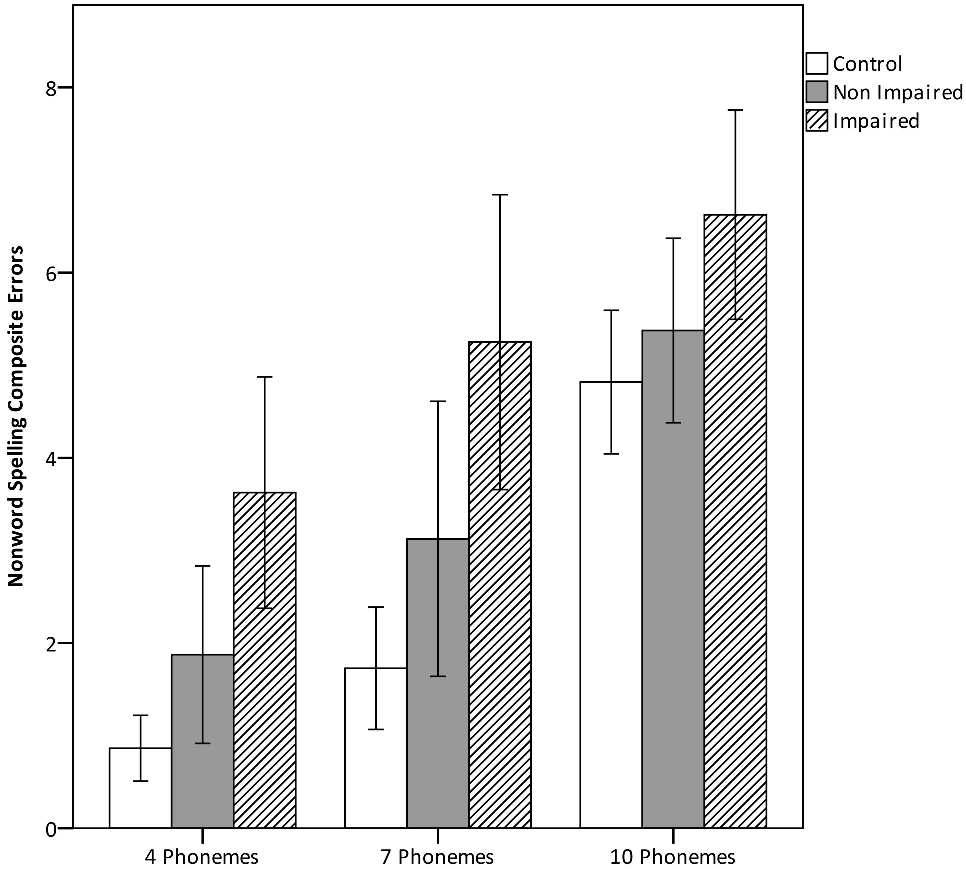


Figure 5.10: Number of errors produced in nonword spelling composite scores according to nonword length for control, MND NLI and MND LI (maximum 8)

5.1.5.6 Nonword Spelling Composite - Serial positions of errors

When MSNW produced by LI participants were analysed in terms of the serial position of errors within MSNW, the observed serial position curve (see Figure 5.11) differed to that formed by word spelling errors (see Figure 5.9) with a greater number of errors in the initial position. However the greatest percentage of errors similarly occurred in the medial 'C' position.

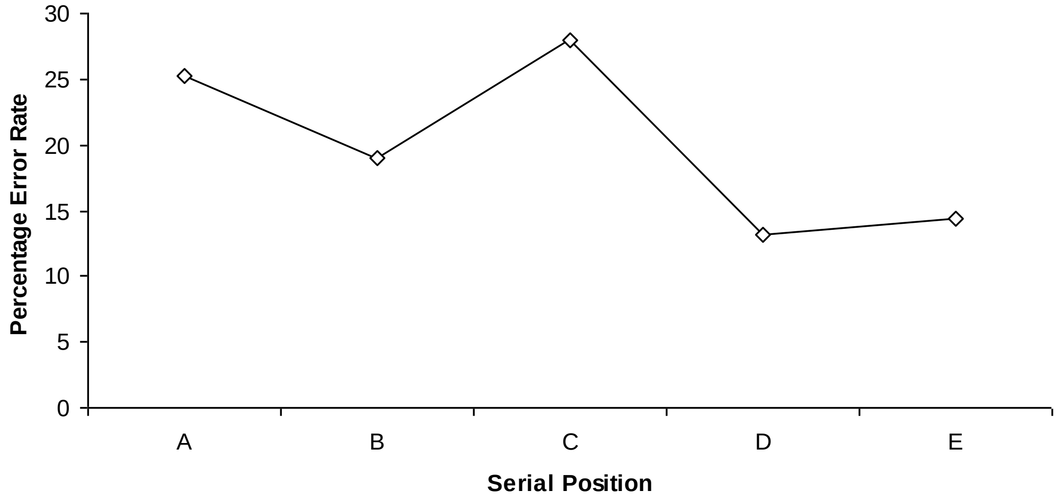


Figure 5.11: Percentage of errors in each serial position for MSNW produced by MND LI participants in the composite nonword spelling

5.2 Individual Patient Characteristics

Table 5.14 (next page) summarises the pattern of impairment for each individual MND participant across the entire test battery. Impairment was measured as a z- score at least 2SD below the control mean. Those participants in the LI group are shown in the bottom half of the table. As the table shows, there is a much greater proportion of impairment ≥3SD below the control produced by participants in the linguistically impaired group. All eleven of the participants in the LI group performed ≥3SD in at least 14% of assessments completed, while only one of the fourteen participants (7.14%) in the NLI group performed ≥3SD on at least 14% of assessments completed. Extending this further, nine of the eleven participants (81.82%) in the LI group performed at least 3SD below the control mean on at least 30% assessments completed, while none of the participants in the NLI group meet this criteria. When considering the percentage of tests where performance was at least 2SD below the control mean (see Table 5.15), all participants in the LI group were impaired on at least

		Language													Working Memory				Executive Functioning			
	Onset site	WSC	NWSC	NWRC	GNT	NNT	W MP	NW MP	PEPS A	PEPS I	PEPS T	SVT	LS	TROG	F D Span	R D Span	F S Span	R S Span	VFI W	VFI WC	VFI S	VFI SC
L146	bulbar																					
G97	bulbar		DNC																			
G100	bulbar			DNC	DNC																DNC	DNC
G92	bulbar																					
G118	bulbar		DNC	DNC																		
L903	bulbar																					
L125	UL		DNC																			
L161	UL		DNC						DNC	DNC	DNC											
L120	UL		DNC	DNC	DNC																	
L51	LL			DNC																	DNC	DNC
L46	LL			DNC																	DNC	DNC
G91	LL																					
L174	LL		DNC						DNC	DNC	DNC											
L121	LL			DNC					DNC	DNC	DNC				DNC	DNC	DNC	DNC				
L107	bulbar			DNC	DNC				DNC	DNC	DNC				DNC	DNC	DNC	DNC			DNC	DNC
L54	bulbar			DNC																	DNC	DNC
L171	bulbar			DNC											DNC	DNC	DNC	DNC			DNC	DNC
L165	bulbar			DNC																	DNC	DNC
L169	bulbar			DNC																	DNC	DNC
L902	bulbar																					
L904	bulbar			DNC																	DNC	DNC
L901	bulbar		DNC	DNC		DNC	DNC	DNC	DNC	DNC	DNC				DNC	DNC	DNC	DNC				
L900	bulbar		DNC	DNC	DNC	DNC			DNC	DNC	DNC								DNC	DNC		
G102	UL			DNC					DNC	DNC	DNC				DNC	DNC	DNC	DNC				
L176	LL		DNC																			

Table 5.14: Individual patient performance across all linguistic and neuropsychological measures 2SD below the control mean ≥3SD below the control mean.

DNC = Did Not Complete. WSC = Word Spelling Composite; NWSC = Nonword Spelling Composite; NWRC = Nonword Repetition Composite; GNT = Graded Naming Test; NNT = Northwestern Naming Test; PEPS = Profiling Elements in Prosodic Systems (A = Affect; I = Intonation; T = Turn End Type); SVT = Spelling Verification Tes; LS = Letter Strings; TROG = Test of Reception of Grammar; FD = Forward Digit; RD = Reverse Digit; FS = Forward Spatial; RS = Reverse Spatial; VFI = Verbal Fluency Index (W = Written; WC = Written Constrained; S = Spoken; SC = Spoken Constrained)

	Linguistically Impaired?	Tests Completed (max 21)	Tests Impaired	Percentage Impairment
L120	No	18	0	0
L121	No	13	0	0
G97	No	20	0	0
L51	No	18	1	5.56
L146	No	21	1	4.76
L903	No	21	1	4.76
L174	No	17	1	5.88
G92	No	21	2	9.52
G91	No	21	2	9.52
L161	No	17	2	11.76
L125	No	20	3	15
G118	No	19	3	15.79
G100	No	17	4	23.53
L46	No	18	7	38.89
L902	Yes	21	4	19.05
L54	Yes	18	7	38.89
L169	Yes	18	8	44.44
G102	Yes	13	6	46.15
L171	Yes	14	7	50
L900	Yes	12	6	50
L904	Yes	18	11	61.11
L165	Yes	18	12	66.67
L176	Yes	20	14	70
L107	Yes	10	8	80
L901	Yes	9	9	100

Table 5.15: Percentage of tests impaired on across the battery for individual MND participants. Hatching highlights borderline cases discussed below.

19% of assessments completed, whereas only two of the fourteen (14.29%) of participants in the NLI group were impaired on more than 19% of assessments.

Considering patterns of impairment between the three areas of assessment (language, working memory and executive functioning), it is evident that while both measures of language and executive functioning are markedly impaired across the LI group, the measures of working memory are not. Two important points can be taken from this observation. Firstly, the relatively small number of participants impaired on the measures of working memory in the LI group suggests that impairment on the linguistic assessments is not attributable to a working memory deficit. This is of particular note when it is considered that the graphemic output buffer, a deficit of which has previously been suggested to be responsible for spelling impairment in MND (Lucchelli & Papagno, 2005; Zago et al., 2008), is a component of working memory. However, as four of the eleven (36%) of participants in the LI group did not complete the working memory assessments, this conclusion can only be tentatively suggested. Secondly, the strong pattern of impairment on measures of executive functioning in the LI group may suggest some connection between language impairment and executive dysfunction. However, whether this association with executive dysfunction is a cause or effect of language impairment is a matter of debate, and will be considered further in the discussion. Additionally, it does not necessarily follow that those participants impaired on measures executive functioning will also be impaired on linguistic measures (or vice versa) as there are some participants for whom there is a dissociation in performance between language impairment and executive function. For example participants G91 and L146 were impaired on verbal fluency measures, but no language measures, while L902 was impaired on several language measures but not verbal fluency.

However, there are a few participants who do not strictly fit the LI/NLI categorisation made on the basis of spelling impairment (highlighted in Table 5.15). Of those in the NLI group, three participants (G118, G100 and L46) performed at least 2 SD below the control mean on over 25% of the language tests they completed. Indeed, while participant G100 performed 2SD below the control mean on 4/11 language assessments completed, suggesting a mild language impairment, participants G118 and L46 performed more than 3SD below the control mean on two language assessments (GNT and NNT for G118; SVT and TROG for L46), in addition to performing 2SD below the control mean on at least one other language assessment. In addition while participant G102 from the LI group has an overall impairment rate of 46.15%, and performing ≥3SD below the control mean on the word spelling composite, she was only impaired on 2/9 of language assessments completed, of which the spelling assessment was the only one she performed ≥3SD below the control mean.

These borderline cases illustrate the importance of multidimensional assessment of language function to identify linguistic impairment. Furthermore, they highlight that defining linguistic impairment in MND patients based on spelling performance may not capture all patients with some level of linguistic impairment. However, using spelling performance as a measure of linguistic impairment captured 84.6% of participants who performed ≥3SD below the control mean on at least one language assessment. This suggests that spelling impairment could be considered useful marker for linguistic impairment in MND patients.

5.3 Case Studies

In order to examine the pattern of impairment seen in participants within the MND LI group in further detail, case studies on three of the most impaired participants are presented here.

5.3.1 Participant L165

L165 was a 55 year old right-handed woman with bulbar onset MND, who previously worked as a cleaner. She reported no difficulty learning when at school and left school to start work aged 16. Both her vision and hearing were normal, which was supported through normal performance on the hearing assessment conducted during testing. She also reported no major medical history prior to her diagnosis, remarking that she had been exceptionally healthy premorbidly. L165 first noticed that her speech was becoming slurred in July 2010, and by May 2011 she had been given a diagnosis of MND. Of note, L165 reported a strong family history of MND, with her mother, uncle and cousin all having had the disease also.

At the time of testing in October 2011, her symptoms were predominantly confined to dysarthria and dysphagia, with an ALS-FRS score of 37. Her speech was characterised by a severe spastic dysarthria, with a harsh, hyper-nasal voice quality and severely distorted articulation. Intelligibility of her speech was affected to the point where she had very little useful speech. However despite the severity of her dysarthria, she appeared to have little insight of her unintelligibility and persisted in attempting to communicate verbally, requiring prompts to use writing as a communication aid throughout the period of assessment.

L165 scored 4 on the anxiety measure and 3 on the depression measure of the HADS, both of which are well below the borderline of 8-10. Additionally she scored 0 on the Epworth Sleepiness Scale, suggesting normal respiratory function. Her digit span was 6 digits forward and 3 digits backwards, the latter of which was impaired in comparison to the control group. Her spatial span was 4 blocks forward and 4 blocks backwards, both which were within normal range. With regards her verbal fluency performance, she was impaired on both the written unconstrained and constrained measures, with particular difficulty following the word length condition of the constrained version, writing only 3 correct items in two minutes.

Linguistic assessment

Table 5.16 shows the performance of L165 across the both the standard and experimental linguistic assessments completed.

Test (Maximum Score)	L165's Score	Control Mean (SD)
Word Spelling Composite (24)	13**	23.16 (0.8)
Nonword Spelling Composite (24)	4**	16.59 (2.906)
Word Minimal Pairs (48)	46*	47.44 (0.651)
Nonword Minimal Pairs (48)	47	47.44 (1.121)
Graded Naming Test (30)	12**	25.45 (2.703)
Northwestern Naming Test (32)	30**	31.72 (0.458)
TROG (40)	33**	39.04 (0.841)
Spelling Verification Test (72)	66**	71.64 (1.036)
Letter String Discrimination (48)	46	47.20 (2.415)
PEPS Affect (16)	9**	15.40 (0.91)
PEPS Intonation (16)	13	14.88 (1.17)
PEPS Turn-End Type (16)	8**	15.28 (1.06)

Table 5.16: Total scores of L165 on standard and experimental linguistic assessments in comparison to control mean. * ≥ 2SD below control mean; **≥ 3SD below control mean

Naming: L165 performed more than 3 SD below the control mean on both the GNT and NNT. Due to her dysarthria, she completed both assessments as written naming tests. Her written naming displayed similar spelling errors to her word spelling to dictation (see below), characterised by both orthographically plausible ('thimbil' for thimble; 'turtell' for turtle) and orthographically implausible ('scargo' for scarecrow; 'corksrew' for corkscrew) errors. In addition, she produced several phonological-lexical type errors, where her response was a real word, or an approximation to a real word, which shared phonological and orthographic similarities e.g. 'trewsers' for tweezers (‘trewsers’ being the Scots word for trousers) and ‘cockel’ for shuttlecock. She also produced several circumlocutory errors, containing appropriate semantic information (e.g. ‘measuring thing’ for sextant; ‘ballet dancer cosume’ for tutu), and no responses. Her written naming performance is suggestive of an impairment in at the level of the orthographic output lexicon, or access to it, and a reliance on partial knowledge of word forms and use of a partially disrupted sublexical phonological to graphemic conversion route. In addition, she demonstrated few semantic errors, suggesting that the semantic system is relatively persevered.

