Cognition and the cerebellum in multiple sclerosis

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Abstract

Cerebellar symptoms are associated with poor prognosis in MS. A small number of studies have reported a specific cognitive profile associated with cerebellar damage, including reduced information processing speed, impairments in visuospatial functions and verbal fluency deficits. The cerebellum is thought to encode models of sensory information, providing mental representations of the world used to plan motor actions. Motor planning may be a key factor in the disability that cerebellar involvement imposes. This study explores how the cognitive profile of those with MS with cerebellar symptoms (RR-MSc) relates to motor planning and motor function, and how this differs from those with MS without cerebellar symptoms (RR-MSnc) and healthy controls (HC).

Participants were assigned to three groups: HC (n = 21), RR-MSnc (n = 21) and RR-MSc (n = 14) using a validated self-report cerebellar symptom questionnaire (NARCOMS-TACS). Participants completed a cognitive test battery: BICAMS (CVLT-II, SDMT, BVMT-R), WLG, PASAT3 and TOPF. For assessment of motor functioning and motor planning, participants completed the 9-hole peg test (9HPT) as a sensorimotor control, and grooved pegboard test (GPT) which has greater motor planning demands. Subtraction of 9HPT from GPT was used to compute a motor planning index (MPI).

One-way ANCOVAs demonstrated significant differences between groups on all cognitive tests other than WLG. Post-hoc tests showed significant differences between RR-MSc and HC on all tests except WLG, and RR-MSc and RR-MSnc on SDMT,

CVLT-II and PASAT3. On 9HPT, GPT and MPI, HC performed significantly better than both MS groups, and the RR-MSnc performed significantly better than RR-MSc. There were significant correlations between neuropsychological variables (other than WLG) and MPI.

RR-MSc showed greater impairment than RR-MSnc on cognitive tests and tasks requiring motor functioning and motor planning. RR-MSc demonstrated a specific cognitive profile associated with more significant and widespread impairments. Clinical implications are discussed.

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1. Introduction

A significant proportion of those with multiple sclerosis (MS) experience cognitive impairment (Benedict & Zivadinov, 2011; Langdon, 2011). Cognitive impairment is associated with worse prognosis and functional difficulties (Amato et al., 1995; 2010; Bruce, Hancock, Arnett, & Lynch, 2010; Bobholz & Rao, 2003; Langdon, 2010). Early research has demonstrated greater cognitive and motor impairment in those with MS with cerebellar involvement (Weier et al., 2015a). Individuals with cerebellar involvement have been shown to have a worse prognosis and appear to benefit less from neurorehabilitation (de Groot et al., 2009; Langdon & Thompson, 1999; Thorpe et al., 2015; Vasconcelos et al., 2016). It is possible that cerebellar involvement in MS could eventually be designated as a differential disease subtype.

1.1. Multiple Sclerosis

MS is a chronic and progressive immune-mediated inflammatory disease of the central nervous system (CNS). It is a demyelinating disease of undetermined aetiology, however many risk factors are identified (Ramagopalan, Dobson, Meier & Giovannoni, 2010). The reported incidence is 203.4/100,000 in the UK (Mackenzie, Morant, Bloomsfield, MacDonald & O'Riordan, 2014). The mean age of onset is approximately 30-years with increased incidence in females (Rejdak, Jackson & Giovannoni, 2010). In Europe and the USA, MS is the foremost cause of non-traumatic neurological disability (Hauser & Okenberg, 2006). It is often considered degenerative, as with time cognitive and behavioural dysfunction accumulates causing more impairment.

1.1.1. MS Pathophysiology

The formation of lesions (sclerotic plaques) that accompanies disease progression in MS is believed to be the culmination of two pathological processes - inflammation and neurodegeneration (Compston & Coles, 2008). The exact order and procedure of pathogenesis in MS is controversial.

(i) Inflammation

MS is considered an autoimmune disorder, as lymphocytes do not effectively distinguish healthy cells from antigens, resulting in inflammation and myelin breakdown. Inflammation is caused by autoreactive lymphocytes (T-cells) moving across the blood-brain barrier (Compston & Coles, 2008). This mediates damage to the myelin sheath of neurons. The myelin sheath is a plasma membrane around the axon of a neuron, which is formed by Schwann cells and oligodendroglial cells (Siegel, Agranoff, Albers, Fisher & Uhler, 1999), which speeds up neural transmission through saltatory conduction. Without this, the communicative function of the neuron is impaired causing expressed symptoms.

During the initial stages of disease progression inflammation is transient, and Schwann cells and oligodendroglial cells cause remyelination, resulting in temporary symptomatic relief (Compston & Coles, 2008). Remyelination is effective at temporarily repairing cells, however this myelin is less durable and endogenous remyelination eventually fails (Chari, 2007; Czepiel, Boddeke & Copray, 2015).

(ii) Neurodegeneration

Repeated inflammation and resultant damage results in the build-up of scar tissue known as plaques or lesions (Compston & Coles, 2008). Plaques can occur in any areas of white matter, however there are several predilection sites including the periventricular regions, brainstem, cerebellum, optic nerves, prefrontal cortices, medial temporal cortices and spinal cord (Donadieu et al., 2016; Wingerchuk, Lucchinetti & Noseworthy, 2001). Cumulative axon loss can result in progression to a higher level of functional disability. Demyelination and axonal loss in MS is known as brain atrophy.

1.1.2. MS Aetiology

The contribution of genetics is compelling, with concordance rates in monozygotic twins of approximately 25-30% (Sadovnick et al., 1993; Willer et al., 2003). Specifically, the human leukocyte antigen (HLA) is implicated (Hillert, 1994). Aetiological hypotheses combine genetics, and environmental factors including: major compatibility complex haplotypes (Dyment et al., 2005; Ramagopalan, Knight & Ebers, 2009), sun exposure and vitamin D (Munger et al., 2006), and the Epstein-Barr virus (Sundqvist et al., 2012). Transcultural studies have also demonstrated relations to geographical latitude with higher incidence in temperate zones (Kurtzke, 2000), as well as countries with predominantly White populations (UK and Norway) (Albor et al., 2017), and in those who have migrated to such countries compared with their ancestral groups (Torjesen, 2016) The aetiology of MS is therefore complex and multifactorial.

1.1.3. Diagnosis and subtypes

A revision of the McDonald (2001) criteria (Polman, 2011) is typically utilised for diagnosis of MS. This requires demonstration of lesions in time and space, as well as ruling out differential diagnosis. MRI is utilised to detect lesions, and neurological dysfunction must occur on at least two occasions (lasting more than 24 hours) of more than 30 days apart.

The onset of MS can occur before the age of 18, known as paediatric MS. However, the present study will focus on adult onset MS, as more widespread cognitive deficits are recognised within paediatric MS possibly due to the impact of the disease on a developing central nervous system (Amato, Krupp, Charvet, Penner, & Till, 2016).

(i) Clinically Isolated Syndrome (CIS)

The first episode of neurological disturbance, associated with a single white matter lesion is known as a CIS. Thirty to 70% of patients subsequently develop MS (Miller, Barkhof, Montalban, Thompson & Filippi, 2005).

(ii) Relapsing and remitting MS (RR-MS)

Approximately 85% of individuals diagnosed with some form of MS present with RR-MS (Leary, Porter & Thompson, 2005). Individuals with RR-MS have distinct attacks of acute or sub-acute neurological symptoms (varying in frequency and severity) followed by partial or complete remission (Leary, Porter & Thompson, 2005). When

symptoms do not fully alleviate, individuals with RR-MS are left with residual symptoms, which accumulate into physical disability (Leary, Porter & Thompson, 2005). Lublin, Baier and Cutter (2003) demonstrated these residual deficits in 42% of patients with expanded disability status scale (EDSS; a measure of disability in MS) of >0.5.

Benign MS is a subdivision of RR-MS that is diagnosed retrospectively, following a significant time without symptoms (Lublin et al., 2014).

(iii) Secondary progressive MS (SP-MS)

SP-MS is diagnosed retrospectively through recognition of progressive worsening over time following an initial relapsing course (Lublin et al., 2014). This is diagnosed following deterioration independent of relapses for more than six months (Katz Sand, Krieger, Farrel & Miller, 2014). There is a possibility for individuals with SP-MS to have 'superimposed relapses' (Leary, Porter & Thompson, 2005). Confavreux and Vukusic (2006) report that the progressive stages of MS typical age of onset is 38.

(iv) Primary progressive MS (PP-MS)

PP-MS accounts for 15% of the MS population and is a gradual accumulation of neurological disability with recognised progressive myelopathy with no periods of remission (Leary, Porter & Thompson, 2005; Lublin et al., 2014). This has a later age of onset than other forms of MS and affects more males than other subcategories (Leary, Porter & Thompson, 2005).

(v) Progressive relapsing MS (PR-MS)

This is a progressive disease from onset with intercalated relapses. This accounts for approximately 10% of the PP-MS population (Leary, Porter & Thompson, 2005).