Comparison of her performance on the GNT and NNT also provides interesting insights into the possible locus of impairment. While her performance on the NNT was much better than the GNT, with a score of 30/32, the NNT comprises higher frequency items than the GNT, suggesting that there may be a frequency effect on performance. This is in keeping with a deficit at the level of the orthographic output lexicon. Furthermore, the two errors that L165 produced on the NNT were in the naming of verbs (‘caching’ for throwing and ‘standing’ for crying). A dissociation in noun-verb processing is consistent with reports in the literature (T. Bak & Hodges, 1997; T. H. Bak & Hodges, 2004; T. H. Bak et al., 2001), but the reason for this dissociation is still not fully understood. Nouns and verbs differ in their grammatical complexity and imageability, with some arguing that previously reported noun-verb dissociations in aphasia literature could be merely a result of these differences, suggesting a semantic rather than lexical deficit (Bird, Howard, & Franklin, 2000; Bird et al., 2002). However, Bak and colleagues suggest an alternative explanation for this dissociation in MND patients. Rather than viewing this as a deficit in processing verbs versus nouns, it could equally be viewed as a deficit in processing ‘actions’ versus ‘objects’ (T. H. Bak et al., 2001). In this way they suggest that this verb-noun dissociation seen in MND patients could be as a result of the relation between the semantic differences of objects and actions and motor systems in the brain. With the predominant motor system deficits in MND, this hypothesis presents new suggestions about the connection between language and motor impairments.

Reading: L165 performed more than 3 SD below the control mean on the SVT, however performance on the letter string discrimination test was within the range of normal performance. This is consistent with the overall group pattern (see chapter 3), and is suggestive of a more central than peripheral deficit of written word processing. On further analysis of her error patterns on the SVT (see Table 5.17), L165 produced the highest percentage of errors in her ability to reject phonologically plausible nonwords. Furthermore, in analysing her pattern of errors in relation to the predictability (or regularity) and frequency of the spoken stimuli, she had a tendency make more errors when the target was lower in frequency and predictability. Both of these findings are consistent with an impairment in the orthographic input lexicon, the receptive equivalent of the suspected impaired process in her written naming ability. Indeed, it has been suggested that a single orthographic lexicon serves both the production and recognition of the written word (Behrmann & Bub, 1992; Burt & Tate, 2002).

Stimuli Type	Percentage Correct
Correct Word	97.2%
Similar Word	100%
Phonologically Plausible Nonword	66.7%
Phonologically Implausible Nonword	91.7%
High Predictability, High Frequency	100%
High Predictability, Low Frequency	88.9%
Low Predictability, High Frequency	88.9%
Low Predictability, Low Frequency	88.9%

Table 5.17: Performance of L165 on SVT according to stimuli type

Prosody: L165's pattern of performance on test of receptive prosody followed that of the LI group as a whole: while her ability to perceive difference in prosodic patterns with no linguistic information was not significantly different to that of controls, her ability to perceive and understand differences in prosody containing linguistic and affective information was impaired. This pattern is consistent with that reported by Rohrer and colleagues when examining receptive prosody in patients with progressive nonfluent and logopenic aphasia (Rohrer et al., 2012).

Phonological awareness: L165's auditory phonological analysis skills were relatively intact, with performance on nonword minimal pair discrimination within similar to that of controls. While her word minimal pair discrimination was statistically impaired, performing 2 SD below the control mean, she was still able to correctly discriminate 95.8% of pairs, suggesting her impaired score may be as a result of ceiling performance amongst controls.

Spelling: L165 performed ≥ 3 SD below the control mean on both the word spelling and nonword spelling composite scores. On examination of the percentage of misspelled word (MSW) types produced across all three word spelling to dictation conditions (see Table 5.18), L165 produced over 50% more orthographically implausible MSW than orthographically plausible. In addition, she produced several phonological verbal paragraphias, which were discounted as possible hearing errors in the overall group comparison ('pump' for bump; 'taint' for tent; 'drab' for grab).

No. of Cons	No. of MSW	% MSW	% Plaus MSW	% Implaus MSW	% Noun MSW	% Verb MSW	% 4 Letter MSW	% 7 Letter MSW	% 10 Letter MSW
3	17	47.22	23.53	76.47	44.44	50	8.33	50	83.33

Table 5.18: Percentage of misspelled word types produced by L165 across the three word spelling conditions completed. Cons = Conditions; Plaus = Orthographically Plausible; Implaus = Orthographically Implausible

While the occurrence of orthographically plausible MSW and phonological verbal paragraphias are consistent with an impairment in the orthographic lexicon as described earlier, the high percentage of orthographically implausible MSW is suggestive of an additional impairment. If an impairment exists in the orthographic lexicon, the sublexical phonological to graphemic spelling route may be employed, which if this too is impaired, could result in orthographically implausible errors. Additionally, the impairment could exist at a more peripheral level. The decrease in accuracy as word length increases is suggestive of an impairment in the working memory operated graphemic output buffer, which would also be consistent with L165's impaired backward digit span performance. However, interestingly L165's word spelling, nonword spelling and written naming all showed evidence of mixed case spellings, both between and within items. For example transplant was spelled 'TRANslpat'; helicopter 'HELicopter'; and jumping 'JUMpiNg'. These mixed case errors could indicate an impairment at the allographic level, and is something that has been observed in cases of progressive dysgraphia in co-occurrence with more central spelling deficits (N. Graham, L. et al., 1997).

When the serial positions of errors within the MSW were analysed using the procedure outlined earlier, the pattern was roughly consistent with the bow-shaped curve expected with a impairment in the graphemic output buffer (see Figure 5.12).

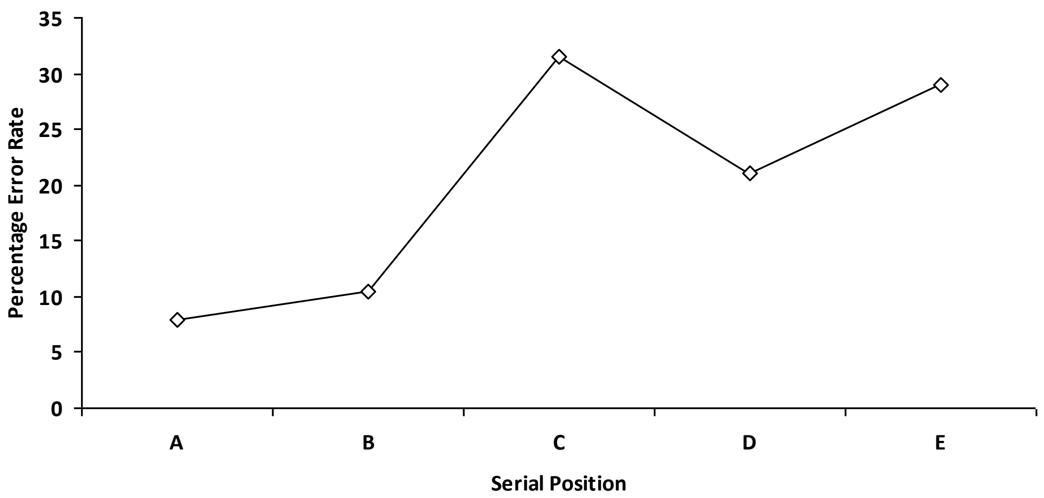


Figure 5.12: Percentage of errors in each serial position for MSW produced by L165

MSW were classified based on guidelines suggested by Caramazza and colleagues (Caramazza et al., 1987). The MSW produced by L165 were characterised by substitutions ('propicanda' for propaganda; 'suptracked' for subtracted), deletions ('transplat' for transplant; 'admister' for administer), insertions ('printied' for printed; 'cabinnet' for cabinet) and combinations of these (deletion and substitution 'contrdick' for contradict; 'ascomer' for astronomer). Nearly 50% of the MSW contained a single error, while the remaining 52% consisted of either multiple errors of the same type or of a combination of types. Figure 5.14 (next page) illustrates the percentage of MSW by error type – complex errors were those MSW comprised of more than two types of error.

Analysis of L165's misspelled nonwords (MSNW) revealed a similar pattern of impairment: decreased accuracy with increasing number of phonemes in the target (see Table 5.19). The serial position of errors within the MSNW produced a curve similar to that seen with the MSW and again consistent with a graphemic buffer impairment (see Figure 5.13).

No. of Cons	No. of MSNW	% MSNW	% 4 Phoneme MSNW	% 7 Phoneme MSNW	% 10 Phoneme MSNW
3	31	86.11	66.67	91.67	100

Table 5.19: Percentage of misspelled nonword types produced by L165 across the three word spelling conditions completed. Cons = Conditions

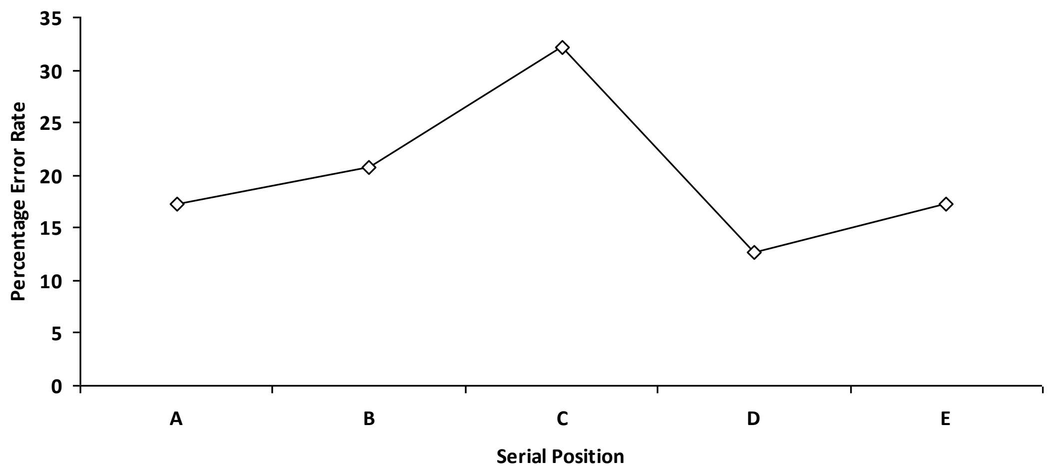
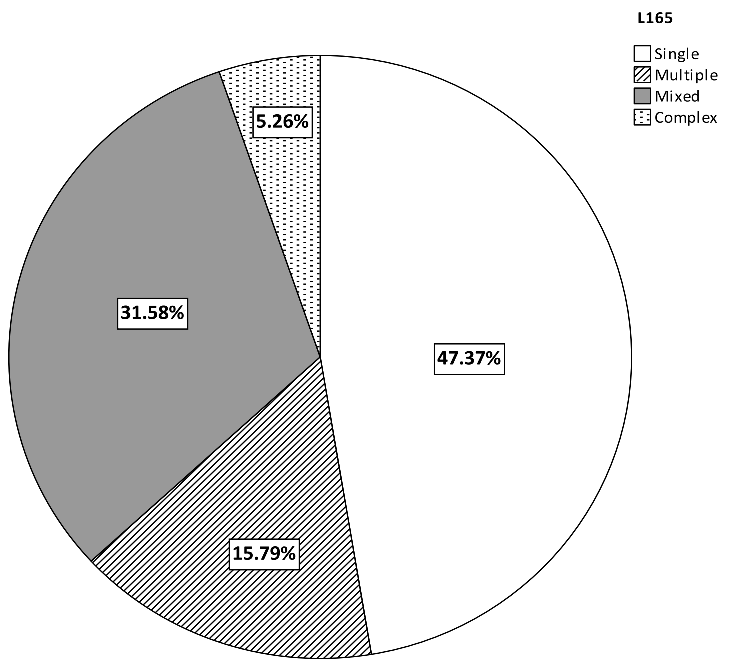


Figure 5.13: Percentage of errors in each serial position for MSNW produced by L165

A



B

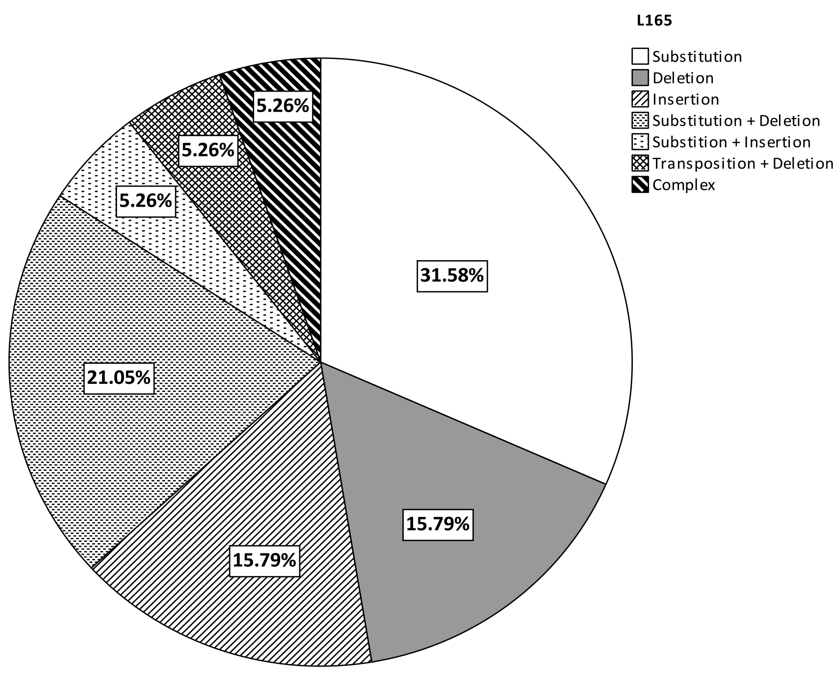


Figure 5.14: Distribution of MSW errors produced by L165.
Chart A shows the percentage of MSW errors according to number; Chart B shows the percentage of MSW errors according to type.