1.1.4. MS Symptoms

MS is a heterogeneous disorder. Compston and Coles (2008) report common symptoms, including cognitive impairment, affective disorders (mainly depression), tremor, poor balance, dysarthria, weakness and spasm, bladder dysfunction and erectile dysfunction (in men), pain, temperature sensitivity and fatigue. These are not disease specific, hence the involvement of imaging in diagnosis. These symptoms impair quality of life (QoL), and accumulation of neurological disability is associated with reduced QoL (Janardhan & Bakshi, 2000).

1.1.5. Treatment and course

There is no cure for MS. Pharmaceutical treatments are available for specific symptoms, as well as acute relapse (typically steroid based treatments including methylprednisolone) (Anlar, 2009). Disease-modifying treatments (DMTs) focusing on the inflammatory process are used to reduce the frequency of relapse, including immunosuppressive and immune-modulating agents (Anlar, 2009). These reduce disability progression. DMTs are split into first generation drugs (beta interferons and glatiramer acetate - released in 1990s) which have moderate efficacy, and second

generation drugs (Tysabri, Fingolimod and Mitoxantrone – the latter rarely used due to cardio-toxicity) which have greater efficacy but more significant risks.

The course of MS is heterogeneous. Prognosis and course is associated with a multitude of factors including age of onset, treatment and relapse frequency. With the advent of DMTs, natural historical studies become irrelevant to those with treatments available (Hum, Lapierre, Scott, Duquette & Mayo, 2017). One study utilised an extensive medical registry to determine stability of MS based on three discrete onset periods (pre-magnetic resonance imaging and pre-DMTs (pre-1995); MRI and first generation DMTs (1995-2004); MRI and second generation DMTs (2005-present) (Hum et al., 2017). Stability (defined as EDSS of three or less with a change of one or less EDSS points over the study period) was demonstrated in most patients diagnosed in the past decade (54% males, 84% females). In the second group, 69% of females and 41% males were observed as stable (thus defined as benign MS). However, very little stability was demonstrated in those diagnosed pre-1995. Greater stability was recognised in females than males diagnosed since 1995. The authors reported that annualised relapse rate (ARR) was associated with a higher disability trajectory (Hum et al., 2017). This is corroborated by other studies demonstrating that high ARR early in disease course is associated with worse prognosis (Leray et al., 2010; Scalfari et al., 2010; Tremlett, Yousefi, Devonshire, Rieckmann, & Zhao, 2009), but later relapses were not so significantly associated (Scalfari et al., 2010; Tremlett et al., 2009). More recently individuals have been shown to reach disability milestones after longer disease durations (Hum et al., 2017; Tremlett, Zhao, Rieckmann, & Hutchinson, 2010). This is possibly associated with improved methods of detection and subsequent early use of DMTs.

1.1.6. Section Summary

MS is a progressive immune-mediated inflammatory disease of the CNS associated with demyelination. It has an uncertain aetiology but this is likely to be a combination of environmental and genetic factors. It is characterised by the formation of sclerotic plaques through inflammation and neurodegeneration. 85% of people with MS are diagnosed with RR-MS, with periods of symptom flare-up with subsequent complete or partial remission. Symptoms of RR-MS include cognitive impairment, physical disability and affective changes and all contribute to reduced QoL. With time, the majority progress to SP-MS which represents a more significant level of accumulating disability.

1.2. MS Neuropsychological profile

1.2.1. Prevalence of cognitive impairment in MS

Cognitive impairment affects 50-60% of patients with MS (Benedict & Zivadinov, 2011; Langdon, 2011). It can occur early within disease progression, and is occasionally the first symptomatic expression (Feuillet et al., 2007; Schulz, Kopp, Kunkel & Faiss, 2006). Neuropsychological profiles can be beneficial for provision of prognosis (Amato et al., 2010), with increased cognitive impairment being associated with worse prognosis. Cognitive impairment can be an independent predictor of conversion from CIS to MS (Zipoli et al., 2010). Another study demonstrated a twofold increase in conversion to SP-MS and a threefold EDSS >4.0 in 10 years in those with cognitive impairment (Moccia et al., 2016).

Cognitive profiles within sub-diagnoses of MS have not been thoroughly investigated, though could provide prognostic, diagnostic, and treatment planning information. This study will help to differentiate between cognitive profiles of those with RR-MS with cerebellar symptoms (RR-MSc), to those without cerebellar symptoms (RR-MSnc).

1.2.2. Cognitive Impairment in MS

In MS, cognitive impairment is related to functional difficulties with work and social activities, physical independence, sexual function, adherence to medication and driving (Amato et al., 1995; Bobholz & Rao, 2003; Bruce, Hancock, Arnett, & Lynch, 2010; Langdon, 2010). Higher premorbid functioning (cognitive reserve) reduces the rate of

cognitive decline associated with brain atrophy (Nunnari et al., 2016; Sumowski et al., 2009). Lengthy periods of formal educational are associated with increased cognitive reserve, and cognitive reserve can be built up by reading, physical activity and cognitively challenging employment (Luerding, Gebel, Gebel, Schwab-Malek & Weissert, 2016).

Reviews of controlled studies demonstrate a decline of cognition with the progression of the condition (Amato, Zipoli & Portaccio, 2006). Progressive decline is somewhat supported by MRI studies, which show a weak correlation between total lesion load and cognitive impairment in MS (Calabrese et al., 2009). Individuals with a progressive phenotype are twice as likely to demonstrate cognitive impairment after controlling for disease and demographic variables (Planche, Gibelin, Cregut, Pereira & Clavelou, 2016).

In some cases, demyelination within specific brain regions can predict which cognitive domains may be affected (Rovaris et al., 2000; Swirsky-Sacchetti et al., 1992; Wishart & Sharpe, 1997). Lesions affecting functional connectivity are strongly associated with cognitive sequelae (Hawellek, Hipp, Lewis, Corbetta, Engel, 2011) as cognitive tests and functions involve networks of neuroanatomical areas. This is of interest in the current study due to the consideration of diffuse projections between the cerebellum and the frontal lobes. One aspect of the present study will consider those with neurological symptoms of cerebellar dysfunction in comparison to the wider heterogeneous group of RR-MS.

1.2.3. Considerations for neuropsychological testing in MS

Visual deficits are common in MS, typically caused by optic nerve inflammation (optic neuritis) resulting in blurred vision. This affects 38-50% of individuals with MS (Arnold, 2005). Other visual deficits, such as loss of colour perception, contrast sensitivity and visual processing difficulties (Vleugels et al., 2000) can occur secondary to brain lesions. Nystagmus (involuntary eye movement) is a common visual symptom associated with lesions to the brain stem and cerebellum (Iyer et al., 2015; Kutzelnigg et al., 2007; Weier et al., 2015b).

Motor dysfunction can confound neuropsychological tests in MS, therefore tasks requiring fine motor control should be avoided (Langdon et al., 2012). Individuals with cerebellar symptoms are likely to have motor symptoms which may impact on neuropsychological tests (Middleton & Strick, 2000). Motor decline appears to be more rapid in older populations, though older age has not been linked to more rapid cognitive decline in MS (Roy et al., 2016).

1.2.4. Cognitive domains affected

1.2.4.1. Attention and Information Processing Speed

IPS is the underlying efficiency of cognition, associated with the time taken to perform a mental task. Tasks that measure IPS require the processing of information as opposed to a reflex response, however are often simple. Attention is the cognitive process that

facilitates selection, focus and sustained processing of information (Costa, Genova, DeLuca, & Chiaravalloti, 2016).

Deficits in IPS and attention are the most common cognitive deficits in MS (Benedict et al., 2017; Costa, Genova, DeLuca, & Chiaravalloti, 2016). Deficits in IPS can be recognised early in the disease progression, including within the CIS (Hynčicová et al., 2017), and are typically the first cognitive deficit to emerge (Van Schependom et al., 2015). A longitudinal study demonstrated worsened performance on the Paced Auditory Serial Addition Test (PASAT) and Symbol Digit Modalities Test (SDMT) one-year post diagnosis demonstrating reduction in IPS and attentional processes with disease progression (López-Góngora, Querol & Escartín, 2015). Compared to healthy controls, individuals performed worse on the SDMT (Drake et al., 2010; Hughes, Denney & Lynch, 2011; O'Connell, Langdon, Tubridy, Hutchinson & McGuigan, 2015), and the PASAT (Drake et al., 2010; Forn, Belenguer, Parcet-Ibars & Ávila, 2008). Extricating the difference between IPS, attention and working memory is challenging, however subsequent analyses of these tasks implicated IPS as the reasons for deficits (Forn et al., 2008; Lengenfelder et al., 2006). Similarly, Lengenfelder et al. (2006) demonstrated that individuals with MS could achieve the same working memory span if greater processing time was allowed, concluding that working memory deficits may be attributable to IPS deficits.

IPS deficits have been associated with reduced QoL in MS (Barker-Collo, 2006; Langdon, 2010). Strober, Chiaravalloti, Moore and DeLuca (2014) showed that the SDMT was the sole predictor of unemployment in a logistic regression analysis

including tests of executive functions, memory, attention, working memory, visuospatial perception as well as on measures of physical functioning.