Syntax: L165 also showed evidence of impairment in both the production and comprehension of grammatical constructs. She performed ≥ 3 SD below the control mean on the TROG, a marked impairment that was characteristic of the LI group. Furthermore, when presented with the Boston Cookie Theft image (see Appendix G), taken from the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass & Kaplan, 1983) and asked to give a written description, her spontaneous writing was agrammatical, with limited function words, formulaic constructions and poorly structured sentences (e.g. 'sink is runnnig water over'; ' the stool is falling the boys on') (see Figure 5.15). This is in keeping with the spontaneous writing errors reported in PNFA patients (Code et al., 2006)

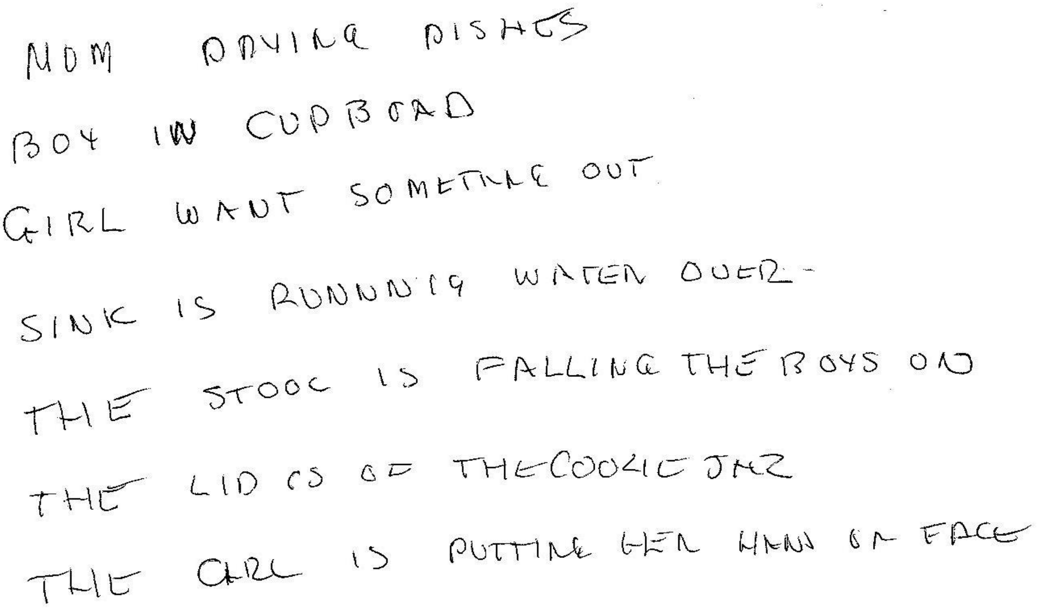


Figure 5.15: L165 Boston Cookie Theft spontaneous writing sample

Summary

L165 demonstrated deficits in word and nonword spelling, naming, written lexical decision making, perception of affective and linguistic prosody and the comprehension and production of syntactic structures. Her spelling errors, both in spelling to dictation and written naming, were characterised by a high percentage of orthographically implausible MSW consisting of substitution, deletion and insertion of letters, which increased with word length, consistent with a graphemic output buffer deficit. In combination with her syntactic comprehension and production deficits, this profile could be compared to that seen in patients with progressive nonfluent aphasia (PNFA) (Henri-Bhargava & Freedman, 2012; Sepelyak et al., 2011). However, she also produced a number of orthographically plausible MSW, particularly in her written naming where spelling is necessarily conducted via the lexical-semantic route. Coupled with her difficulty rejecting phonologically plausible nonwords in the visual lexical decision test, this could suggest an additional deficit at a more central lexical-semantic level, more commonly associated with semantic dementia (SD) (Wilson et al., 2009)or logopenic progressive aphasia (LPA) (Sepelyak et al., 2011). Indeed, the linguistic impairments seen in LPA are most commonly attributed to a phonological loop deficit (Gorno-Tempini et al., 2008), which L165 also shows evidence of through her impaired backward digit span. Thus, L165's pattern of linguistic impairment can be compared to linguistic impairment reported in PPA, but evidences characteristics of a mixture of subtypes.

5.3.2 Participant L107

L107 was a 76 year old right-handed English woman with bulbar onset MND, who previously worked as a university professor. She reported no difficulty learning when at school and was premorbidly very high functioning, as reflected through her profession. Both her vision and hearing were normal, which was supported through normal performance on the hearing assessment conducted during testing. However, she did report noticing that her vision had changed slightly in the few months prior to testing, remarking that she now found it difficult to read and follow rugby matches on television. Interestingly she also reported noticing that her spelling had started to deteriorate approximately two weeks prior to testing. She also, like L165, reported no major medical history prior to her diagnosis, remarking that she had been exceptionally healthy premorbidly. L107 first noticed that her speech was becoming slurred in August 2010, and by October 2010 she had been given a diagnosis of MND.

At the time of testing in March/April 2011, her symptoms were predominantly confined to dysarthria and dysphagia, but with increasing difficulty with her upper and lower limb functions, and an ALS-FRS score of 30. She was completely anarthric at the point of assessment, which she reported had been the case since January 2011, and writing was her main communication method.

L107 scored 10 on the anxiety measure and 13 on the depression measure of the HADS, the former of which is classed as a borderline score, and the latter of which was > 3 SD below the control mean. She scored 0 on the Epworth Sleepiness Scale, suggesting normal respiratory function. With regards her verbal fluency performance, she was impaired on both the written unconstrained and constrained measures, naming only two items in two minutes in the unconstrained condition, and only one in the constrained condition. Unfortunately her health deteriorated rapidly during the process of assessment and some measures, including working memory measures were unattainable. L107 passed away a month after the last testing session.

Linguistic assessment

Table 5.20 shows the performance of L107 across the both the standard and experimental linguistic assessments completed.

Test (Maximum Score)	L107's Score	Control Mean (SD)
Word Spelling Composite (24)	20**	23.16 (0.8)
Nonword Spelling Composite (24)	5**	16.59 (2.906)
Word Minimal Pairs (48)	46*	47.44 (0.651)
Nonword Minimal Pairs (48)	48	47.44 (1.121)
Graded Naming Test (30)	DNC	25.45 (2.703)
Northwestern Naming Test (32)	26**	31.72 (0.458)
TROG (40)	35**	39.04 (0.841)
Spelling Verification Test (72)	67**	71.64 (1.036)
Letter String Discrimination (48)	47	47.20 (2.415)
PEPS Affect (16)	DNC	15.40 (0.91)
PEPS Intonation (16)	DNC	14.88 (1.17)
PEPS Turn-End Type (16)	DNC	15.28 (1.06)

Table 5.20: Total scores of participant L107 on standard and experimental linguistic assessments in comparison to control mean. * ≥ 2SD below control mean; **≥ 3SD below control mean

Naming: L107 did not complete the GNT, however she performed more than 3 SD below the control mean on the NNT. Due to her dysarthria, she completed the NNT as a written naming test. Her written naming was relatively free of spelling errors with the only notable spelling error being 'zib' for zip. In terms of her lexical retrieval, she produced two no responses on fruit and vegetable items (apple and corn) and was delayed in her response to a third (pepper), which suggests a category specific deficit. This was particularly surprising given that L107 had previously studied botany as an undergraduate at university. In addition L107 produced four verb errors including 'catching' for throwing and 'cooking' for stirring, resulting in greater number of verb than noun errors, similar to L165.

Reading: L107 performed more than 3 SD below the control mean on the SVT, however performance on the letter string discrimination test was, like L165, within the range of normal performance. This is again suggestive of a more central than peripheral deficit of written word processing. On further analysis of her error patterns on the SVT (see Table 5.21), L107. like L165, produced the highest percentage of errors in her ability to reject phonologically plausible nonwords. Furthermore, in analysing her pattern of errors in relation to the predictability (or regularity) and frequency of the spoken stimuli, there was no real effect of frequency or predictability. This pattern of increased errors rejecting phonologically plausible nonwords is, like L165, suggestive of an impairment in the orthographic input lexicon.

Stimuli Type	Percentage Correct
Correct	94.4%
Similar Word	100%
Phonologically Plausible Nonword	83.3%
Phonologically Implausible Nonword	91.7%
High Predictability, High Frequency	94.4%
High Predictability, Low Frequency	88.9%
Low Predictability, High Frequency	94.4%
Low Predictability, Low Frequency	94.4%

Table 5.21: Performance of L107 on SVT according to stimuli type

Phonological awareness/auditory processing: L107's auditory phonological analysis skills were relatively intact, with performance on nonword minimal pair discrimination within similar to that of controls. While, like L165, her word minimal pair discrimination was statistically impaired, performing 2 SD below the control mean, she was still able to correctly discriminate 95.8% of pairs, suggesting her impaired score may be as a result of ceiling performance amongst controls. However, this difference could reflect an effect of lexicality, and therefore suggest impaired lexical knowledge as discussed in chapter 4.

Of note and relevant to the discussion regarding L107's auditory processing skills, she demonstrated a particular difficulty recognising words produced by the female West coast Scottish accent as real words. Throughout item presentation on the SVT, minimal pairs and spelling tests she requested representation of items several times, remarking that pronunciation was difficult to understand, and that some real words were not words. In a study examining accent processing in Alzheimer's Disease (AD) and PNFA Hailstone and colleagues found that, in comparison to both the control and AD groups the PNFA group showed reduced comprehension of words spoken in an unfamiliar international accent than their own Southern English accent (Hailstone et al., 2012). Interestingly they also suggest that, as another example of metalinguistic vocal signal integrating segmental, suprasegmental and semantic features, similarities could be drawn between accent processing and the processing of prosody. Unfortunately L107 deteriorated before her ability to process prosody could be assessed.

Spelling: L107 performed ≥ 3 SD below the control mean on both the word spelling and nonword spelling composite scores. On examination of the percentage of misspelled word (MSW) types produced across all three word spelling to dictation conditions (see Table 5.22), L107 produced 50% more orthographically implausible MSW than orthographically plausible. She produced one verbal phonological paragraphia ('tint' for tent), and one unrelated non word ('pretics' for critics), this being one of the words that she struggled to understand despite repeated presentation and initially wrote 'no word'. Although significantly impaired in comparison to controls, as L107 produced only a few MSW on the composite word spelling, it is difficult to draw conclusions about the likely locus of impairment. However the pattern appears to be similar to that seen in L165, though of a lesser severity.

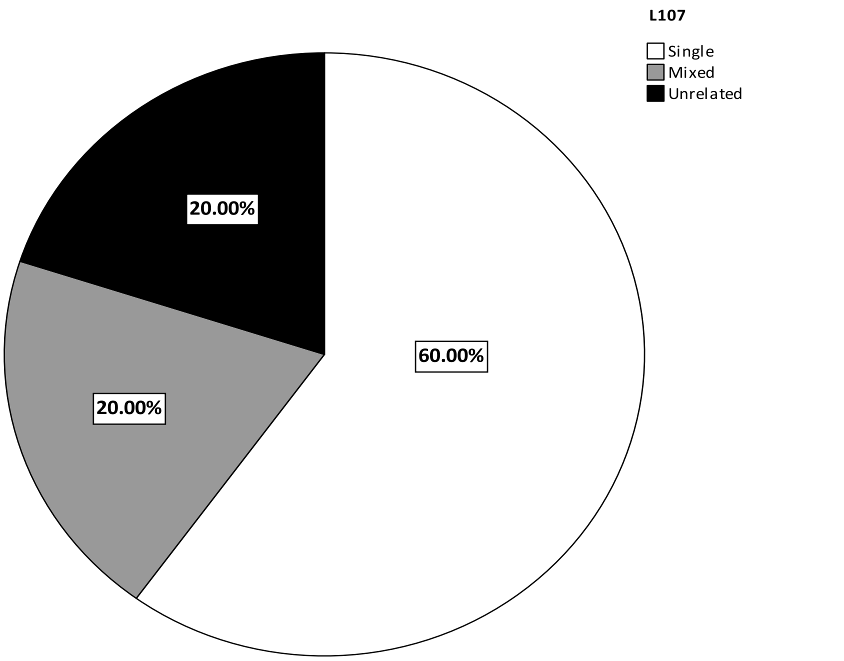
No. of Cons	No. of MSW	% MSW	% Plaus MSW	% Implaus MSW	% Noun MSW	% Verb MSW	% 4 Letter MSW	% 7 Letter MSW	% 10 Letter MSW
2	4	16.67	25	75	33.33	0	12.5	12.5	25

Table 5.22: Percentage of misspelled word types produced by L107 across the two word spelling conditions completed. Cons = Conditions; Plaus = Orthographically Plausible; Implaus = Orthographically Implausible

When the serial positions of errors within the MSW were analysed, the pattern was roughly consistent with the bow-shaped curve expected with a impairment in the graphemic output buffer (see Figure 5.16), though again the limited number of MSW means only tentative conclusions can be drawn.

Figure 5.16: Percentage of errors in each serial position for MSW produced by L107

A



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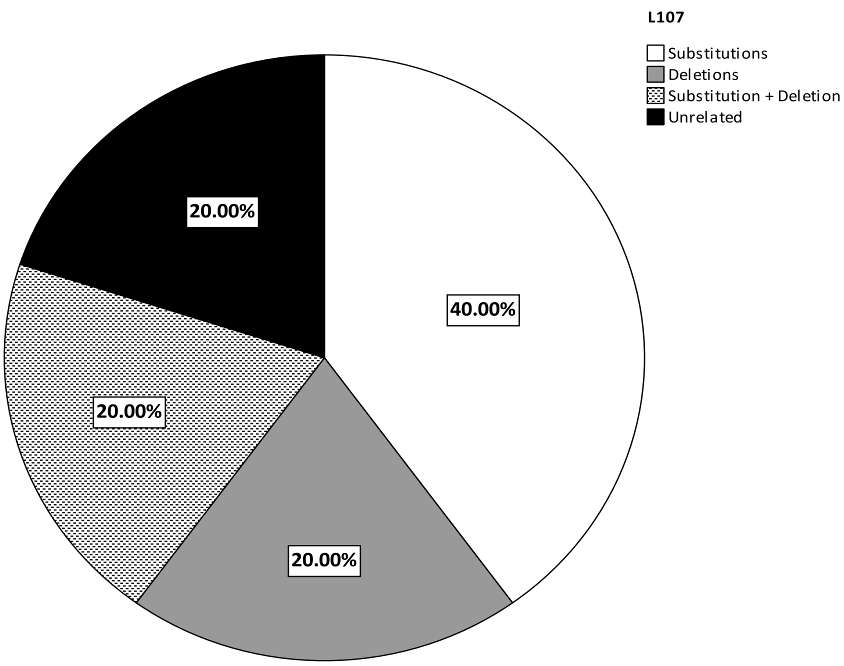


Figure 5.17: Distribution of MSW errors produced by L107.
Chart A shows the percentage of MSW errors according to number; Chart B shows the percentage of MSW errors according to type.

The MSW produced by L107 were characterised by substitutions ('astranomer' for astronomer; 'tint' for tent), deletions ('construct' for constructs) and combinations of these (deletion and substitution 'statisccs' for statistics). Sixty percent of the MSW contained a single error, while the remaining MSW were unrelated or comprised of a combination of types. Figure 5.17 illustrates the percentage of MSW by error type.

Analysis of L107's misspelled nonwords (MSNW) revealed a slightly different pattern of impairment (see Table 5.23). She produced a much greater number of MSNW than MSW, and while there was an increase in the percentage of MSNW with increased phoneme length, the increase was small. In addition, the serial position of errors within the MSNW produced a different, flatter pattern to that seen with the MSW and not typical of a graphemic buffer impairment (see Figure 5.18).

No. of Cons	No. of MSNW	% MSNW	% 4 Phoneme MSNW	% 7 Phoneme MSNW	% 10 Phoneme MSNW
2	19	79.17	62.5	75	87.5

Table 5.23: Percentage of misspelled nonword (MSNW) types produced by L107 across the two word spelling conditions completed. Cons = Conditions

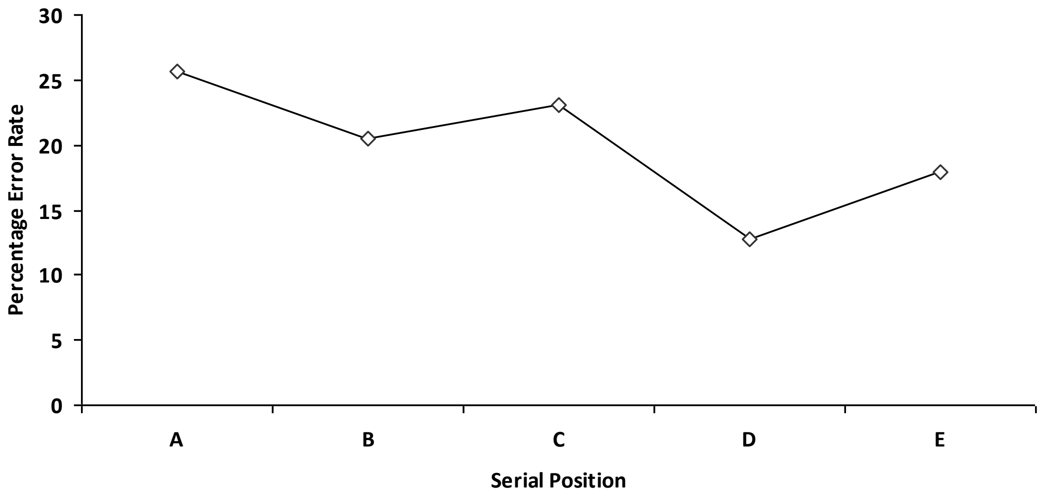


Figure 5.18: Percentage of errors in each serial position for MSNW produced by L107

The MSNW produced by L107 were characterised by substitutions (‘thracelit’ for praslet; ‘gibolot’ for gibolop), combinations of errors (deletion and substitution ‘stut’ for shroop; transpositions, substitutions and deletions ‘sterchflan’ for stredgelifan), and lexicalisations, substituting entire or partial real words (‘dipped’ for gept; ‘onemoment’ for mombolment; ‘ghost’ for goffs). This difficulty with nonword spelling, particularly the appearance of lexicalised MSNW is suggestive of a deficit in the sublexical phoneme to grapheme conversion process and a reliance on the lexical spelling route.