Demyelination of white matter which impairs communication between cortical areas are neuroanatomical correlates of reduced IPS. In a meta-analysis, Rao et al. (2014) report a moderate to strong correlation between the SDMT and PASAT scores and T2 lesion volume in patients with mixed-MS subtypes. Similarly, in a meta-analysis, brain volume loss was associated with worse scores on PASAT (Vollmer et al., 2016). The corpus callosum, nerve fibres connecting both hemispheres of the brain and a predilection site for atrophy in MS, has been linked to reduction of IPS and attentional processes (Bergendal et al., 2013; Morrow, Menon, Rosehart, & Sharma, 2017; Ozturk et al., 2010). Moroso et al. (2017) showed an association between grey matter volume decrease in the posterior lobules and reduced IPS. Atrophy of the anterior and superior left thalamus surface has been related to reduced IPS in MS patients (Bergsland, Zivadinov, Dwyer, Weinstock-Guttman and Benedict, 2016; Debernard et al., 2015).

The current evidence base suggests that IPS deficits are often observed early in disease course, and can be recognised utilising the PASAT and SDMT. IPS deficits possibly act as fundamental deficit that creates inefficiencies in other cognitive domains. Degeneration of white matter, lesions to areas associated with neuroanatomical networking, as well as atrophy of predilection sites for MS appear to be correlates.

1.2.4.2. Executive Functions

Executive functions are higher-order processes, which involve planning, problem solving, mental flexibility, abstract reasoning, initiation, inhibition and judgement. There is no typical profile of executive functions within MS (Chiaravalloti & DeLuca, 2008). Though mild executive deficits are commonplace in MS, extensive deficits only present in a small proportion (Drew, Tippett, Starkey & Isler., 2008). Individuals with MS typically perform poorly on tests of problem solving – especially when mental flexibility is required (Cerezo Garcia, Plasencia & Benito, 2015; Langdon, 2010; Roman & Arnett 2016) as well as tasks requiring set-shifting, fluency, working memory, inhibition (Cerezo Garcia, Plasencia & Benito, 2015; Drew et al., 2008; Henry & Beatty, 2006; Parmenter et al., 2007), planning and sequencing (Arnett et al., 1997; Voelbel et al., 2011), categorizing, temporal ordering, and conceptualising (Cerezo Garcia, Plasencia, Benito, Gomez, & Maros, 2009; Roca et al., 2008; Roman & Arnett, 2016). Cerezo García, Plasencia and Benito (2015) conclude that flexibility, abstraction, and inhibition were the three components of executive function that were most deficient. However, most studies used timed tasks, thus IPS might be responsible for purported executive deficits (Genova, DeLuca, Chiaravalloli & Wylie, 2013; Leavitt et al., 2014; Owens, Denney & Lynch, 2013). Therefore, tests of executive functions may be less specific with this population.

Executive dysfunction has been linked to higher EDSS scores and a progressive phenotype (Cerezo Garcia, Plasencia & Benito, 2015; Hanssen, Beiske, Landrø & Hessen, 2014). However, dysexecutive symptoms can be recognised early in disease

course (particularly verbal fluency deficits), including CIS (Hynčicová et al., 2017; Viterbo Iaffaldano & Trojano, 2013).

These deficits impact day-to-day activities, including financial decision-making (Tracy, Basso, Marson, Combs & Whiteside, 2017) bill-paying and cooking (Voelbel et al., 2011), however these may be associated with planning time (implicating IPS), not performance (Denney, Hughes, Owens & Lynch, 2012; Drew, Trippett, Starkey & Isler, 2008). There are equivocal findings regarding executive functions and QoL. Executive dysfunction has been associated with maladaptive coping and poor emotional regulation strategies (Grech et al., 2016; Phillips et al., 2014), however some studies report no relation to QoL (Grech et al., 2015).

Frontoparietal networks, deep grey matter nuclei, and atrophy of the thalamus and insula have been implicated in executive functioning in MS in fMRI paradigms (Kern et al., 2015; Koini et al., 2016; Llufriu et al., 2016; Muhlert et al., 2013). Perseverative errors have been related to frontal white matter lesions (Arnett et al., 1994), and verbal fluency to the anterior and posterior corpus callosum (Bodini et al., 2013; Morrow, Menon, Rosehart, & Sharma, 2017) as well as higher cortical lesion loads particularly in the anterior cingulate cortex (Calabrese et al., 2009; Geisseler et al., 2016; Lazeron et al., 2005).

There is no typical executive function profile due to the heterogeneity of MS and neuroanatomical correlates are likely associated with networks of cortical and subcortical areas. Consideration of subgroups of RR-MS may help provide clarity.

Verbal fluency will be considered within the present study due to its recognised presentation early in disease course.

1.2.4.3. Memory

Within neuropsychological research, memory is theoretically divided into different systems. Working memory has a limited capacity and maintains and manipulates multimodal information for a short period (Kreutzer, DeLuca & Caplan, 2011). There are many differing long-term memory subsystems. Episodic memory refers to events that have been personally experienced, whereas semantic memory refers to knowledge gained about the world without a specific timestamp. Differing systems are also identified for verbal or visual memory systems. Neuropsychological evaluation and research often considers free recall and cued recognition differentially. In a meta-analysis including 3891 participants with MS, memory deficits of at least moderate effect sizes were recognised in all memory domains (Prakash, Snook, Lewis, Motl, & Kramer, 2008).

Working memory deficits are common in MS. They can present in CIS, and deficits worsen with disease progression (Panou et al., 2012). According to a review the central executive of Baddeley's model (Baddeley, 2000) is most impaired in MS, with significant impacts of reduced IPS (Brissart et al., 2012; Lengenfelder et al., 2006). The involvement of IPS was corroborated by individuals showing improvement in working memory performance when additional time was given (Leavitt, Lengfelder, Moore, Chiaravolloti & DeLuca, 2011). Working memory deficits can cause cognitive-motor interference in MS. For instance, carrying out working memory tasks whilst walking

was shown to interfere more with the cognitive tasks in CIS than within healthy controls (Jakob, Remšak, Jazbec, Ledinek & Rot, 2017). Cognitive reserve and intellectual enrichment is positively associated with greater working memory spans (Sandry & Sumowski, 2014).

Long-term memory function deficits are recognised in 40-60% of people with MS (Rao et al., 1993) and are typically due to registration of information (DeLuca et al., 1998; DeLuca, Leavitt, Chiaravalloti & Wylie, 2013; Gmeindl & Courtney, 2012; Langdon, 2010). This is known as the acquisition hypothesis (Lafosse, Mitchell, Corboy & Filley, 2013), which implicates IPS or attentional systems (Chiaravalloti, Stojanovic-Radic & DeLuca, 2013). Empirical support comes from studies using the selective reminding task, whereby initial acquisition of memories is supported by a lengthy learning phase. Individuals with MS take longer to acquire information (DeLuca et al. 1994; Demaree et al., 2000; Lafosse et al., 2013), but recall is equitable to healthy controls (DeLuca et al., 1994; 1998). However, some studies suggest difficulties with registration are associated with earlier stages of MS, instead implicating retrieval in those with higher EDSS scores (Brissart, Morele, Baumann & Debouverie, 2012), or progressive phenotypes (Drake, Carra, Allegri & Luetic, 2006). Difficulties with memory tasks can be noted as early as the CIS (Hynčicová et al., 2017).

Some MS patients demonstrate deficits in autobiographical memory (Ernst et al., 2015; Paul, Blanco, Hames & Beatty, 1997), which has been negatively correlated with QoL, perhaps caused by dissonance between pre-morbid coping and coping following disease progression (Kenealy, Beaumont, Lintern & Murrell, 2000; Langdon 2010). In a study of MS participants with working memory and long-term memory functions,

prospective memory (memory for planned actions) was shown to be impaired compared to controls in a virtual week paradigm (Rendell, Jensen & Henry, 2007).

Demyelinating lesions and atrophy of the limbic system (Sahin, Selouan, Markowitz, Melhelm, & Bilello, 2016) or reduced activation of the hippocampus (González Torre et al., 2017; Hulst et al., 2015; Planche et al., 2016; Sumowski et al., 2016) have been associated with memory dysfunction. Left hippocampal atrophy has been associated with verbal memory impairments (Pardini et al., 2014; Sacco et al., 2015), and right hippocampal lesions have been associated with spatial memory dysfunction (Pardini et al., 2014).

The current evidence base suggests that individuals with MS often have impaired memory functions, which typically increase with disease progression. The prevailing opinion is that these are initially more associated with registration of memories (implicating IPS and attention) and later in disease progression, associated with retrieval. The limbic system and hippocampus have been implicated.

1.2.4.4. Language

A historical cohort study demonstrated that language functions are typically intact in MS (Rao et al. 1991). Specific language deficits such as aphasias are rare aside from large cortical lesions (Jónsdóttir, Magnússon & Kjartansson, 1998), and such dysfunction has been reported predominantly in single case investigations (Barwood & Murdoch, 2013). Examinations of the verbal comprehension index on the Weschler Adult Intelligence Scale (WAIS-III; Wechsler, 1997; WAIS-IV; Wechsler, 2014)

demonstrate relatively preserved verbal comprehension index (VCI) compared to premorbid estimates (Clemmons et al., 2004; Drew, Tippett, Starkey & Isler., 2008). Connick, Chadran and Bak (2013) showed some impaired language functions in progressive MS, however these are likely associated with frontal executive dysfunction such as verbal fluency as opposed to posterior-parieto-temporal-occipital areas.

The current evidence base predominantly suggests that linguistic functions remain largely intact in MS. Thus, this domain will not be considered within the current study.

1.2.4.5. Visuospatial and visuoconstructive functions

Approximately 25% of patients with MS demonstrate deficits with visuospatial and visuoconstructive functions, which often correlate with parietal-temporal-occipital lesions (Marasescu, Cerezo Garcia & Benito, 2016). Lesions to these areas are common, however the small prevalence of such impairment may be associated with low activation of brain volume or a replacement of connections following atrophy (Marasescu et al., 2016). They reported an association between higher EDSS and worse performances on picture completion tasks and block design tasks within the WAIS-III (Wechsler, 1997), the Rey-Osterrieth complex figure task (ROCFT; Osterrieth, 1944) and other tasks of visuomotor and visuoconstructive tasks. However, the ROCFT is confounded by MS sensorimotor impairment. Conversely, deficits have also been recognised in individuals with CIS, associated with lower white matter volumes (Hynčicová, et al., 2017).

Aside from visuospatial memory, there is little research into visuospatial functions in MS, nor the impact of impairment on QoL. Visuospatial learning is a significant predictor of cognitive impairment in MS (Langdon et al., 2012). Therefore, visuospatial learning tasks should be incorporated into assessments of cognitive dysfunction for those with MS.

1.2.5. The effect of common mental illness on cognition in MS

Common mental illness rates are raised in MS. Boeschoten et al. (2017) report a 31% prevalence of depression in MS populations in a large meta-analysis, and Murphy et al. (2017) report 50% will experience a post-diagnosis depressive episode within their lifetime. This population pose a higher risk of suicide and parasuicide (Brenner et al., 2016). Clinically significant anxiety is also common within MS with a reported prevalence of 22% (Boeschoten et al., 2017). Anxiety disproportionately influences females to males with MS (Théaudin, Romero, & Feinstein, 2016), and often reduces six-months post-diagnosis (Giordano et al., 2011), perhaps associated with the 'theory of resilience' where an individual develops psychological resilience to overcome adversity (Chwastiak & Ehde, 2007; Murphy et al., 2017).

Morrow, Rosehart and Pantazopoulos (2015) showed a worsened IPS, visual-spatial memory and executive function in individuals with depressive symptoms. Also, depression has been linked to reduced performances on the selective reminding test, the SDMT and the PASAT (Niino et al., 2014). In a review by Arnett et al. (2008), a negative association was found between depression and cognitive functioning in studies that were adequately powered. Bruce, Hancock, Arnett and Lynch (2010) suggested

that self-reported cognitive impairments (specifically, memory functions) were associated with self-report of depression, anxiety and neuroticism. However, these did not typically corroborate objective cognitive assessments. Golan et al. (2017) demonstrated a significant yet small correlation between depression and cognitive function when controlling for EDSS, fatigue, comorbidities and psychotropic medications, as well as a small correlation with motor function.

Depressive symptoms are commonly associated with reduction of IPS in the general population, however depression in RR-MS reduces IPS further than in healthy counterparts (Lubrini et al., 2016). Individuals with depression in the context of MS are more likely to perform worse in executive tasks (Arnett, Higginson & Randolph, 2001; Chiaravolloti & Deluca 2008; Hanssen, Beiske, Landrø & Hessen, 2014; Raimo et al., 2016). Causality is hard to determine as depression may exacerbate cognitive impairment, or perhaps depression is a secondary symptom of dysexecutive syndrome (Portaccio, 2016). However, most neuropsychological studies exclude those with mental health diagnoses and these still report executive dysfunction. In a study excluding those with depression but measuring depressive symptomology, scores on the PASAT and delayed recall on selective reminding test were associated with Beck's Depression Inventory (BDI; Beck, Steer & Brown, 1996) score and the neuropsychiatric inventory (NPI; Cummings et al., 1994) (Figved et al., 2008), showing subthreshold psychiatric impacts on cognitive performance.

Morrow, Rosehart and Pantazopoulos (2015) report worsened IPS, visual-spatial memory and working memory in RR-MS in those with significant anxiety compared with those without. Goretti et al. (2014) showed an association between state anxiety

reduced performance on SDMT and PASAT, which remained when depression and fatigue were statistically removed. However, causality cannot be demonstrated, as significant impairment may cause state anxiety during testing. Anxiety appears to impact working memory (Arnett et al., 1999; Arnett, Higgonson & Voss, 1999; Niino et al., 2014; Thornton & Raz, 1997) IPS and attentional deficits, as well as possible long-term memory dysfunction (Niino et al., 2014).

The impact of common mental illness on cognition in MS provides implications for treatment. Individuals with diagnosed common mental illnesses are often excluded from research trials due to the confounds that inclusion may carry. Thus, within the present study those with a diagnosed psychiatric illness were excluded. However, greater incidence of symptoms of common mental illness are considered part of the overall syndrome.

1.2.6. Fatigue and cognition in MS

Fatigue refers to a subjective recognition of exhaustion, or an overpowering lack of mental or physical energy, whereas cognitive fatigue refers to subjective difficulties concentrating or thinking clearly (Golan et al., 2017; Kluger, Krupp, & Enoka, 2013).

Sixty-five to 80% of individuals with MS report experiencing clinically significant fatigue (Minden et al., 2006; Weiland et al., 2015), and many consider this as one of the most disabling symptoms (Amato et al., 2001; Bakshi, 2003) which is significantly independently associated with lower QoL (Janardhan & Bakshi, 2002). There are mixed reports of the effect of fatigue on neuropsychological test performance in MS. Some

have demonstrated deficits in executive functioning, IPS, verbal fluency, sustained attention and working memory tasks due to subjective fatigue (Diamond, Johnson, Kaufman & Graves, 2008; Krupp & Elkins, 2000; Rotstein, O'Connor, Lee, & Murray, 2012; Weinges-Evers et al., 2010). However, several studies found no association between fatigue and cognitive performance when fatigue is based on self-report (Beatty et al., 2003; Bol, Duits, Hupperts, Verlinden, & Verhey, 2010; Hanken, Eling & Hildebrandt, 2015; Johnson, Lange, DeLuca, Korn & Natelson, 1997; Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009; Niino et al., 2014; Parmenter, Denney, & Lynch, 2003; Paul et al., 1998). A comprehensive review reported the cognitive signature of MS related fatigue to be solely associated with reduced alertness and vigilance (Hanken, Eling & Hildebrandt, 2015).

In an ecologically valid examination, Beatty et al. (2003) noted increased self-report of fatigue during employment, but this did not translate to performance reduction. Bol, Duits, Hupperts, Verlinden and Verhey (2010) demonstrated that mental fatigue contributed to 39% of the total variance for cognitive complaints (using the multidimensional fatigue inventory), and physical fatigue was non-significant. However, these were not reflected on objective cognitive tests. The findings that subjective fatigue impacts cognitive complaint, but not cognitive test performance, was replicated by Jougleux-Vie et al. (2014) for verbal episodic memory.

Reported reduced alertness and vigilance (Hanken, Eling & Hildebrandt, 2015) could potentially be explained by symptomatic overlap of depression and fatigue (Golan et al., 2017). Thus, Golan et al. (2017) examined the independent associations between depression and subjective cognitive fatigue on objective cognitive test performance

whilst controlling for disability, comorbidities and psychotropic medications. They reported no independent correlation of fatigue and cognitive test performance, but a small effect for depression (depression and fatigue combined only accounted for 1-6% of the variance in cognitive scores). Of importance to the current study was the significant impact of fatigue on motor function independent of EDSS, depression, and other confounds (Golan et al., 2017).

Krupp (1997) report that the pathogenesis of fatigue is an amalgamation of neurobiological factors (nerve conduction and degeneration), psychological factors (depression and anxiety) and cognitive decline. Hanken, Eling and Hildebrandt (2015) suggested atrophy in the fronto-parietal networks, and subcortical structures including hypothalamus and thalamus were implicated in those with fatigue on alertness and vigilance tasks. Wilting et al. (2016) also implicated the thalamic region with fatigue. Reduced cerebellar volumes have not been found to contribute to development of fatigue (Weier et al., 2014).

Fatigue affects a large proportion of individuals with MS and this has significant impacts on their self-reported functioning and QoL. However, overall subjective cognitive fatigue appears not to be linked to objective cognitive performance.