Syntax: L107 also showed evidence of impairment in both the production and comprehension of grammatical constructs. She performed ≥ 3 SD below the control mean on the TROG. Furthermore, her spontaneous writing from picture description was markedly agrammatical (see Figure 5.19). Phrases were perseverative and contained evidence of word finding difficulties. In addition she produced a number of lexical-semantic errors, writing ‘cooking tin’ for cookie jar (which is particularly noteworthy as the word ‘cookie jar’ is written in the picture), and selecting the inappropriate verb ‘attacking’ to describe the boy’s action. Again, like L165, these features are characteristic of the spontaneous writing errors seen in patients with PNFA.

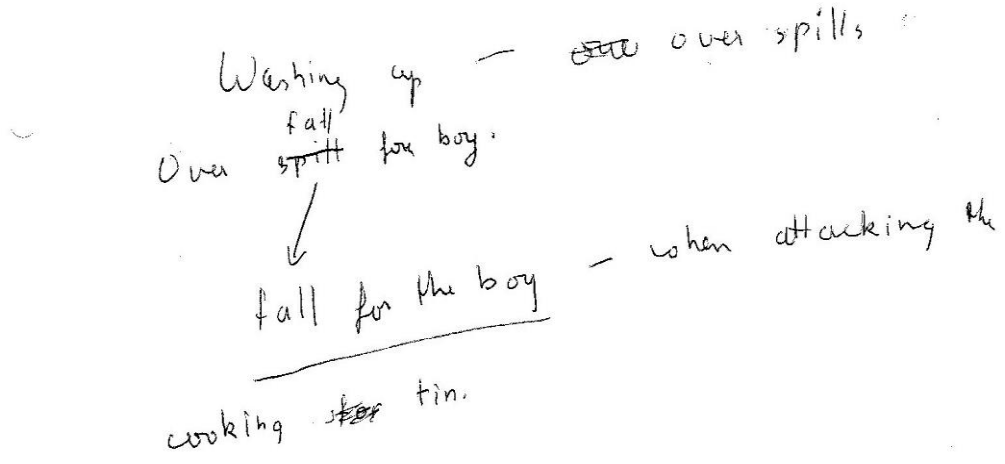


Figure 5.19: L107 Boston Cookie Theft spontaneous writing sample

Additional assessment

As L107 reported changes in her vision, the dot counting, number location and cube analysis subtests of the Visual Object and Spatial Perception Battery (VOSP) (Warrington & James, 1991) were administered to test visuo-spatial skills. Although she gave a number of delayed responses and complained that her ‘eyes were sore’ when completing the tests, she score 10/10 on the dot counting, 9/10 on number location and 9/10 on cube analysis, suggesting that her visuospatial skills were relatively persevered.

Summary

L107 demonstrated deficits in word and nonword spelling, naming, written lexical decision making and the comprehension and production of syntactic structures. While her word spelling and ability to reject phonologically plausible nonwords on the SVT was better than L165, the overall pattern of impairment was similar. It could be suggested that this slight difference in impairment pattern to L165 could be as a result of behavioural brain reserve, due to L107’s higher educational attainment and occupational status, which has been reported to protect against the effects of dementia (Valenzuela & Sachdev, 2006a, 2006b). However, these variations in performance could also indicate a different pattern of impairment, more in keeping with the profile reported in PNFA. Her particular difficulty with nonword spelling, characterised by lexicalisations of nonwords and a flattened serial position curve, not in keeping with a graphemic buffer pattern, is suggestive of a deficit in the sublexical phoneme to grapheme conversion process, while her agrammatic spontaneous writing sample is characteristic of the type produced by patients with PNFA (N. Graham, L., 2000).

5.3.3 Participant L901

L901 was a 65 year old right-handed English man with bulbar onset MND, which was later revealed to be MND-FTD. He reported no difficulty learning while at school, leaving school to join the paratroopers aged 16. He reported that both his vision and hearing were normal, although formal assessment of his hearing was not conducted.

At the time of testing in March/April 2012, his symptoms were predominantly confined to dysarthria and dysphagia, but with increasing difficulty with his upper and lower limb functions, and with an ALS-FRS score of 38. His speech was characterised by a mild-moderate mixed dysarthria, with a hyper-nasal monotone voice quality, slow rate of speech, and distorted articulation. Intelligibility of his speech was moderately affected, however he was still understandable to an unfamiliar listener and used speech as his main method of communication.

No measure of anxiety and depression was obtained, however he scored 4 on the Epworth Sleepiness Scale, which was within normal range suggesting normal respiratory function. With regards his verbal fluency performance, she was impaired on both the written and spoken unconstrained and constrained measures, with particular difficulty following the word length condition of the constrained version, naming only one correct item in two minutes for the written version and unable to name any correct items in one minute for the spoken version. Unfortunately his health deteriorated rapidly during the process of assessment and some measures, including working memory measures were unattainable. L901 passed away three months after the last testing session.

Linguistic assessment

Table 5.24 shows the performance of L901 across the both the standard and experimental linguistic assessments completed.

Test (Maximum Score)	L901's Score	Control Mean (SD)
Word Spelling Composite (24)	3**	23.16 (0.8)
Nonword Spelling Composite (24)	DNC	16.59 (2.906)
Word Minimal Pairs (48)	DNC	47.44 (0.651)
Nonword Minimal Pairs (48)	DNC	47.44 (1.121)
Graded Naming Test (30)	20**	25.45 (2.703)
Northwestern Naming Test (32)	DNC	31.72 (0.458)
TROG (40)	28**	39.04 (0.841)
Spelling Verification Test (72)	62**	71.64 (1.036)
Letter String Discrimination (48)	40*	47.20 (2.415)
PEPS Affect (16)	DNC	15.40 (0.91)
PEPS Intonation (16)	DNC	14.88 (1.17)
PEPS Turn-End Type (16)	DNC	15.28 (1.06)

Table 5.24: Total scores of participant L901 on standard and experimental linguistic assessments in comparison to control mean. * ≥ 2SD below control mean; **≥ 3SD below control mean

Naming: L901 did not complete the NNT, however he performed more than 3 SD below the control mean on the GNT. As his dysarthria was not as severe as that of L165 and L107, he was able to complete the GNT as a spoken naming test. His spoken naming was characterised by phonological paraphasias ('handcock' for handcuffs), mixed semantic and phonological paraphasias ('bishop's cassum (cassock)' for mitre, 'Chinese gondola' for pagoda), semantic errors ('theodolite' for sextant, 'pegasus' for centaur, 'scarf' for cowl), circumlocutions ('45 degrees, centre' for radius, 'veil, muslim' for yashmak) and one self corrected metathetic error ('carescrow' for scarecrow). Additionally, errors increased with decreased frequency, which, like L165, is suggestive of a lexical access deficit. However, as L165 and L901 used different output methods (written and spoken respectively), yet show a similar error pattern, this raises questions about the interconnectivity of the phonological and orthographic output lexicons.

Reading: L901 performed more than 3 SD below the control mean on the SVT, however, unlike L165 and L107, was also impaired on the letter string discrimination test. On further analysis of his error patterns on the SVT (see Table 5.25), L901 like L165 and L107, produced the highest percentage of errors in his ability to reject phonologically plausible nonwords, scoring just above chance level. He also demonstrated a tendency to accept similar words as correct spellings (e.g. on hearing 'cash', he accepted crash as a correct spelling). Furthermore, in analysing his pattern of errors in relation to the predictability (or regularity) and frequency of the spoken stimuli, he produced most errors when the spoken stimuli was low in predictability and frequency. This pattern is, like L165 and L107, suggestive of an impairment in the orthographic input lexicon, but to a greater severity than the other two case examples.

Regarding L901's impaired performance on the letter strings discrimination test, this is suggestive of a more peripheral deficit, at the level of visual orthographic analysis. Of particular note, he produced most errors in recognising when nonword pairs written in different cases were the same (e.g. when presented with the pair AIHCN – aihcn, he scored this as 'different').

Stimuli Type	Percentage Correct
Correct	100%
Similar Word	75%
Phonologically Plausible Nonword	58.3%
Phonologically Implausible Nonword	83.3%
High Predictability, High Frequency	83.3%
High Predictability, Low Frequency	94.4%
Low Predictability, High Frequency	88.9%
Low Predictability, Low Frequency	77.8%

Table 5.25: Performance of L901 on SVT according to stimuli type

Spelling: L901 performed ≥ 3 SD below the control mean on the word spelling composite, however deteriorated before the nonword spelling test could be administered. On examination of the percentage of misspelled word (MSW) types produced across all three word spelling to dictation conditions (see Table 5.26), 100% of MSW produced by were orthographically implausible. Of these orthographically implausible MSW, he produced several phonologically similar real word MSW, ('fag' for flag; 'tint' for tent), and three no responses. He produced more errors when spelling nouns over verbs and also showed decreased accuracy with increased word length, similar to L165 and L107.

No. of Cons	No. of MSW	% MSW	% Plaus MSW	% Implaus MSW	% Noun MSW	% Verb MSW	% 4 Letter MSW	% 7 Letter MSW	% 10 Letter MSW
3	31	86.11	0	100	94.44	77.78	66.67	91.67	100

Table 5.26: Percentage of misspelled word types produced by L901 across the three word spelling conditions completed. Cons = Conditions; Plaus = Orthographically Plausible; Implaus = Orthographically Implausible

When the serial positions of errors within the MSW were analysed, the pattern was consistent with the bow-shaped curve expected with a impairment in the graphemic output buffer (see Figure 5.20).

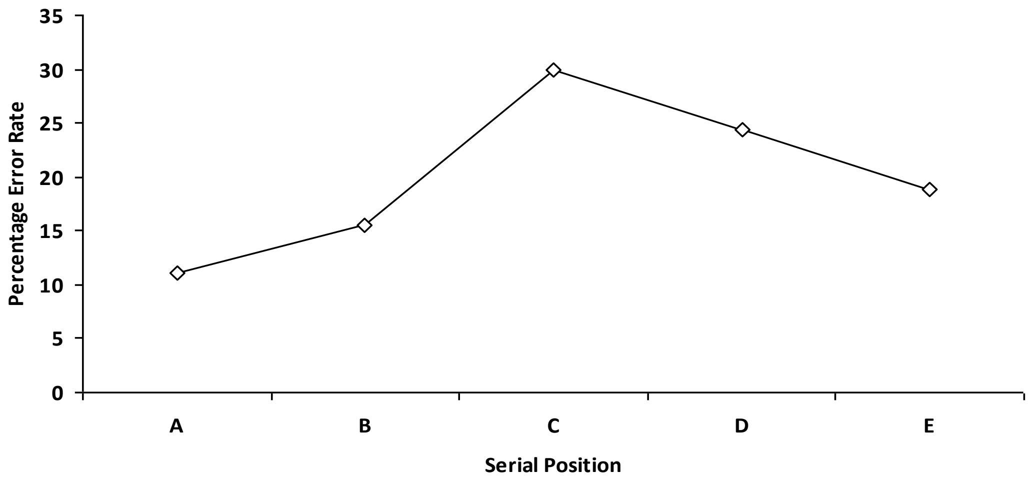
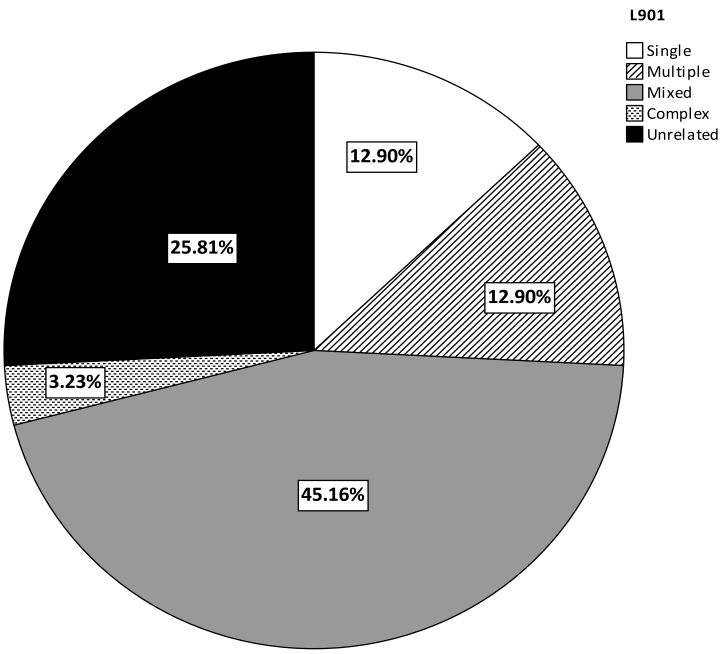


Figure 5.20: Percentage of errors produced in each serial position for MSW produced by L901

The MSW produced by L901 were characterised by substitutions ('boob' for bump; 'tint' for tent), deletions ('inpect' for inspect; 'tanpant' for transplant), insertions ('jumped' for jump) and combinations of these (deletion and substitution 'deefip' for develop, 'popecana' for propaganda; transposition and substitution 'suskpet' for suspect; deletion and transposition 'oromer' for astronomer; insertion and deletion 'crittis' for critics). Over a quarter of errors were no responses or unrelated – where MSW showed little connection to the target (e.g. 'crivet' for gift). Only 12.5% of the MSW contained a single error, with a further 12.5% of MSW comprising multiples of the same type of error, meaning that 75% of MSW consisted of mixed, complex and unrelated errors (see Figure 5.21).

A



B

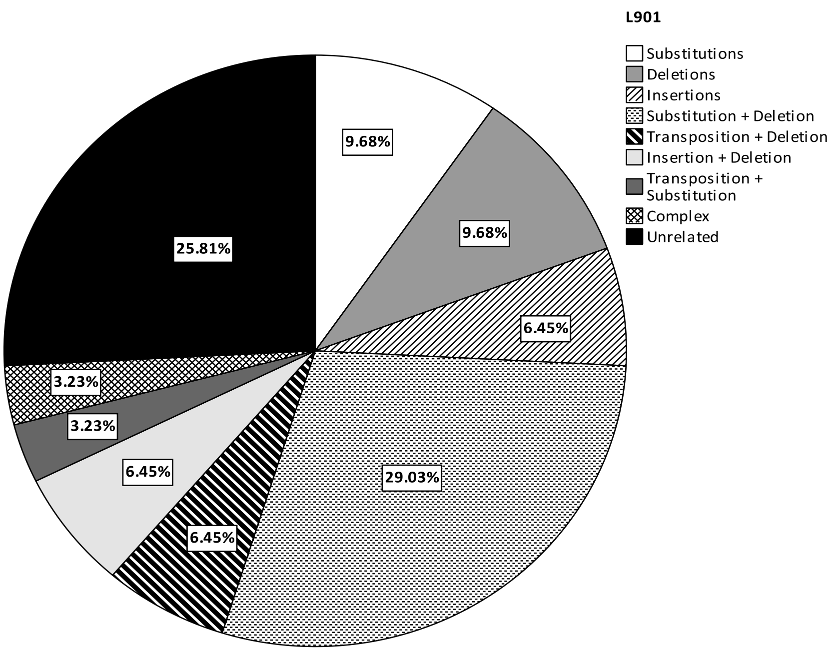


Figure 5.21: Distribution of MSW errors produced by L901.
Chart A shows the percentage of MSW errors according to number; Chart B shows the percentage of MSW errors according to type.