1.2.7. Medication and cognition in MS

The effectiveness of disease-modifying treatments on cognition is unclear (Amato, Portaccio & Zipoli, 2006; Langdon, 2010). One RCT of interferon-beta 1a demonstrated a slight improvement in verbal learning and recall, as well as auditory

working memory (Fischer et al., 2000), however it is hard to draw conclusions as the study was terminated early. A study of interferon beta 1-b (IFN β-1b) demonstrated improved performance in delayed visual memory recall when comparing those on a lower dose of IFN β-1b than those receiving a higher dose (Paty & Li, 1993), however this study was greatly underpowered. Another IFN β-1b study demonstrated improved attention and visual learning/recall in RR-MS matched for EDSS (Barak & Achiron, 2002), however again this was underpowered. In a larger prospective study of IFN β-1a, a comprehensive cognitive assessment was conducted at baseline and two-year follow up, which revealed significant changes in cognition compared to placebo in the domains of IPS, learning and memory (Fischer et al., 2000). This also suggested that IFN β-1a prevented decline in PASAT performance (Fischer et al., 2000). Cohen et al. (2002) reported that in a large study of SPMS, two years of IFN β-1a treatment did not significantly improve PASAT performance. IFN β-1a was associated with stability of cognitive impairment in a large three-year longitudinal study, and five-year follow-up in individuals with mild RR-MS – particularly in females (Patti et al., 2010; 2013). In a review of DMTs on cognition, criticisms of studies were associated with being underpowered, only considering subgroups of participants, or focusing on cognition as a minor aspect of the study (instead focusing on clinical outcome such as relapse rates) (Patti, 2012). Now that DMTs are standard care in MS, it is difficult to conduct RCTs evaluating their efficacy (Patti, 2012). There appear to be some benefits of DMTs on cognitive performance, however these may be secondary to reduced relapse frequency or other neurologic phenomena.

Effectiveness of symptomatic treatments on cognition are also unclear. RCTs of donepezil and rivastigmine on memory impairment in MS demonstrated no significant

differences between the intervention and control groups (Krupp et al., 2011; Shaygannejad, Janghorbani, Ashtari, Zanjani, & Zakizade, 2008). A Cochrane review of pharmacological interventions for memory disorder in MS concluded that there are no effective pharmacological treatments of memory impairments in MS (He, Zhou, Gou, Hao & Wu, 2011). Jensen, Ravnborg, Mamoei, Dalgas and Stenager (2014) report significant improvements on the SDMT for individuals taking slow-release Fampridine-SR treatments. A small medication trial of 60 participants over four weeks demonstrated greater improvements in PASAT performance in the placebo arm compared to the Fampridine-SR trial. Morrow & Rosehart (2015) demonstrated a medium effect size improvement on the SDMT (though no significant difference on PASAT) for use of mixed amphetamine salts extended release. However, this used a very small sample size and involved only a single dose on the morning of testing. Early trials have indicated positive effects of L-amphetamine sulphate on learning and memory (Morrow et al., 2009) and has showed promise for slowed IPS (Benedict et al., 2008). A review paper indicated that, except for L-amphetamine, symptomatic drug treatments do not have an impact on cognitive performance (Patti, 2012).

Polypharmacy (the use of four or more medications simultaneously) is common in MS, due to the constellations of symptoms and requirement to reduce disease progression. Polypharmacy has been demonstrated to worsen prospective memory and increase self-reported fatigue (Thelen, Lynch, Bruce, Hancock & Bruce, 2014).

Research on pharmacological-based impacts on cognition is limited, and this is an area which warrants further investigation. It is possible that differential medication use could add confounds to research in MS.

1.2.8. Summary

Cognitive impairment affects a significant proportion of people with MS. The profile of impairment varies and typically worsens with disease progression. This has significant impacts on QoL and daily functioning. High cognitive reserve appears to be somewhat protective of cognitive decline. The most common and severe impairments are of attention and IPS. Memory difficulties and executive dysfunction are common within MS, however it is likely that attention and IPS have a significant impact on timed tasks of executive functions, and the registration of memories. Psychiatric symptomology appears to have a significant negative impact on individual performance on cognitive tests, and therefore individuals with psychiatric diagnoses are typically excluded from studies examining cognitive profiles. However increased symptoms of depression and anxiety are typically recognised when comparing the MS group to controls. The clinical population demonstrates variability, and thus subcategories of individuals with RR-MS should be considered. Considerations of sub-diagnostic categories, may facilitate understanding of more specific cognitive profiles. The present study aims to find differences between individuals who have cerebellar involvement in MS compared to those who do not.

1.3. Role of Cerebellum in Cognition

1.3.1 Cerebellar structure and anatomy

The cerebellum (translated literally from Greek as 'little brain') is caudal to the cerebral cortex. It is divided into two hemispheres, separated by the vermis. It occupies 10% of the intercranial space, and has five times more neurons than the entire cerebral cortex (Herculano-Houzel, 2009; Miall, 2013). It has three lobes (anterior, posterior and flocculonodular). The cerebellum connects with the brainstem via the brachium conjunctivum, brachium pontis and restiform body, and afferent projections stem from deep nuclei, of which the cerebellum is wrapped around (Maill, 2013). These serve as the only output fibres from the cerebellum.

1.3.2. Cerebellar Function

Historically, the cerebellum was considered a group of subcortical nuclei solely responsible for motor control. This is one aspect of cerebellar function, and damage can result in motor symptoms such as stiffness, rigidity, tremor and akinesia (Middleton & Strick, 2000) as well as ataxia, dysmetria, dysarthria and dysphagia (Schmahmann, 2004), loss of coordination, hypotonia, nystagmus, ocular dysmetria, and dysdiadochokinesia (Weier et al., 2015a; 2015b). Postural and intention tremors are two of the most common cerebellar symptoms in MS (Weier et al., 2015a). A survey revealed that these postural and intention tremors are reported in 58%, though asymptomatic in 20% of these (Alusi et al., 1999).

It is now acknowledged that the cerebellum has a much wider role. This is shown clinically in the 'cerebellar cognitive affective syndrome' (CCAS) (Schmahmann & Sherman, 1998; Schmahmann, 2004) recognised in patients with focal lesions to the cerebellum. Symptoms include executive dysfunction (deficits in shifting, abstract reasoning, working memory, verbal fluency, inhibition and planning) and other cognitive deficits (spatial cognition and visual-spatial memory) (Schmahmann & Sherman, 1998; Schmahmann, 2004) as well as affective and personality changes, dysmetria, dysarthria and ataxia (Manto et al., 2012). CCAS is suggestive of wide ranging neural connections from the cerebellum to cortical areas.

Schmahmann et al. (1998) reported those with CCAS without executive dysfunction showed anterior cerebellar damage and no posterior cerebellar damage (thus leading to motor, as opposed to cognitive changes). This reflects a functional topographical organisation of the cerebellum, with anterior areas associated with motor control (projecting to the sensorimotor cortex) and posterior lobes being involved in higher-order processes (projecting to frontal areas). Evidence of this functional topographical architecture is found in a meta-analysis utilising fMRI activation likelihood estimates (ALE) (Stoodley & Schuhmann, 2009). This implicated lobule V, VI and VIII in sensorimotor tasks, lobules VIIIA/B in motor activation, and VIIIB in somatosensory activation (Stoodley & Schuhmann, 2009). Higher-order processes are associated with the posterior lobule. Lobule-VI and Crus-I are associated with language and working memory, Crus-I and lobule-IV for emotional processing and language and executive functions on Crus-I and lobule-VII (Stoodley & Schmahmann, 2009).

1.3.3. Corticocerebellar loops

Neuronal tracing has confirmed the existence of cerebellar loops which facilitate communication between the cerebellum and cortical areas (Kelly & Strick, 2003; Middleton & Strick, 2000), including premotor, prefrontal, oculomotor and inferotemporal areas, with each loop associated with specific cognitive or behavioural functions (Kelly & Strick, 2003; Middleton & Strick, 2000).

These 'loops' involve neocortical projections from different lobules of the cerebellum, via the pontine nuclei, and back to the cerebellum through the thalamus (Balsters & Ramnani, 2011). Afferents from the primary motor cortex project to lobules IV, V, VI, and parts of HVIIB and HVIII, whereas afferents from the pre-frontal cortex project to Crus-I and Crus-II (Kelly & Strick, 2003; Koziol et al., 2014). Habas et al. (2009) demonstrated structural and functional connectivity of the cerebellum to areas of the cortex utilising resting state functional connectivity MRI.

1.3.4 Cerebellar lesions in MS

Within MS focal white matter lesions can occur in any area of the CNS, however there are predilection sites in the cerebellar peduncles and hilar regions of dentate and olivary nuclei due to their proximity to the ventricular system (Weier et al., 2015a). Calabrese et al. (2010) recognised cerebellar lesions and atrophy in all MS phenotypes. Primary cerebellar symptomology in MS appears in 11-33% of patients (Rot, Ledinek & Jazbec, 2008; Weinshenker, Issa & Bakerville 1996).