Syntax: L901, like L65 and L107 also showed evidence of impairment in both the production and comprehension of grammatical constructs. He too performed ≥ 3 SD below the control mean on the TROG. Furthermore, his spontaneous writing from picture description was markedly agrammatical and filled with spelling errors to the point where the description would be unintelligible without the context of the picture (see Figure 5.22). Sentences were telegraphic with limited function words and perseverative formulaic constructions. Spelling errors were in keeping those seen in spelling to dictation, with mixed semantic and phonemic paragraphias ('sleave' for steal; 'cooks' for cookies; 'cince' for sink), and difficulty spelling both nouns and verbs.

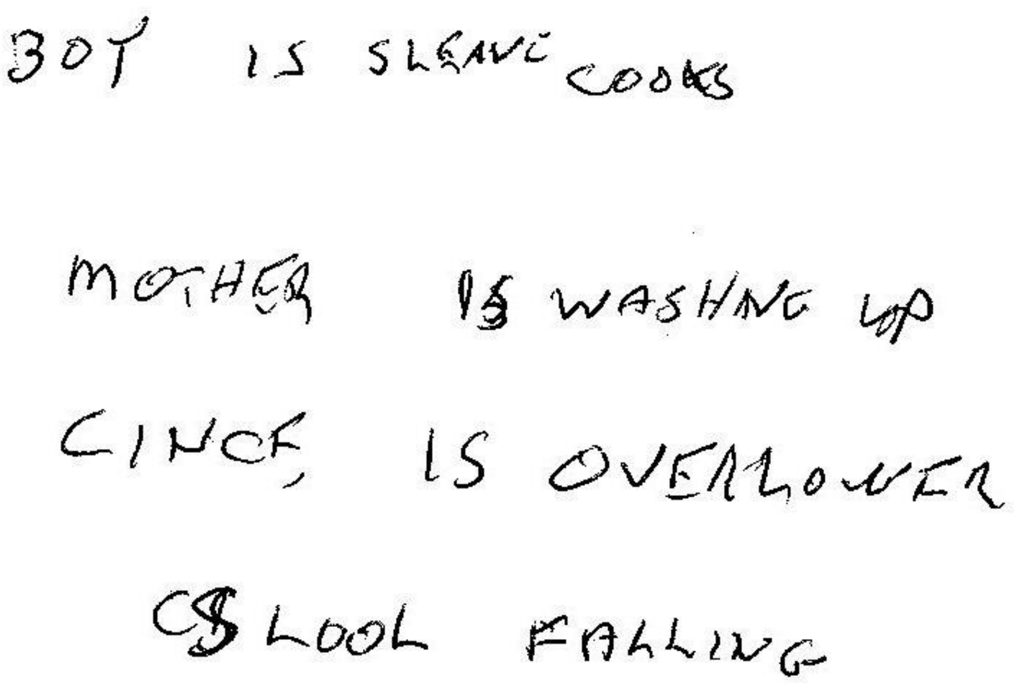


Figure 5.22: L901 Boston Cookie Theft spontaneous writing sample

Additional assessments

Although L901 deteriorated before the assessment battery could be completed, two weeks prior to assessment starting he participated in a parallel cognitive study administered by the University of Edinburgh. As part of this study he completed a series of other linguistic and cognitive neuropsychological assessment, the results of which are detailed here.

Delis-Kaplan Executive Function System (DKEFS) sorting task (Delis, Kaplan, & Kramer, 2001): In this test of problem solving and reasoning, participants are presented with six cards each displaying written words and characterised by varying perceptual features. The participant is then asked to sort the cards into two groups of three, giving the reasoning behind each categorisation. There are eight different categorisations possible: three based on what is defined by the authors as 'verbal-semantic' information, based on the written word stimuli, and five based on the visual spatial features of the cards. However, further examination of the stimuli type provides interesting performance in terms of phonological and orthographic skills. L901 was able to categorise according to the two possible semantic categories (animals/transport and items from the air/land), and two of the visual spatial categorisations relating to the shape and colour of items on the cards. However he was unable to make the third 'verbal-semantic' categorisation based on the number of syllables in the written stimuli (1/2 syllables), and was also unable to make the visual categorisation based on letter case of the written stimuli (upper/lower). His inability to make the categorisations requiring phonological awareness and orthographic analysis skills, yet little difficulty recognising the two semantic categories could provide further support for a relatively intact semantic system with degraded phonological and orthographic analysis.

Pyramids and Palm Trees test (PPT) (picture version) (Howard & Patterson, 1992) and Kissing and Dancing Test (KDT) (picture version) (T.H. Bak & Hodges, 2003): The Pyramids and Palm Trees and Kissing and Dancing tests assess the nonverbal ability to infer semantic associations between nouns/objects (PPT) and verbs/actions (KDT). L901 scored 43/52 on the PPT and 42/52 on the KDT, both of which were below mean control performances of 51.1 and 50.4 respectively, as reported in the literature (T.H. Bak & Hodges, 2003). Furthermore, his pattern of performance on both of these measures is similar to the impairment pattern exhibited by patients with SD (ibid.).

Boston Naming Test (BNT) (Kaplan et al., 1983): L901 was also presented with the Boston Naming Test, which contains higher frequency items than the GNT. On this naming measure he obtained a score of 56/60, which supports suggestions that the BNT is less sensitive to naming deficits seen in MND (Cobble, 1998). Similar to his performance on the GNT, errors consisted primarily of circumlocutory errors ('stand for camera' for tripod; 'tweezer for ice' for tongs) and some semantic errors ('bed' for hammock). He was also stimulable to phonemic cueing on one item where, after producing 'Egypt' for pyramid given the initial phoneme was able to produce the correct response. This is suggestive of impaired access to the lexicon from the semantic system, and not in the semantic system or phonological output lexicon itself.

Noun and Verb spelling (adapted from Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) 41 Grammatical Class spelling) (Kay et al., 1992): L901 also completed two further spelling tests. In this first test, examining influence of grammatical class on spelling to dictation, he was presented with five nouns and five verbs. In keeping with the experimental test administered in this study, he produced more MSW when writing nouns than verbs, correctly spelling two nouns and four verbs. One of the errors was phonologically plausible ('ignor' for ignore), one was phonologically similar ('taxt' for task), one was visually similar ('cliete' for client) and one was unrelated ('imet' for image), patterns in keeping with those observed in this study.

Graded Difficulty Spelling Test (Baxter & Warrington, 1994): This second additional spelling to dictation test presents a series of 30 items increasing in difficulty based on frequency, regularity and word length. As seen in the experimental test, shorter words were spelled with greater accuracy than longer words, but unlike the experimental test, he produced a number of phonologically plausible MSW in addition to implausible, particularly for irregular words. Forfeit was spelled 'forfitt'; languid as 'langwad' and plait as 'plat', suggesting a reliance on the phoneme to grapheme conversion process. However, he was able to spell some irregular words correctly (e.g. sword) and demonstrated knowledge of irregular spellings even when realisations were not accurate (e.g. 'concieve' for conceive). Consistent with the experimental spelling test in this study he produced a large number of phonologically implausible MSW ('slatve' for survey; 'teconil' for technical; 'mowchas' for moustache; 'flacketing' for trafficking; and 'ixcrope' for kaleidoscope). Overall he obtained a score of 8/30.

Summary

L901 was the most severely impaired of all the MND participants in this study, and the only one to be identified with MND-FTD. However while he produced the most amount of errors across all measures in which he was assessed, the pattern and nature of these errors was similar to those of the other case studies outlined here. His spelling to dictation and written naming exhibited errors attributable to both lexical and sublexical deficits, and his picture description writing sample was arguably the least cohesive and coherent of all the participants. Again, this overall pattern of impairment is not necessarily compatible with those reported with regards individual subgroups of PPA, but perhaps reflects a mixed SD-PNFA profile.

5.4 Discussion

The synthesis of results across the battery of linguistic and neuropsychological measures provides interesting insights into the nature of language deficits in people with MND. Individual patterns of spelling performance revealed a distinctive subgroup of linguistically impaired participants, accounting for 44% of the participants tested. All LI MND participants were impaired on at least 19% of the language measures, and LI participants were impaired on a significantly higher percentage of tests across the battery than those classed as non-linguistically impaired. This 44% linguistic impairment rate across the MND group is consistent with the figure of 43% who were impaired on a composite language measure as reported by Taylor and colleagues (Taylor et al., 2013). While classification of linguistic impairment based on word spelling performance may not identify all patients exhibiting evidence of language deficits, it was a salient marker for linguistic impairment.

5.4.1 Clues from Spelling and Reading

Not only was overall word spelling to dictation performance a marker for linguistic impairment, but examination of word and nonword spelling error patterns also revealed further information about the integrity of lexical and sublexical processes in our participants. However, pinpointing the impairment to a particular single process deficit is less than straightforward.

The significantly higher proportion of orthographically implausible MSW over plausible MSW in the linguistically impaired group is the hallmark of a sublexical graphemic buffer impairment (Caramazza et al., 1987). This coupled with the pattern of deletion, substitution and insertion of letters, increasing errors with word length, and similarity of errors across word and nonword spelling is consistent with the buffer deficit suggested as responsible for spelling errors in MND patients in the literature (Lucchelli & Papagno, 2005; Zago et al., 2008). However the, picture is not entirely clear as although the LI group were significantly worse than the NLI group on the reverse digit span measure of working memory, only two of the seven LI participants who completed this measure demonstrated the working memory deficit expected with a buffer impairment.

Nonword spelling performance also provides further mixed information about the likely contributions to spelling impairment. While there was no significant group difference between nonword spelling performance in the LI and NLI groups, 62.5% of LI participants who completed the nonword spelling test were impaired. As nonwords do not have lexical representations, they must be spelled via the sublexical phoneme to grapheme conversion process. That LI participants were impaired on nonword spelling, with some participants (see case L107) producing lexicalisations of nonwords could indicate an impairment in the phoneme to grapheme conversion process, and could account for the errors producing phonologically based kana letters reported in Japanese patients (Ichikawa, Koyama, et al., 2008; Ichikawa, Miller, et al., 2011). However, while LI MND participants performed worse in nonword spelling than word spelling, consistent with a phoneme to grapheme conversion deficit, this pattern of performance was also true of NLI MND participants and controls (see chapter 4). Thus, it could be suggested that there is no greater an effect of lexicality upon the spelling performance of LI MND patients than NLI patients, pointing again to a post lexical buffer deficit.

However, there are also suggestions that there may also be a more central lexical deficit contributing to the pattern of spelling impairment. While LI participants produced a significantly higher percentage of orthographically implausible MSW than the NLI participants, semantic and phonological paragraphias were also present. Semantic and phonological paragraphias observed particularly in written naming, where spelling is necessarily produced via the lexical-semantic route could suggest a deficit in the orthographic output lexicon or access to it. This may also account for the mixed reports regarding naming impairment in MND. While some researchers have found no impairment in naming using assessments containing higher frequency items, such as the BNT (P. R. Talbot et al., 1995), naming assessments including higher frequency items, such as the GNT, have highlighted the existence of naming deficits (Abrahams et al., 2004; Cobble, 1998; Rakowicz & Hodges, 1998). While items on the spelling to dictation test used in this study were matched for frequency, meaning interpretations cannot be fully made about the effects of frequency on spelling, written naming performance does suggest some influence of frequency. Frequency effects in spelling are most commonly attributed to a deficit in the orthographic lexicon or access to it, while a deficit in the graphemic output buffer should not be sensitive to lexical influences.

While there was little evidence of an effect of frequency on the performance of LI MND participants in reading performance, there was some suggestion of a lexical level deficit. Although LI participants were significantly worse than NLI participants in the ability to reject both phonologically plausible and implausible nonwords in the SVT lexical decision task, there was a higher percentage of errors with phonologically plausible stimuli. This is the pattern of impairment commonly associated with surface dyslexia and attributed to a deficit in the orthographic lexicon (Whitworth, Webster, & Howard, 2005). There is however also the suggestion that some of the most impaired participants may display an additional peripheral reading deficit as demonstrated through impaired performance on the LS discrimination test. This could suggest that as linguistic impairment progresses, errors become increasingly peripheral in nature. This may also explain the correlation between the number of orthographically implausible MSW produced in word spelling to dictation and the percentage of tests MND participants were impaired on across the battery.

This hypothesis is one that is suggested by Graham and colleagues in the observation of co-occurring central and peripheral spelling impairments in patients with progressive dysgraphia (N. Graham, L. et al., 1997). They reported two patients in whom a central surface dysgraphia was the presenting pattern of impairment, but over a four year period increasing numbers of phonologically implausible errors were produced, eventually becoming the predominant spelling pattern. They suggest that rather than explaining the dysgraphia seen in these patients as the result of multiple loci of impairment in the logogen model outlined in chapter 4, it may be more conceptually coherent to consider it in the setting of a interactive connectionist model such as that posited by McClelland and Rumelhart (McClelland & Rumelhart, 1981). This model proposes that representations about features (e.g. allographs, acoustic features), letters (e.g. graphemes) or phonemes, words (lexical items) and higher levels (semantic items) interact in a simultaneous, bidirectional 'top-down' and 'bottom-up' process. Every level in the system consists of a series of 'nodes', one for every feature at that level (i.e. a node for every word we know at the word level, a node for every letter in each letter position as the letter level). Connections between levels are twofold: excitatory and inhibitory. Thus simultaneous information confirming and denying nodes at each level can be obtained from both higher and lower levels. Graham and colleagues suggest that the central to peripheral deficit seen in their patients was as a consequence of an initial word level deficit, but that continued deterioration in word level representations then resulted in a knock on effect to letter and feature levels due to reduced top-down activation or inhibition (N. Graham, L. et al., 1997).

The observation of sublexical graphemic buffer type spelling deficits with co-occurring lexical influences reported in stroke patients have also been considered in these terms (Pate & Margolin, 1990; Sage & Ellis, 2004). Sage and Ellis propose that the amount of top-down activation reaching the letter representations is dependent on the strength of the connections between the semantic 'higher' level and the word level and between the word level and the letter level, and that the strength of these connections can be influenced by 'lexical' features such as frequency and imageability. Furthermore they suggest that these lexical influences on what would be traditionally considered a post lexical deficit are more pervasive than might be widely believed. Thus the appearance of more lexical type errors in the spelling patterns of the LI MND patients in this study may still be compatible with a graphemic buffer deficit.

However, whether the spelling impairment observed in MND patients start primarily as a deficit at the word level, progressing to letter level, or whether the deficit is primarily at a letter level with word level influences is uncertain, and something which could be explored through longitudinal study. Furthermore, further investigation into the influence of various lexical variables upon spelling and reading performance may provide additional insights into the nature of the linguistic impairment.