Specific impairments in cognition, motor skills and locomotion have been linked to cerebellar damage (Weier et al., 2015a). Cerebellar grey matter pathology contributes to cognitive and motor dysfunction in MS independent of cortical pathology (Damasceno, Damasceno, & Cendes, 2014). In one study, cerebellar lesion load was demonstrated to be the sole significant predictor of EDSS (including the cerebellar functional system score), and arm and leg function (Damasceno, Damasceno, & Cendes, 2014). Motor function (measured by the nine-hole peg test; 9HPT) can be indicative of cerebellar atrophy (Ruet et al., 2014; van de Pavert et al., 2016).

1.3.5. Prognosis and rehabilitation outcome in those with cerebellar symptoms

Cerebellar lesions in MS have been linked to poor prognosis and poor rehabilitation outcomes (de Groot et al., 2009; Langdon & Thompson, 1999; Thorpe et al., 2015; Vasconcelos et al., 2016).

Regarding prognosis, Thorpe et al. (2015) report that higher baseline scores in the cerebellar functional system (FS) (as well as bowel/bladder, brainstem, and cerebral functional systems) are predictive of later institutionalisation and thus a worsened prognostic outcome. Functional systems are not discrete systems and thus the cerebral/mental functional system could also be impacted by cerebellar lesions. A longitudinal cohort study of individuals recently diagnosed with MS considered predictors for cognitive and physical functioning three years post-diagnosis (de Groot et al., 2009). Impairment of the cerebellar tract was associated with an inability to walk more than 500 meters as well as impaired dexterity (de Groot et al., 2009). Similarly, Vasconcelos et al. (2016) demonstrated that cerebellar (and pyramidal) dysfunction

according to functional systems, was associated with a worse prognosis in a Brazilian mixed-race cohort. Stewart et al. (2017) reported that relapse phenotype differentially promoted disability accumulation with the most pronounced being pyramidal, cerebellar and bowel/bladder functional systems.

Regarding rehabilitation outcome, Langdon and Thompson (1999) report that cerebellar dysfunction (measured on the cerebellar functional system) is an independent predictor of poor rehabilitation outcome in a sample of individuals predominantly within the progressive phase of MS. This has been associated with poor prognosis for transfers and balance when sitting. Cerebellar function combined with vocabulary skills accounted for 57% variance in functional independence measure (FIM) change scores from admission to discharge.

1.3.6. The cerebellum and automation of motor functions

Cerebellar involvement in motor learning is longstanding and widely suggested (Balsters & Ramnani, 2011; Ito, 2000). The cerebellum develops the capacity to programme motor actions by creating subcortical representations of cerebral commands, requiring minor inputs to carry out the action (Marr & Thatch, 1991). This disencumbers frontal regions for higher-order tasks, known as automation. Automation is an ability to perform one task simultaneously with a cognitively demanding task, with little or no interference in performance (Poldrack et al., 2005). Automated actions are more stereotyped, less influenced by feedback and increasingly efficient requiring reduced attention (Shiffrin & Schneider, 1984).

fMRI have demonstrated increased excitation of the cerebellar region following practice resulting in automation of an action (Putteman et al., 2005; Ramnani, Toni, Josephs, Ashburner, & Passingham, 2000). One study demonstrated that cerebellar damage can prevent automation of movements, requiring individuals to recruit increased attention (Lang & Bastian, 2002). This used a duel-task paradigm, where participants performed a novel arm movement, whilst carrying out an auditory vigilance task (counting frequencies of a given letter in a string of letters). Individuals with cerebellar damage only mildly improved their performance with practice, and practice effects ameliorated when an attentional task was added (Lang & Bastian, 2002). Two studies utilised positron emission tomography (PET) to examine healthy participants learning of sequential finger movements (Jueptner et al.,1997; Jueptner, Frith, Brooks, Frackowiak & Passingham, 1997). Increased medial cerebellar activation (as well as activation of deep dorsal areas of the cerebellar nuclei) occurred when carrying out previously learned actions compared to new actions which were associated with prefrontal areas (Jueptner et al., 1997; Jueptner, Frith, Brooks, Frackowiak & Passingham, 1997). This suggests that monitoring and execution of new actions utilises executive functions within prefrontal areas, with subsequent automation being conducted by the cerebellum. None of these studies utilised populations with MS.

This process involves cerebellar encoding of internal models providing mental representations of the world for motor-planning (Ito, 1969; 2008). Internal models are neural representations of strategies that mimic sensory and/or output data of motor and cognitive processes (Kawato, 1999), known as embodied representations. During an experience, all perceptual systems capture a representation within their modality of the experience (e.g. with proprioception and visuospatial representations), which

amalgamate into a multimodal representation, or model, of the experience. Within motor function, afferents from the premotor cortex, anterior cingulate gyrus or supplementary cortex instructs the motor cortex to move muscles. Sensory feedback is received by the cerebellum, which creates an internal model (Ito, 2008). This provides a template for reactivation and simulation, which contributes to an individual's predictive abilities (Pezzulo, 2008). These mental representations are not pure reproductions, but instead can be manipulated mentally and internally re-enacted (Barsalou, 1999; Pezzulo, 2011). Ito (2008) describes forward and inverse models for controlling movement. Forward models include reference to the internal feedback, whereas inverse models replace the feedback control entirely (Ito, 2008). This includes motor planning, as the primary motor cortex interacts with specific cerebellar lobules (Kelly & Strick, 2003).

In motor control, the human body requires the ability to anticipate an array of musculo-skeletal inputs, CNS latency, and response dynamics (Herreros, Arsiwalla & Verschure, 2016). This relies on anticipatory control loops with the cerebellum, whereby the cerebellum learns to anticipate events based on experience (Herreros & Verschure, 2013). The role of the cerebellum in anticipatory control loops is associated with adaptive filtering and creation of mental bodily representations based on predictions of sensory inaccuracies (Koziol et al., 2014; Shadmehr & Krakauer, 2008). This includes using implicit memory to create sensory predictions (D'Angelo, 2011; Spencer & Ivry, 2009). This is required as action potential of neurons travel too slowly and are too 'noisy' to gain accurate feedback (Shadmehr, Smith & Krakauer, 2010). An example of this process is in compensatory eye movements, whereby humans maintain images centrally on the retina during head and body movements. Frens and Donchin

(2009) implicated the cerebellar flocculus in forward model prediction – which is an estimation of state following the movement. Afferents from the flocculus interact with pontine areas and the medulla to integrate this prediction with current state estimates and consequential feedback movements. Therefore, the role of the cerebellum in voluntary motor control includes timing and co-ordination of each muscle working in tandem, the relationship between motor actions and sensory results, and to predict the sensory outcomes of performing an action (Moberget & Ivry, 2016).

The ability to create mental simulations of eventualities and experiences allows humans to create goal-directed actions. This requires the integration of mental models and executive functions, to select, inhibit alternatives, and evaluate the simulation (Pezzulo & Castelfranchi, 2009). This is most easily conceptualised within the motor domain, but can be expanded to include cognitive internal models (Koziol et al., 2014).

The implicated neuroanatomical structures involve olivary cells and purkinje cells. Individual olivary cells are associated with fundamental movements, by responding to messages from the cortex to produce a sequence of patterns of firing. This means that simple cerebral messages may be sufficient to implement more complex actions (Marr & Thach 1991). Therefore, the cerebellum can develop a representation of information developed in the motor cortex during motor acquisition, which can be automatically reproduced (Marr & Thach, 1991). This disencumbers frontal regions for higher-order tasks.

Therefore, within the motor domain, the cerebellum is thought to play a role in encoding internal models of the world for motor planning. It does this by initially integrating

sensory feedback into models in the cerebellum which are augmented through continual feedback. Summoning mental models reduces reliance on comparatively noisy and latent CNS feedback, thus allowing for predictions of sensory inaccuracies, estimation of state, and the ability to plan motor actions. The present study aims to investigate this phenomenon in MS by comparing performance on a simple peg test of extremity function (9HPT) and a peg test requiring greater levels of motor planning (grooved pegboard test; GPT; Matthews & Klove, 1964), comparing healthy controls with RR-MS and RR-MSc. It is hypothesised that the latter group would have more difficulties with the GPT, due to the greater involvement of motor planning and thus the cerebellum.

1.3.7. Cognitive profile in MS with cerebellar symptoms

Of significance to the cognitive profile of individuals with RR-MS with cerebellar symptoms (RR-MSc) are the connections between the corticocerebellar loops, which support higher-level cognitive functions (Cerasa et al., 2013). There is an increased risk of cognitive impairment in RR-MSc than RR-MS individuals without cerebellar symptoms (RR-MSnc) and RR-MSc demonstrate a different cognitive profile (Valentino et al., 2009; Weier et al., 2014). However, the current evidence base examining the influence of cerebellar involvement on the cognitive profile of RR-MS is limited.