5.4.2 The Value of Naming Tests as a Diagnostic Tool

As discussed, naming tests can be an invaluable resource in the identification and exploration of linguistic impairments in MND patients. However, while naming deficits in MND have previously been reported, little qualitative information exists on the nature of these errors. Qualitative analysis of the types of errors produced can help differentiate between core semantic deficits and impairment in the lexicon (Howard & Gatehouse, 2006). Naming errors produced by the patients included in this study suggest a lexical access deficit rather than a central semantic one. Errors were characteristically no responses, circumlocutions and phonemic paraphasias/paragraphias, rather than purely semantic errors. It is for this reason that when assessing naming ability in MND patients stimuli should measure for lexical variables such as frequency, word length, age of acquisition and word class. The latter of these variables is particularly relevant to MND patients as previous studies have identified a particular deficit naming verbs (or actions) over nouns (or objects) (T. Bak & Hodges, 1997; T. H. Bak et al., 2001). While there was no significant within group difference in either the LI or NLI subgroups in naming of nouns and verbs in this study, this may be as a result of the small number of test items (sixteen of each word class) and is something which should be explored further with a larger number of test items.

5.4.3 Further Insights from Prosody

The assessment of receptive prosody has provided some interesting and new insights into linguistic impairment in people with MND. While comparison of the performance of the entire MND group to the control group revealed only significant difference between the groups in the perception of affective prosody (see chapter 3), subdivision of the MND group into LI and NLI participants revealed a further deficit in the perception of turn-end type prosody in the NLI group. This pattern of deficit echoes that reported by Rohrer and colleagues in their study of receptive prosody in nonfluent progressive aphasia (Rohrer et al., 2012). This could suggest that there is a connection between the pattern of deficit seen in PNFA and LPA and linguistic impairment seen in MND patients. However, unlike the PPA patients reported by Rohrer and colleagues, MND participants did not show any significant difference in performance on the non linguistic intonation contour discrimination task in comparison to controls, thus indicating that this is not an acoustic processing deficit and confirms the linguistic nature of the deficit.

The difference in performance between the LI and NLI subgroups could suggest that there is some gradient of processing difficulty between perception of linguistic and affective prosody. Sammler and colleagues propose that decoding the speaker's intended meaning from prosodic patterns requires the integration of motor simulation and theory of mind mechanisms (Sammler, Bestelmeyer, & Belin, 2013). The former helps to identify what the speaker is doing in terms of pitch variation, while the latter helps to indentify the intention is behind this prosodic action. It could be argued that in order to perceive affective prosody there is a greater demand on the theory of mind mechanism, in addition to the motor simulation mechanism. This could suggest that there may be a deficit in the ability to infer mental states in both the NLI and LI groups, while the LI group have an additional difficulty with the motor simulation mechanism. However further investigation into the nature of these prosodic processing deficits are required before conclusions can be made.

5.4.4 Executive Dysfunction and Language Impairment

Significant differences between the LI and NLI groups on all measures of executive functioning used in this study would suggest that there may be some connection between executive dysfunction and linguistic impairment in MND patients, and is something which has been reported in previous studies (Abrahams et al., 2000; P. R. Talbot et al., 1995; Taylor et al., 2013). However, while earlier studies have suggested that this relationship could indicate that language impairment is merely a result of executive dysfunction, Taylor and colleagues highlight that there may be another explanation for this relationship. They argue that impairments reported in the executive domain may partly reflect language impairment, as a number of tests used to assess executive functioning have a strong linguistic component (Taylor et al., 2013). The same could be said regarding patient performance on executive measures in this study. The only test of executive functioning used in this study was verbal letter fluency, a measure which has a heavy reliance on linguistic ability, and something which people with lexical access issue would find difficult, regardless of executive functioning. However, non verbal measures of executive functioning have also demonstrated a relationship between executive dysfunction and language impairment in order related disorders. In a study examining differences in the linguistic profiles of patients with PNFA and those with nonfluent stroke aphasia, Patterson and colleagues attributed the particular connected speech deficit of PNFA patients to poor performance on the Wisconsin Card Sorting Task, a nonverbal measure of frontal executive function, which was not present in the non progressive patients (K. Patterson et al., 2006). Thus there is some suggestion that linguistic impairment in MND patients could be connected to frontal pathology, which has been previously reported in imaging studies (Abrahams et al., 2004; Tsermentseli, Leigh, & Goldstein, 2012).

Yet, this is not the whole picture regarding the relationship between language impairment and executive dysfunction. Again, in keeping with the study by

Taylor and colleagues, this study also found some dissociation in performance between the two domains. Two participants from the NLI group were impaired on measures of verbal fluency with intact performance on all language measures, while one participant from the LI group exhibited evidence of impairment in word spelling, naming, perception of linguistic prosody and comprehension of syntactic structures, but no verbal fluency deficit. This suggests that while there is a strong relationship between executive dysfunction and language impairment in MND, the two are not mutually inclusive.

5.4.5 Relationship with PPA and Dichotomous Subgroups

A number of comparisons can be drawn between the patterns of impairment seen in these linguistically impaired MND patients and those described in people with PPA. Of the three subtypes of PPA, semantic dementia (SD), progressive nonfluent aphasia (PNFA), and logopenic progressive aphasia (LPA), the closest comparison can be drawn to PNFA. Significantly impaired comprehension and production of complex syntactic structures as observed through performance on the TROG and agrammatic writing samples is characteristic of patterns reported in PNFA (Code et al., 2006; Grossman & Ash, 2004; Knibb et al., 2009). In an analysis of the spelling error patterns observed in a cohort of PPA patients, Sepelyak and colleagues noted a high number of phonologically implausible nonword responses and a word length effect, similar to that observed in the LI MND participants in this study, in one participant with PNFA (Sepelyak et al., 2011). A further two PNFA participants produced omissions and unrelated word responses indicating impaired access lexical representations and a disturbed phoneme to grapheme conversion process, which was also characteristic of errors produced by some LI participants in this study. Moore and colleagues have reported confrontation naming deficits in people with PNFA attributable to limited lexical retrieval and phonological assembly, which again echoes the error patterns observed here (P. Moore, Dennis, & Grossman, 2003). Additionally the recently explored prosodic skills of people with nonfluent primary progressive aphasias revealed similar patterns of impairment in the perception of linguistic and affective prosody (Rohrer et al., 2012). These close comparisons could suggest that the linguistic impairment seen in MND patients is another manifestation of PNFA.

However, there were some features of linguistic impairment observed in the LI MND participants which are normally attributed with the SD or LPA subtypes of PPA. For example, the production of a number of orthographically plausible MSW when writing via the lexical-semantic route and high acceptance of phonologically plausible nonwords in the visual lexical decision test could suggest the presence of an additional lexical-semantic deficit, more commonly associated with semantic dementia (SD) (Wilson et al., 2009) or logopenic progressive aphasia (LPA) (Sepelyak et al., 2011). Yet Sajjadi and colleagues have reported that the subtype classification of patients with PPA is often not as clear cut as has been previously described (Sajjadi, Patterson, Arnold, Watson, & Nestor, 2012). They report that 41.3% of 46 PPA patients they tested did not fulfil the diagnostic recommendations for any of the three proposed variants (SD, PNFA and LPA) of PPA, despite having definite diagnoses of PPA. This suggests that strict categorisation may not always be applicable or necessarily appropriate when dealing with progressive neurological conditions where there is a continually changing pathological profile and likely to be much individual variation.

The division of MND participants into dichotomous groups, based on the presence of spelling deficit as a marker for linguistic impairment, points towards the suggestion of language impairment in MND as a distinctive disease subtype. While the division of this particular group of participants may not be as ‘cut and dried’ as presented here, as evidenced through the small number of borderline cases discussed earlier, it is clear that most participants fall into either a ‘linguistically impaired’ or ‘linguistically intact’ group. However, within the LI group, there also seems to be a continuum of impairment. Bak has explored these notions of continuum versus distinctive diseases in considering the relationship between MND, FTD and language impairment (T. H. Bak, 2010). While previously considering MND and FTD as two extremes on the same continuum, he posits that it may be more useful, in the light of increasing evidence of distinct language impairment, to consider a separate MND dementia-aphasia syndrome. This proposal would fit with the suggested mixed PPA linguistic profile. Furthermore Bak and Chandran propose that a possible explanation for the pattern of cognitive involvement in MND is a spreading degeneration along functionally connected cell assemblies (T. H. Bak & Chandran, 2012). Considering this hypothesis in combination with the connectionist models of language processing discussed earlier, it could be suggested that this can also account for the continuum of impairment seen within the LI subgroup. However the pattern and progression rate of this spread of connective deterioration is something which requires further investigation.

5.4.6 Written and Spoken Language Correlates

As the severity of dysarthria precluded analysis of spoken language production in many of our participants, only written language could be accurately assessed. However this reflects the main method of communication for a large number of MND patients and can sometimes be the clue to a central language impairment. However, due to the relative lack of data collected in the spoken modality form this cohort of participants, we cannot say with any accuracy whether these deficits are restricted to writing or whether they are more pervasive and affect spoken language also. Indeed there has been some suggestion that the poverty of spoken output reported in MND patients could be attributable not only to dysarthria, but also to a spoken aphasia (Caselli et al., 1993), thus patients, including participants in this study, who are considered anarthric, could indeed be anarthric-aphasic. Examining the relationship between non-orthographic semantic and phonological processing and written output in PPA patients, Henry and colleagues have suggested that common networks support semantic and phonological processes used in spoken and written output, and that spoken language performance is predictive of orthographic performance (Henry, Beeson, Alexander, & Rapcsak, 2012). This being the case and with the similarities between the language impairments seen in patients with MND and PPA patients, it could be suggested that the reverse is also true: that written performance is predictive of spoken language performance in MND patients. If this is the case, this highlights the usefulness of written assessment in the identification of a pervasive language impairment in MND patients. However further assessment of parallel spoken and written language functions in patients for whom spoken and written assessment is physically possible is required to test this hypothesis.

5.4.7 Bulbar Onset, Dysarthria and Language Impairment

The relationship between disease onset, dysarthria severity and language impairment in MND patients is another theme that has been discussed throughout this thesis and the wider literature. That a significantly greater number of bulbar than non-bulbar onset participants in this study were in the LI group is another point of interest, and something which has been similarly found in other studies examining cognitive dysfunction (Abrahams et al., 1997; Portet et al., 2001; Schreiber et al., 2005) and writing errors (Ichikawa, Koyama, et al., 2008; Ichikawa, Takahashi, et al., 2008). Ichikawa and colleagues (Ichikawa, Koyama, et al., 2008; Ichikawa, Takahashi, et al., 2008) suggest that this relationship could be as a result of the neuroanatomical proximity of Broca's area (Brodmann 44 and 45) responsible for language production and comprehension, and the orolingual motor cortex connecting to bulbar areas. However comparisons of performance between bulbar and non-bulbar onset groups in earlier chapters of this thesis have produced a mixed message, with the majority of neuropsychological, standard linguistic and experimental linguistic measures showing no significant difference between the two onset groups.

Several comments can be made on this finding. Firstly not all participants in the LI group had bulbar onset symptoms. Two of the eleven LI participants had limb onset symptoms, suggesting that linguistic impairment, as documented in this study is not purely confined to those with bulbar onset symptoms. Secondly, not all bulbar onset participants were in the LI group, indicating that bulbar onset symptoms are not necessarily a clinical marker for linguistic impairment. Thirdly, as the aim of this thesis was to investigate the nature of language impairment in MND patients experiencing communication difficulties, and as bulbar onset patients will experience communication difficulties earlier in the disease progression whilst still maintaining reasonable overall health to allow them to participate in the research, a higher number of bulbar-onset patients were assessed as consequence of these conditions. While the difference in background and health characteristics between the two groups was not significant (see chapter 2), there were still 20% more bulbar onset participants than non-bulbar participants. For any firm conclusions about the differences between linguistic functioning in bulbar onset and non bulbar onset to be made, equal numbers of patients should be studied.

The relationship between dysarthria severity and linguistic impairment in this study also raises a number of important points. The lack of significant difference between the LI and NLI groups in terms of dysarthria severity highlights that the severity of the communication impairment is not necessarily dictated by the severity of the dysarthria. A person with a severe dysarthria with no language impairment may be viewed as having a severe communication impairment, but given the right augmentative and alternative communication (AAC) strategies could become an effective communicator once again. Equally, a patient with mild dysarthria may present with a marked language impairment that has a greater impact on communicative functioning than the dysarthria. However, because the communication impairment in the second patient may not be as overt, it may be missed without appropriate assessment. This highlights the second important point that although there was no significant relationship between dysarthria severity and linguistic impairment, over 63%

of the participants in the LI group were anarthric or severely dysarthric. Therefore there may be a high proportion of MND patients for whom severe dysarthria or anarthria may not only be a significant speech difficulty, but could also be masking other linguistic deficits. This message has consequences for the clinical management of MND patients, as will be discussed in chapter 6.

Chapter 6: Conclusions

6.1 The Nature of Language Impairment in MND

The results of this study have revealed a number of remarkable new findings which, in combination with confirmation of some of the previous results, help to clarify the profile of language impairment in MND.

6.1.1 Association with PPA – A Distinct Pattern of Impairment?

Multidimensional language assessment exposed a distinct subgroup of MND participants impaired on measures of naming, grammatical comprehension, linguistic prosody, reading and spelling. Indeed assessment of spelling proved to be a good indicator for linguistic impairment and as a result of these findings spelling assessment has been incorporated into the newly developed Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (Abrahams, Newton, Niven, Foley, & Bak, 2013). Error patterns revealed indications of deficits at both a lexical and sublexical level, adding further qualitative information about the nature of spelling impairment in MND to the growing body of evidence supporting its existence (Doran et al., 1995; Ferguson & Boller, 1977a; Ichikawa et al., 2010; Ichikawa, Koyama, et al., 2008; Lucchelli & Papagno, 2005; Taylor et al., 2013). Assessment of reading processes also revealed a more central linguistic deficit than a peripheral or attentional one, and may point to an impairment in a shared orthographic lexicon. However, while this is the first study to examine in depth the nature of spelling impairment in a group of MND patients, further investigation is required to explore the influence of lexical variables such as frequency, regularity and imageability upon performance to ascertain the extent to which it is a lexical impairment.

Assessment of prosody perception also revealed some new and striking findings. That the MND group as a whole was significantly worse than controls on the perception of affective prosody is in keeping with previous reports investigating social cognition in MND (Meier et al., 2010). However the linguistically impaired group also exhibited an additional deficit in processing linguistic prosody. This finding, previously unreported in MND patients, echoes findings from research exploring prosodic processing in patients with primary progressive aphasia (Rohrer et al., 2012). Again this further supports the suggestion of a distinctive, linguistically impaired subgroup within the MND population and strengthens the association with primary progressive aphasia (PPA).

Indeed, as discussed chapter 5 (see section 5.4.5), a number of comparisons can be drawn between the patterns of impairment seen in the linguistically impaired MND patients and those described in people with PPA, particularly progressive nonfluent aphasia (PNFA). Impaired comprehension and production of complex syntactic structures, high numbers of phonologically implausible nonword spelling errors, and confrontation naming impairments attributable to lexical retrieval and phonological assembly deficits found in the linguistically impaired MND patients in this study have also been reported in PNFA patients (Code et al., 2006; Grossman & Ash, 2004; Knibb et al., 2009; P. Moore et al., 2003; Sepelyak et al., 2011). However, a number of other features, such as difficulty rejecting phonologically plausible nonwords in the lexical decision task, normally associated with the semantic or logopenic variants of PPA were also observed (N. L. Graham et al., 2000; Wilson et al., 2009). This mixed presentation across the linguistically impaired subgroup could suggest that the linguistic impairment observed in MND patients does not necessarily fit within the PNFA or SD profile, but is in fact a separate profile combining elements of both frontal and temporal deficits. Furthermore, the individual variation in performance between patients within the linguistically impaired group could reflect a continually changing pathological profile in parallel with disease progression. However, in order to investigate this hypothesis longitudinal testing is required.