It is thought that motor and cognitive dysfunction occur simultaneously from onset in RR-MSc (Weier et al., 2014). The RR-MSc profile is characterised by more severe deficits in IPS, language, verbal fluency and working memory compared to RR-MSnc,

recognised by impaired performance on the SDMT, PASAT and Controlled Oral Word Association Test (COWAT) (Bozzali et al., 2013; Cerasa et al., 2012; Damasceno, Damasceno & Cendes, 2014; Ruet et al., 2014; Valentino et al., 2009; van de Pavert et al., 2016; Weier et al., 2014). Ceresa et al. (2013) also demonstrated further deficits with immediate and delayed spatial memory with the ROCFT.

Weier et al. (2014) utilised the cerebellar FS score to differentiate 172 individuals with a range of MS phenotypes into non-cerebellar (cerebellar FS = 0) or cerebellar (cerebellar FS > 0). This neurologic differentiation was corroborated by significantly reduced normalised cerebellar volume within the cerebellar group. The cerebellar group had a significantly higher EDSS, older age and longer disease durations. This group also had significantly worse performances on the 9HPT and measures of IPS (SDMT/PASAT). Hierarchical multiple linear regression analyses revealed that cerebellar signs and age predicted 26% of the total variance on the SDMT and these variables with T2 lesion volume predicted 23% of the PASAT. They reasoned that cerebellar symptoms appear to contribute to disability however, not independently of normalised brain volume and T2 lesion volume.

Damasceno, Damasceno and Cendes (2014) compared healthy controls with individuals with RR-MS. A higher burden of cerebellar intracortical lesions were associated with worse SDMT scores, and higher burden of cerebellar leukocortical lesions were associated with lower PASAT scores (Damasceno, Damasceno & Cendes, 2014). Similarly, Bozzali et al. (2013) associated PASAT scores with reduced anatomical connectivity with the corpus callosum right hippocampus and cerebellum in a study comparing healthy controls to RR-MS. Cerasa et al. (2012) showed reduced

scores on the paced visual serial addition task (PVSAT) in RR-MSc with reduced connectivity (demonstrated on fMRI) between left cerebellum crus-1/Lobule-IV (posterior areas) and right superior parietal lobe. IPS reduction has been associated with reduced Crus-II (Lesage et al., 2010) and inferior middle cerebellum (Bozzali et al., 2013) connectivity to prefrontal circuits.

IPS reductions may be due to overwhelmed compensatory strategies following cortical reorganisation due to corticocerebellar loop damage (Rocca et al., 2012; Ruet et al., 2014). These include overuse of compensatory 'higher' cortical areas for basic tasks due to inefficiencies in the cerebellum, and a saturation effect of cognitive load results in cognitive deficits. This is demonstrated by an imaging study by Ceresa et al. (2012) where MS patients with damage to corticocerebellar loops demonstrated increased activity in parietal areas and worse neuropsychological performance.

Reduced functional connectivity between the cerebellum and cortical areas has also been shown to impact executive functions in RR-MSc (Ceresa et al., 2012). Increased response times were associated with reduced bilateral cerebellar activations during the incongruent condition of the Stroop task (Rocca et al., 2012; Trennery, 1989). Similarly, grey matter cerebellar lesion load and reduced cerebellar volume have been linked to executive dysfunction in Hayling Sentence Completion Task (Burgess & Shallice, 1997).

van de Pavert et al. (2016) found an association with cerebellar lesion load and volume and reduction of memory performance on the Adult Memory and Information Processing battery (AMIPB; Coughlan & Hollows, 1985) (specifically on story recall

immediate and delayed; figure recall immediate and delayed), and word and face recognition on the Recognition Memory Test (Warrington, 1984). However, in one study of MS patients with a minimum disease duration of ten years, when all cognitive domains are examined simultaneously, there was no relationship between cerebellar lesions (assessed with a multimodal MRI) and cognitive impairment (Daams et al., 2016). Similarly, Valentino et al. (2009) reported no significant relationship between total lesion load in the cerebellum (and cortex) and cognitive impairment.

Findings from the above research imply correlations between cerebellar atrophy, neuroanatomical connections and performance on neuropsychological test performance. However, more research is needed in the area to gain a fuller understanding of the cognitive profile of those with RR-MSc. One aspect of the present study will further consider the cognitive profile in RR-MSc.

1.3.8. The interrelation of cerebellar cognitive impairment and motor function/planning

The action-based view of cognition posits that higher-order cognitive phenomena have evolved out of the structures available from the motor domain (Pezzulo, 2011). These structures create models involved within several social and cognitive abilities such as perspective taking, imitation, understanding others' actions (Pezzulo, 2011), creativity and innovation (Vandervert, Schimpf & Liu, 2007). Similarly, Gallese et al. (2003) suggested that this was required for effective empathy and through generations of mental representations of affective states. Use of the same neural structures have been demonstrated for language comprehension (Scorolli, Borghi and Glenberg, 2009),

verbal working memory tasks (Küper et al., 2016; Marvel & Desmond, 2010; Sweet, Rao, Mayer & Cohen, 2004) and whilst perceiving others carry out actions (Rizzolatti & Craighero, 2004).

Schmahmann (2004) recognised the anatomical uniformity of the cerebellum and thus hypothesised a uniform functionality for interactions with other areas of the cortex – the 'universal cerebellar transform'. This is "an oscillation dampener maintaining function automatically around a homeostatic baseline and smoothing out performance in all domains" (Schmahmann, 2004, p374-375), implying that external stimuli interact with internal representations, which produces automated self-generated responses (Koziol et al., 2014). The universal cerebellar impairment is suggested to be dysmetria (dysfunction in performance of sharp alternating movements) involving the motor domain, but broadening to cognitive dysmetria. This is witnessed in the symptomology of CCAS (Schmahmann & Sherman, 1998).

In accordance with the universal cerebellar transform, lesions to the cerebellum would result in universal cognitive impairment, whereby comparable dysfunction would be evident across the domains – a disruption around a homeostatic mechanism (Koziol et al., 2014; Schmahmann, 2004). This is likely to result in disrupted behaviours that are inconsistent with the external environment. Several fMRI studies have demonstrated that increased cerebellar activation results in more rapid cognitive performances in healthy controls, but the same is not true for those with MS (Bonnet et al., 2010; Genova et al., 2009; Moroso et al., 2017; Rocca et al., 2012). Moroso et al. (2017) found that SDMT was associated with atrophy of the posterior cerebellum, though was not associated with total cerebellar atrophy. They suggested that failures of the posterior

cerebellum prevent rapid cognitive performances, due to lack of optimisation and automation of cognitive function (Moroso et al., 2017). This conclusion is associated with the recognition that the cerebellum is involved in typically 'frontal' cognitive functions, via the recognised diffuse projections from posterior regions to the prefrontal cortex.

One suggested cognitive mechanism is the role of the cerebellum in automisation of attentional demands (through cerebellar modulation), by creating an internal representation of the cognitive task, which disencumber cortical regions. This is a stereotyping of cognitive processes by integrating internal representations, and consequently amalgamating these models with external visual stimuli (Moroso et al., 2017). This results in a more efficient processing thus greater IPS, due to the disengagement of the cerebral cortex and automatic responses from the cerebellum. Moroso et al. (2017) suggest that failings of cerebellar-frontal projections result in employment of the medial prefrontal cortex as a compensatory mechanism. Bonnet et al. (2010) termed this 'cognitive compensation failure'. They recognised that medial prefrontal regions were activated in those with RR-MS compared to healthy controls who would activate cerebellar regions (during a go/no go paradigm). This results in cognitive impairment due to utility of higher-level decision making areas of the brain to carry out the tasks that would be automated in healthy controls. The cognitive compensation failure theory, posits that the limited cognitive load available to carry out tasks results in reduction of speed of response.

Similar neuroanatomical processes are implicated in higher-order domains as in the motor domains for automation. Koziol et al. (2014) implicates synaptic strengthening

between Purkinje cells, and suggests that the process involves the receipt of information from the prefrontal cortex which strengthens the internal representation that most similarly matches the external stimuli (Koziol et al. 2014; Moroso et al. 2017). This disengages the cortex and incorporates the cerebellar generated automatic response, thus increasing competency within tasks (Koziol et al., 2014; Moroso et al., 2017).

Binétray et al. (2016) demonstrated an experimental separation of cognitive processes and motor speed. This compared two crossing-off tests (COTs) with RR-MS and healthy controls (HC). One COT replicated visual exploration (sweeping visuomotor movements) and one COT replicated writing habits (left/right visuomotor movements). The former develops at an earlier age and thus is more naturalistic, whereas the latter is a more composite task requiring greater processing of information due to inhibition and switching by returning to the left side of the page. Within the visual exploration COT, there were no differences between HC and RR-MS. In the writing habit COT, significant differences were reported, and this was associated with reduced IPS. It is possible that this difference was associated with decreased cerebellar activation and thus reduced ability to generate automatic processes. Therefore, RR-MS were slower at this task due to reduced IPS, potentially from inefficiencies of automated cerebellar models. This study had a small sample of MS patients who had very low levels of disability (EDSS 0-1) and there were no measures of cerebellar dysfunction. Similarly, cognitive status was minimally assessed. The present study will utilise a reasonably exhaustive cognitive battery, a larger sample, considering motor planning (not just function) and includes a measure of cerebellar function. A broader range of disability will also be included, which will increase generalisability of findings to the clinical population.