6.1.2 Distribution of Impairment

The prevalence of linguistic impairment within the MND patients included in this study was remarkably high. That 44% of participants were classed as linguistically impaired according to performance on measures of spelling is higher than the 35% average cognitive impairment rate reported in the literature (Phukan et al., 2012; Ringholz et al., 2005). However, it is in keeping with the recent findings from the study by Taylor and colleagues investigating the prevalence of language impairment and the relationship with executive dysfunction, who reported language impairment in 43% of MND patients (Taylor et al., 2013). Furthermore, the presence of a distinct subgroup of linguistically impaired patients within the MND group in this study is consistent with other reports (Cobble, 1998; Rakowicz & Hodges, 1998). This finding may suggest that linguistic impairment in MND is not on a continuum across the patient population but rather a separate disease phenotype. Indeed Bak has argued that language impairment in MND should be considered a separate subtype of impairment within the consensus criteria in much the same way that ALS with cognitive impairment (ALSci) and ALS with behavioural impairment (ALSbi) have been delineated (T. H. Bak, 2010).

6.1.3 Influence of General Cognition and Disease Variables

The lack of significant difference between patients and controls on measures of working memory suggests that performance on measures of language were not attributable to an impairment of working memory and/or attention. While the linguistically impaired MND participants performed significantly worse than the non linguistically impaired group on the reverse digit span, only two were impaired in comparison to control performance. This suggests that while some patients may be affected by a working memory deficit, it cannot explain the widespread linguistic impairment across the group.

The high prevalence of impairment on measures of verbal fluency both within the linguistically impaired group and across the MND group as a whole supports previous findings within the literature (Abrahams et al., 2004; Abrahams et al., 2000; Mantovan et al., 2003; P. R. Talbot et al., 1995). The strong co-occurrence of language impairment and executive dysfunction has led some to suggest that language impairment in MND may be due to executive dysfunction, discounting the existence of a separate language deficit (Abrahams et al., 2000). However as a number of measures of executive function have a strong linguistic component, it could be argued that language deficits may also be impacting on performance on executive measures. This is of particular note considering the use of verbal fluency as a frequently used assessment of executive dysfunction in MND. Furthermore dissociation in performance on executive and language assessments for some patients in this study, and others (Taylor et al., 2013) demonstrates that the two functions are, some extent, dissociable, thus supporting the argument of a separate linguistic impairment.

As there was no significant difference between the linguistically impaired and non linguistically impaired MND groups on measures of disease duration, disease severity and respiratory function, the differences in performance on measures of language are unlikely to be attributable to effects of overall health. This is also supported through error patterns on linguistic assessment, particularly spelling. Some previous reports of spelling errors in MND patients have been dismissed as due to upper limb weakness, explaining the occurrence of omitted and inserted letters (Cobble, 1998). However this study revealed no significant difference in the percentage of misspelled words shorter than the target word produced by MND patients in comparison to controls. In addition, only one patient was impaired on every assessment completed. Evidence of areas of strength, particularly on cognitively demanding working memory tasks, weakens the argument for a global impairment attributable to general fatigue or issues with respiratory function.

The effect of premorbid functioning on performance within this study is uncertain. While all participants were questioned as to the existence of any prior learning difficulties, including dyslexia, and information about levels of education were obtained, no formal measure of premorbid IQ was obtained. This was a deliberate decision as a large proportion of measures designed to test premorbid IQ, such as the National Adult Reading Test (NART) (Nelson, 1982) and Wechsler Test of Adult Reading (WTAR) (Holdnack, 2001), have a strong linguistic bias and are not suitable for use with aphasic or anarthric patients. While participants within this study, both patient and control, represented a cross section of educational backgrounds, this is only a very rough estimate of IQ. Similarly, while none of the participants within the study reported a history of learning disabilities or dyslexia, two MND patients and one control reported finding spelling difficult on occasion. Given that the participants within this study were largely of a generation where learning disabilities such as dyslexia were less commonly diagnosed, it is possible that some participant performances were affected by developmental dyslexia/dysgraphia. Yet as the control group was matched to the patient group on background variables, it would be expected that there would be an equal likelihood of developmental dyslexia/dysgraphia affecting performance of control participants. Some have suggested a link between a family history of learning disability, especially dyslexia, and onset of primary progressive aphasia, however any such connection cannot be made with the data collected within this study (Rogalski, Johnson, Weintraub, & Mesulam, 2008).

6.1.4 The Relationship Between Bulbar Onset, Dysarthria Severity and Language Impairment

As discussed in chapter 5 (see section 5.4.7) the relationship between disease onset, dysarthria severity and language impairment in MND patients is a widely debated issue. As all participants recruited in this study had some degree of dysarthria it is difficult to contribute to the argument that cognitive and/or language impairment is related to dysarthria as previous researchers have suggested (Massman et al., 1996; Sterling et al., 2010). Investigations into the relationship between the severity of dysarthria and language impairment in the participants within this study did not reveal any significant difference in severity levels between those who were linguistically impaired and those who were not. Yet there was a greater percentage of participants who were severely dysarthric or anarthric within the linguistically impaired group, unrelated to overall disease duration, which could support the suggestion of a relationship between dysarthria and linguistic impairment in MND. However, while all participants had a degree of dysarthria, not all participants were linguistically impaired, thus it does not necessarily follow that the relationship between dysarthria and language impairment in MND is linear. Thus while these results reveal that there may be a large number of MND patients for whom dysarthria may be masking more central linguistic deficits, equally they reveal that dysarthria and linguistic impairment are not mutually inclusive.

Similarly, investigations within this study into the relationship between language impairment and bulbar onset are inconclusive, echoing the message from across the literature. While some researchers have argued for a connection between cognitive impairment and bulbar onset (Abrahams et al., 1997; Portet et al., 2001; Schreiber et al., 2005); (Ichikawa, Koyama, et al., 2008; Ichikawa, Takahashi, et al., 2008; Sterling et al., 2010), others have contradicted this finding (Cooper et al., 2008; Rakowicz & Hodges, 1998; Ringholz et al., 2005). Throughout the thesis, comparisons in performance between the bulbar and non bulbar onset groups on the majority of neuropsychological and linguistic measures have revealed no difference in performance. However, when the proportion of bulbar and non bulbar onset participants within the linguistically impaired group was examined, the group was found to consist of a significantly greater number of bulbar onset participants. Thus while the result from this study may suggest some relationship between linguistic impairment and bulbar onset, the evidence is still inconclusive and further investigation is required.

6.1.5 Suggestions about the C9ORF72 Mutation

Although this study was not designed to investigate the genetic or pathological changes relating to language impairment and cognitive deficits in MND the results provide tentative suggestions about the relationship between the recently discovered C9ORF72 mutation and language impairment in MND. None of the three linguistically impaired MND participants tested for the C9ORF72 mutation were identified as having the mutation, while one of the five tested in the non linguistically group had the mutation. While the limited number of participants tested prevents any firm conclusions from being drawn, these results would suggest that there is no connection between the C9ORF72 mutation and language impairment, supporting similar reports in the literature (B. F. Boeve et al., 2012; Byrne et al., 2012; Chio et al., 2012). This raises the question as to whether there may be another, as yet undiscovered, genetic mutation related to language impairment in MND.

6.2 Limitations of Study and Future Suggestions

6.2.1 Limitations of participants

While this study included one of the largest cohorts of MND patients specifically tested for language impairments, a larger sample of patients would provide a clearer insight into the nature and prevalence of linguistic impairment. In addition, as a consequence of the selection criteria and the primary aim of this study, only those with existing communication difficulties were tested. While this enabled an exploration of communication impairment beyond surface of dysarthria, it also limited this exploration and therefore conclusions about the prevalence and nature of language impairments in the wider MND population can not be suggested. Also, the severity of the dysarthria many of the participants exhibited prevented assessment of spoken language. In order to compare performance in spoken and written modalities, explore the relationship between language impairment and dysarthria and draw conclusions about MND patients as a wider population it may be useful for future studies to assess language functions in patients both with and without dysarthria.

6.2.2 Limitations of Assessment Selection

Although a wide range of linguistic processes were assessed in this study, a number of areas were not examined. The integrity of non verbal semantics was not assessed here, the exploration of which may help to identify the extent to which the pattern of impairment follows that of semantic dementia. In addition further exploration of reading and auditory comprehension, particularly with regards to lexical-semantic processes would again help to differentiate between the contributions of central and peripheral deficits. With regard to background measures, while estimated respiratory function measures were obtained, these were based on patients' own subjective reports and no objective measurement was obtained. Given the increasing recognition of the impact respiratory dysfunction can have on cognitive function, an objective measure, such as forced vital capacity, would be important to include in further studies (Miller et al., 2009; Newsom-Davis et al., 2001).

6.2.3 Limitations of Experimental Assessment Design

Through the experimental spelling assessment used in this study previously unreported findings regarding the nature and prevalence of spelling impairment in MND patients were documented. However the findings were limited to what could be revealed using the selected stimuli. Selection of a wider range of word items measuring for effects of syllable length, in addition to phoneme length, and syllable complexity may help to investigate the integrity of phonological representations. Measuring for effects of lexical variables such as frequency, regularity, imageability would also enable further investigation of lexical-semantic effects connections. However these limitations were due, in part, to the fact that previous reports regarding spelling impairment in MND were limited and little was known about the locus of the errors. In addition, while spelling assessment has proved to be an invaluable tool in the investigation of language impairment, particularly in those whose dysarthria prevents assessment of spoken language, comparison of performance on a matched set of word and nonword items in spelling and repetition with those patients who are able to do so would help to disentangle the contribution of phonological and orthographic deficits on performance. Finally, given the wide spread use of naming assessments as a diagnostic tool for language impairment in clinical practice, and that a large number of MND patients rely on written communication, the development of a naming test that also has the capability to assess for phonological and orthographic variables would enable maximum information to be obtained from minimum assessment.

6.3 Contribution of Study and Implications

This study is the largest to date to conduct an in depth investigation into the nature of language impairment in MND. Of particular note is the contribution of the detailed exploration of spelling deficits, previously only examined as case studies, and of which none were from an English speaking MND population. Not only do these findings contribute to our understanding of the disease, they have important implications for the future clinical management of MND patients. Clinicians should consider the possibility that underlying linguistic impairment may affect a patient's ability to understand important clinical decisions, particularly with regard to non-oral feeding and ventilation. Furthermore, and perhaps more directly, the presence or absence of linguistic impairment will have a significant impact on decisions regarding suitability of AAC devices. Traditionally MND patients with marked dysarthria have been provided with text to speech voice output devices to aid communication. However, such devices require the user to have relatively intact spelling and linguistic skills in order to be used effectively which, as this study has revealed, may not always be present. Thus clinicians may need to consider alternative strategies and systems using each individual patient's relative linguistic and physical strengths to enable effective communication.

Appendix A: NHS Ethics Approval Letter

Lothian NHS Board

South East Scotland Research
Ethics Committee 03
Waverley Gate
2-4 Waterloo Place
Edinburgh
EH1 3EG
Telephone 0131 536 9000
Fax 0131 536 9088

www.nhslothian.scot.nhs.uk
Date
Our Ref
Enquiries to Joyce Clearie
Extension 35674
Direct Line 0131 465 5674
Email joyce.clearie@nhslothian.scot.nhs.uk

NHS
Lothian

09 February 2011

Dr Thomas Bak
Lecturer in Human Cognitive Neuroscience
University of Edinburgh
Department of Psychology, PPLS
7 George Square,
Edinburgh
EH8 9JZ

Dear Dr Bak

Study Title: **The Nature of Speech and Language Impairment in Motor Neurone Disease**
REC reference number: **10/S1103/53**

Thank you for your letter of 28 January 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered by the chair on behalf of SESREC 3.

Confirmation of ethical opinion

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

Ethical review of research sites

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

Conditions of the favourable opinion

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

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

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research 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 the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

INVESTOR IN PEOPLE

POSITIVE ABOUT DISABLED PEOPLE

Headquarters
Waverley Gate, 2-4 Waterloo Place, Edinburgh EH1 3EG

Chair Dr Charles J Winstanley
Chief Executive Professor James J Barbour O.B.E.
Lothian NHS Board is the common name of Lothian Health Board

Appendix B: Patient Information & Consent Form

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

Information Sheet for People with MND

Study title: "Speech and Language in Motor Neurone Disease (MND)"

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. Please do not hesitate to ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?
Whilst it is known that MND affects speech in some people, this has traditionally been thought to be solely due to motor neurone damage, causing a motor speech disorder called 'dysarthria'. However, recent studies suggest that other aspects of communication, such as spelling, may be also affected in some patients. Using a number of spoken, written and listening tests and questionnaires we hope to investigate the nature of speech and language problems experienced by some people with MND.

Why have I been chosen?
As our research aims to understand better the nature of speech and language problems in MND, we are recruiting around 25-30 people with MND who are experiencing speech or language (e.g. spelling, reading) difficulties, not experienced prior to developing MND. As someone who fits into this category, and has expressed an interest in research, you have been referred to the research team by a member of your care team. Your participation would contribute towards information about how communication is affected in people with MND.

Do I have to take part?
You are free to decide whether or not you would like to take part. Even if you decide to take part you are free to withdraw at any time and without giving a reason. A decision not

to take part or to withdraw will not affect the standard of care you receive, now or in the future.

What will happen to me if I take part?

If you do decide to take part you will be asked to sign a consent form on the first day of testing. We will also ask you for permission to access your medical records and ask you whether you would allow us to inform your General Practitioner in a letter about your participation.

The study will consist of 2 or 3 sessions, during which you will undertake a series of simple tasks, similar to word games, some of which will take place on a computer. We will also ask you to complete a few questionnaires. The study will take approximately 3-4 hours in total, with each session lasting around 1.5-2 hours and regular break opportunities will be provided. The sessions 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. If you do decide to come to the University of Edinburgh your travelling expenses will be fully reimbursed.

The type of tasks you will be asked to perform are spelling, repetition, reading and listening based (for example, repeating nonwords, spelling words of increasing length, judging whether or not two words/sounds sound the same) and last between 5 and 30 minutes each. None of the tasks are of an invasive nature. During the interview we will need to audio-record your voice whilst you are performing some of the tasks, and the sessions will also be video recorded. We ensure that there will be nothing on the audio recording that could identify you in person and that these recordings will be destroyed once the data has been obtained and evaluated.

What are the possible disadvantages and risks of taking part?

We do not anticipate any health risks from taking part in this study. You will not have to come off medication or undergo any invasive procedure. Most tests are in the forms of interviews, questionnaires or puzzle-like tests. If you are unable to write we will assist you in filling out the questionnaires and any written tests. If you are unable to speak we may skip certain tests that rely on spoken answers.

Due to the length of the interview you may find testing to be tiring. However the tests in this study are of a non-invasive nature and have been specifically designed and selected with people with MND in mind. At all times care will be taken towards ensuring your comfort and willingness to participate. The researcher is a qualified speech and language therapist, and a qualified clinical psychologist (joint supervisor Dr. Sharon Abrahams) will be on hand to offer advice in managing any distress that may arise from participating in the study.

Procedures have been designed in such a way to minimise any discomfort or fatigue. We will provide plenty of opportunity for frequent breaks during testing, and by spreading the test battery over a number of days if required. Patients will be allowed to stop at any point discomfort is felt. If you feel distressed at all by the interview please do not hesitate to contact Dr Thomas Bak (project leader): 0131 6503441.

What are the possible benefits of taking part?
There will be no direct benefit to you or your carer by taking part, and your individual results will not be revealed to you. However, if you wish, we will make any future publications of the findings available to you. We hope that this research will improve our knowledge relating to MND and may influence care practices in the future.

What if something goes wrong?
We do not anticipate any adverse effects from taking part in this study. 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 will 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 and the MND-clinical team at your hospital will have access to your medical records and notes. 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.

What will happen to the results of the research study?
The results of the research will be presented at scientific and clinical conferences and published in scientific and clinical journals for distribution to other healthcare professionals. In all cases, your name and personal details will not be identified.

Who is organising the research?
The study is being organised by Dr. Thomas H. Bak (Chief Investigator), Dr. Sharon Abrahams and Phillipa Rewaj (PhD student) from the University of Edinburgh, in collaboration with MND centers at the Western General Hospital (Edinburgh), Ninewells Hospital (Dundee), Falkirk Royal Infirmary and the Southern General Hospital (Glasgow).

Who has reviewed the study?
This study has been reviewed by the South East Scotland Research Ethics Service.

Contact for Further Information
If you wish to ask anything further please contact:

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Edinburgh EH8 9JZ

Thank you for reading this information sheet. This is your copy to keep.

Whether you wish to participate or not, it would be greatly appreciated if you could please complete the attached reply slip on the next page and send it to us (in the pre-paid envelope), or contact us directly via the phone or email addresses given above. Thank you for your time.

Participant Identification Number:

REPLY SLIP

Title of Study: Speech and Language in MND

Please tick the relevant box and send in the enclosed envelope

☐ I would like to participate in the study

☐ I would like more information on the study before deciding and would like a phone call from one of the researchers

☐ I do not wish to participate in the study at this stage, but would like to be contacted again at a later date (approximately 2-3 months)

☐ I do not wish to participate in the study

CONSENT FORM

Speech and Language Impairment in Motor Neurone Disease

Name of Researchers: Dr. Thomas Bak, Phillipa Rewaj

Please initial box

1) I confirm that I have read and understood the information sheet for the above study and have had an opportunity to ask questions. ☐

2) I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. Should I withdraw, my medical care or legal rights will not be affected. ☐

3) I understand that any sections of my medical notes may be examined by the responsible individuals from regulatory authorities and Research Team where it is relevant to my taking part in the research.
   I give permission for these individuals to have access to my records. ☐

4) I agree to storage, processing and transfer of the data in the way described in the information sheet. ☐

5) I understand that I will be audio and video taped for research purposes. ☐

6) I understand that I will not benefit financially from taking part in this study. ☐

7) I agree to take part in the above study. ☐

8) I agree that my GP or family doctor can be informed that I am taking part in this study. ☐

Name of Patient: ____________________ Date:

Signature: ____________________

Where the patient is physically unable to sign a proxy can complete the form and sign on their behalf as long as the proxy is satisfied that the patient has understood the information sheet and the consent form.

Name of proxy: _______________________ Date:

Signature of Proxy: _______________________

Name of Witness: _______________________ Date:

Signature _______________________

Appendix C: Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS – R)

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Table 1
The ALS Functional Rating Scale — Revised (ALSFRS-R)

1. Speech	
4	Normal speech processes
3	Detectable speech disturbance
2	Intelligible with repeating
1	Speech combined with nonvocal communication
0	Loss of useful speech
2. Salivation	
4	Normal
3	Slight but definite excess of saliva in mouth; may have nighttime drooling
2	Moderately excessive saliva; may have minimal drooling
1	Marked excess of saliva with some drooling
0	Marked drooling; requires constant tissue or handkerchief
3. Swallowing	
4	Normal eating habits
3	Early eating problems — occasional choking
2	Dietary consistency changes
1	Needs supplemental tube feeding
0	NPO (exclusively parenteral or enteral feeding)
4. Handwriting	
4	Normal
3	Slow or sloppy: all words are legible
2	Not all words are legible
1	Able to grip pen but unable to write
0	Unable to grip pen
5a. Cutting food and handling utensils (patients without gastrostomy)?	
4	Normal
3	Somewhat slow and clumsy, but no help needed
2	Can cut most foods, although clumsy and slow; some help needed
1	Food must be cut by someone, but can still feed slowly
0	Needs to be fed
5b. Cutting food and handling utensils (alternate scale for patients with gastrostomy)?	
4	Normal
3	Clumsy but able to perform all manipulations independently
2	Some help needed with closures and fasteners
1	Provides minimal assistance to caregiver
0	Unable to perform any aspect of task
6. Dressing and hygiene	
4	Normal function
3	Independent and complete self-care with effort or decreased efficiency
2	Intermittent assistance or substitute methods
1	Needs attendant for self-care
0	Total dependence
7. Turning in bed and adjusting bed clothes	
4	Normal
3	Somewhat slow and clumsy, but no help needed
2	Can turn alone or adjust sheets, but with great difficulty
1	Can initiate, but not turn or adjust sheets alone
0	Helpless
8. Walking	
4	Normal
3	Early ambulation difficulties
2	Walks with assistance
1	Nonambulatory functional movement
0	No purposeful leg movement
9. Climbing stairs	
4	Normal
3	Slow
2	Mild unsteadiness or fatigue
1	Needs assistance
0	Cannot do

Table 1. (*Continued*)

10. Dyspnea (new)	
4	None
3	Occurs when walking
2	Occurs with one or more of the following: eating, bathing, dressing (ADL)
1	Occurs at rest, difficulty breathing when either sitting or lying
0	Significant difficulty, considering using mechanical respiratory support
11. Orthopnea (new)	
4	None
3	Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows
2	Needs extra pillows in order to sleep (more than two)
1	Can only sleep sitting up
0	Unable to sleep
12. Respiratory insufficiency (new)	
4	None
3	Intermittent use of BiPAP
2	Continuous use of BiPAP during the night
1	Continuous use of BiPAP during the night and day
0	Invasive mechanical ventilation by intubation or tracheostomy

Appendix D: Word & Nonword Minimal Pair Stimuli

Word

Item	Stimuli	Same/Different	Difference	Position
P1	Dip – Tip	D	Voice	Initial
P2	Bag – Bag	S		
P3	Sack – Tack	D	Manner	Initial
1	Roam – Roam	S		
2	Railing- Raining	D	Manner	Medial
3	Debt – Ted	D	Voice	Metathetic
4	Bus – Buzz	D	Voice	Final
5	Fluff – Flush	D	Place	Final
6	Debt – Debt	S		
7	Toad – Toad	S		
8	Raving – Raising	D	Place	Medial
9	Piggy – Picky	D	Voice	Medial
10	Sheep – Sheep	S		
11	Tick – Tick	S		
12	Name – Mane	D	Place	Initial
13	Deal – Deal	S		
14	Bun – Bud	D	Manner	Final
15	Nail – Lane	D	Manner	Metathetic
16	Cap – Cab	D	Voice	Final
17	Zeal – Deal	D	Manner	Initial
18	Sail – Sail	S		
19	Name – Name	S		
20	Toad – Dote	D	Voice	Metathetic
21	Lane – Lane	S		
22	Den – Ten	D	Voice	Initial
23	Sheep - Seep	D	Place	Initial
24	Ten – Ten	S		
25	Dog – Dog	S		
26	Fluff – Fluff	S		
27	Piggy – Piggy	S		
28	Puddle – Puzzle	D	Manner	Medial
29	Saver – Saver	S		
30	Simmer – Simmer	S		
31	Seen – Niece	D	Manner	Metathetic
32	Raising – Raising	S		
33	Bus – Bus	S		
34	Puddle – Puddle	S		
35	Bun – Bun	S		
36	Safer – Saver	D	Voice	Medial

37	Tail – Sail	D	Manner	Initial
38	Cab – Cab	S		
39	Robe – Roam	D	Manner	Final
40	God – Dog	D	Place	Metathetic
41	Zip – Zip	S		
42	Seen – Seen	S		
43	Zip – Sip	D	Voice	Initial
44	Railing – Railing	S		
45	Hen – Hem	D	Place	Final
46	Simmer – Sinner	D	Place	Medial
47	Kick – Tick	D	Place	Initial
48	Hem - Hem	S		

Nonword

Item	Stimuli	Same/Different	Difference	Position
P1	Dooz – Tooz	D	Voice	Initial
P2	Mig – Nig	D	Place	Initial
P3	Ped – Ped	S		
1	Mef – Mef	S		
2	Siddum – Siddum	S		
3	Nol – Lon	D	Manner	Metathetic
4	Remmy – Rebby	D	Manner	Medial
5	Zenin – Zenin	S		
6	Ged – Ged	S		
7	Guk – Guk	S		
8	Riz – Riv	D	Place	Final
9	Soov – Soov	S		
10	Heefel – Heesel	D	Place	Medial
11	Boog – Boog	S		
12	Keeb – Keeb	S		
13	Fap – Vap	D	Voice	Initial
14	Saz – Saz	S		
15	Vot – Vot	S		
16	Diz – Diz	S		
17	Deg – Ged	D	Place	Metathetic
18	Maz – Naz	D	Place	Initial
19	Lon – Lon	S		
20	Remmy – Remmy	S		
21	Diz – Zid	D	Manner	Metathetic
22	Tusset – Tuzzet	D	Voice	Medial
23	Maz – Maz	S		
24	Tib – Tib	S		
25	Wuch – Wuk	D	Manner	Final

26	Min – Nim	D	Place	Metathetic
27	Vib – Vib	S		
28	Sillum – Siddum	D	Manner	Medial
29	Vip – Vib	D	Voice	Final
30	Geeb – Keeb	D	Voice	Initial
31	Tuzzet – Tuzzet	S		
32	Zife – Dife	D	Manner	Initial
33	Mef – Mev	D	Voice	Final
34	Min – Min	S		
35	Waddy – Waddy	S		
36	Vot – Vos	D	Manner	Final
37	Zife – Zife	S		
38	Tib – Tid	D	Place	Final
39	Toov – Soov	D	Manner	Initial
40	Saz – Zas	D	Voice	Metathetic
41	Heesel – Heesel	S		
42	Waddy – Watty	D	Voice	Medial
43	Zemin – Zenin	D	Place	Medial
44	Fap – Fap	S		
45	Kug – Guk	D	Voice	Metathetic
46	Riz – Riz	S		
47	Wuk – Wuk	S		
48	Boog – Goog	D	Place	Initial

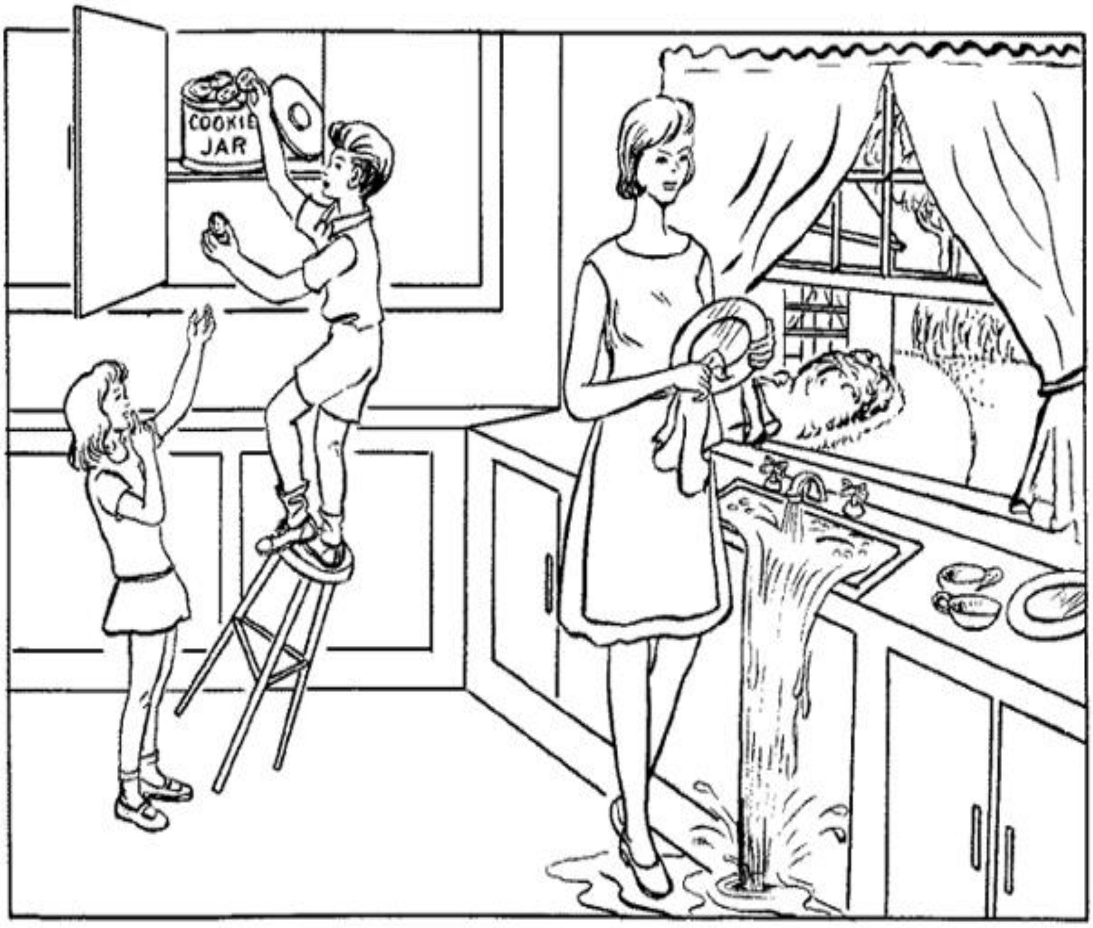
Appendix E: Word Spelling Stimuli

Immediate	Delayed	Delayed with Suppression
Bump	Jump	Hunt
Melt	Drag	Grab
Flag	Gift	Lamp
Skin	Tent	Mask
Develop	Monitor	Printed
Suspect	Neglect	Inspect
Blanket	Element	Plaster
Vitamin	Critics	Cabinet
Transplant	Administer	Contradict
Constructs	Comprehend	Subtracted
Helicopter	Instrument	Propaganda
Astronomer	Statistics	Economists

Appendix F: Nonword Spelling & Repetition Stimuli

Immediate	Delayed	Delayed with Suppression
Voost /vust/	Goffs /gɔfs/	Drob /drɔb/
Gept /gɛpt/	Fleem /flim/	Vant /vant/
Blom /blɔm/	Prool /prul/	Stib /stɪb/
Shroop /ʃrup/	Lisk /lɪsk/	Gunch /gʌntʃ/
Clomsin /klɔmsɪn/	Strempt /strɛmpt/	Holprot /hɔlprɔt/
Praslet /praslɪt/	Voonspak /vunspak/	Agispra /agɪsprə/
Zeeblust /ziblʌst/	Gugshroot /gʌgʃrut/	Vagronch /vagrɔntʃ/
Nimlaft /nɪmlaft/	Jibolop /dʒɪbəlɔp/	Blabsot /blabsɔt/
Stredgelifan /strɛdʒlɪfan/	Chagronstap /tʃagrʌnstap/	Spleebaluft /splibaluft/
Crospreebon /krɔspribɔn/	Thrambrongo /θrambrɔŋgo/	Gaftampron /gaftamprɔn/
Mombolment /mɔmbɔlmənt/	Shiblapraky /ʃɪblapraki/	Jibrafelin /dʒɪbrafɛlən/
Lensmishran /lɛnzmɪʃran/	Fleerabisty /flirabɪsti/	Dromonelish /drɔmɔnelɪʃ/

Appendix G: Boston Cookie Theft Image



Taken from the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass & Kaplan, 1983)

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