Being able to understand and measure the interrelation of cerebellar cognitive impairment, motor function impairment and motor planning impairment may help to identify a subtype of MS. The current research aims to gain clarity on the interplay of these neurological variables whilst differentiating RR-MSc, RR-MSnc and HC. This, in turn would allow for different treatment and rehabilitation strategies.

One aspect of the present study was to examine the notion that RR-MSc may lack the ability to efficiently optimise and automate cognitive functions resulting in impairments in motor function. They may lack efficient integration of executive functions with cerebellar models required in motor planning, causing impairment in motor planning. Since the same structures involved in motor planning are utilised in cognitive automation, it is possible that there may be a link between motor planning deficits and IPS reductions due to increased recruitment of higher cortical areas of limited information processing capacity (as opposed to summoning cognitive 'subroutines' form cerebellar models). Alternatively, it may be all cognitive domains are equally effected due to simultaneous reductions in motor function and cognition associated with a universal cerebellar transform.

The present study aims to understand how cerebellar damage underpins motor planning, and whether this relates to cognitive function. To the author's knowledge, this is the first study to look at this association in MS.

1.3.9. Summary

The cerebellum is a predilection site for atrophy and lesions in MS. Corticocerebellar loops which connect the cerebellum to cortical areas are likely to be involved in the increased cognitive and motor impairment in RR-MSc. A link between the cerebellum and automatic tasks has been demonstrated. The cerebellum is thought to develop subcortical models of sensory experiences for motor planning. Atrophy and lesions to the cerebellum are thus likely to impair motor planning and function, which will be investigated within the present study. The cognitive profile of RR-MSc is thought to be associated with further reduced IPS, and more executive dysfunction, however more research is required within this area. One theoretical explanation of increased cognitive impairment within RR-MSc is that it is due to inefficiencies of the capacity of the cerebellum to create subcortical representations, or models, based on information from all perceptual and cognitive systems. These models interact with external stimuli to coordinate performance in all cognitive domains (universal cerebellar transform), implying that damage will create universal cerebellar impairment. Another, perhaps complementary, theoretical explanation is that the cerebellum automates cognitive processes which results in reduced attentional input for aspects of cognition. Consequently, the process becomes more efficient by disencumbering the cortex to focus on higher-order tasks. This inefficiency of creation of subcortical models for automation has been thought to create both cognitive and motor symptoms simultaneously. Thus it is likely that inefficiencies of motor planning will be associated with cognitive decline, particularly IPS. Such impairment has not yet been demonstrated in the MS population.

1.4. Outline of the research: Objectives and Rationale

The first aspect of the study is to ascertain the differences in cognitive profile between the groups: RR-MSnc, RR-MSc and HC. To the author's knowledge, this is the first study with the chosen test battery with RR-MSc individuals. This has clinical and theoretical implications, including differential diagnosis, prognosis markers, and increased theoretical understandings of MS phenotypes.

The second aim is to experimentally test for motor functioning and planning deficits comparing RR-MSc, RR-MSnc and HC. This may provide insight into understanding motor difficulties experienced by this clinical population. This has clinical implications regarding the management, understanding, and treatment of individuals with MS and to the author's knowledge has not yet been studied.

The final aim is to provide clarity on whether differences in motor functioning and planning will be related to cognitive function, particularly IPS. The hypothesised association with IPS is due to the notion that cerebellum disencumbers 'higher' cortical areas for higher-order tasks through automation. Thus, reduced cerebellar function may lead to inefficient processing of information due to the cognitive compensation failure, thus reduce IPS. However, the theory that the cerebellum acts as a universal transform would also suggest that other cognitive deficits will relate to motor functioning impairment. This study helps to consider these two, perhaps complimentary theories. To the authors knowledge, this is the first time this has been considered in MS.

This research has significant clinical implications of beginning to identify a cognitive subtype of MS, which may provide prognostic information that will have implications for treatment and rehabilitation. It will also further theoretical understanding of the cerebellar contribution to motor functioning, motor planning and cognitive function.

1.4.1. Hypotheses

1. RR-MSc will have a different cognitive profile to RR-MSnc and HC, demonstrated by worse performances on tests examining IPS, verbal memory, visual memory and verbal fluency.
2. Individuals with RR-MSc will perform worse than RR-MSnc and HC on tasks of motor planning
3. Differences in motor functioning will be related to cognitive function, most significantly IPS.

2. Methodology

2.1. Research Approval

Confirmation of a favourable ethical opinion was received from the NHS Health Research Authority, following Proportionate Review (See *Appendix 1).* Subsequently, the Research and Development (R&D) department in a Middlesex NHS Foundation Trust gave permission for recruitment of MS participants (See *Appendix 2* and *Appendix 3*). Ethical approval was then obtained from the research ethics committee at Royal Holloway, University of London. Insufficient numbers of participants were identified at the initial research site, and consequently an application to add participant identification centres (PICs) to the project was granted from the NHS Health Research Authority. Finally, R&D was granted from an additional Greater London NHS Foundation Trust as a PIC for recruitment of MS participants (See *Appendix 4*).

2.2. Design

The study took an independent-groups design comparing three groups: individuals with relapsing-remitting multiple sclerosis with cerebellar symptoms (RR-MSc), those with relapsing-remitting multiple sclerosis without cerebellar symptoms (RR-MSnc), and healthy controls (HC). A neuropsychological test battery, questionnaire battery and two peg tests were administered to participants in each group. The cognitive tests in the study have published norms, however, these have been published at different times and from different locations. Similarly, considerations of cognitive tests outside of specific batteries involves confounds such as order effects and fatigue effects. Therefore,

inclusion of a control group for the basis of comparison serves to reduce these confounds.

2.3. Participants

A total of 56 participants were recruited. Twenty-one were allocated to the healthy control group, with ten males, a mean age of 37.05 and a mean premorbid IQ of 115.34. Twenty-one were allocated to the RR-MSnc group with six males, a mean age of 39.81 and a mean premorbid IQ of 109.22. Fourteen individuals were allocated to the RR-MSc group with seven males, and mean age of 40.57 and a mean premorbid IQ of 99.83.

2.3.1. Inclusion / Exclusion Criteria

Participants were included in the study if they met all the below inclusion criteria, and did not meet any of the exclusion criteria.

- Inclusion
    - All participants were fluent English speakers, whose first language is English.
    - All participants were aged 18-60 years of age.
    - *MS participants only:*
        - All MS participants must have a diagnosis of RR-MS by a Consultant Neurologist based on Polman et al. (2011) criteria or equivalent.

        - All MS participants had an EDSS 0-5.0 (able to walk 200 meters without aid or rest) as identified on Extended Disability Status Scale, telephone version (Lechner-Scott et al., 2003 – explained later, see *section 2.8.2.1.*).

- Exclusion
    - Those affected by psychosis, substance misuse disorders, epilepsy, head injury or significant diagnosed pre-morbid depression or anxiety disorders.
    - Those who demonstrated significant visual, motor, or hearing impairments which would deny full engagement in cognitive tests.
    - Those who lacked capacity to consent to the study.

      Multiple sclerosis participants only:

        - Those with MS who had a clinical relapse or steroid treatment in the previous two months.
        - Following saturation of the RR-MSnc group, participants were excluded if they scored >4 on NARCOMS-TACS (North American Research Committee on MS Registry Tremor and Coordination Scale; NARCOMS-TACS; Marrie & Goldman, 2011 – explained later see *section 2.8.2.2*).

2.4. Recruitment

2.4.1. MS Participant Identification

MS participants were recruited from NHS Foundation Trusts in Greater London and Surrey. Participants were approached by the clinical teams who provided participant information sheets (see *Appendix 5*) and gained permission for the researcher to make telephone contact. Alternatively, participants were provided with the option to contact the researcher via telephone or email. Upon contact, a home visit appointment was arranged to gain written informed consent (See *Appendix 6*) and for data collection. Participants with MS were well known to the treatment team, and had numerous home visits as part of their care, thus home visits were deemed safe and appropriate. An invitation letter was sent to individuals whom requested it (see *Appendix 7*). The researcher informed participants with MS that they are free to withdraw at any time, without giving a reason, and that this would not affect the standard of care they receive or their legal rights. This was provided both verbally and on the participant information sheets.

Participants were assigned to RR-MSnc or RR-MSc based on the NARCOMS-TACS (Marrie & Goldman, 2011 – explained later see *section 2.8.2.2.*), as tremor and loss of co-ordination in MS is indicative of cerebellar involvement. In MS populations of mild-moderate disability, this scale has demonstrated adequate construct validity (for detection of cerebellar symptoms), as well adequate criterion validity (Marrie & Goldman, 2011). Individuals were allocated to the RR-MSc group if they scored four or five out of a possible five on the NARCOMS-TACS indicating at least 'severe tremor

or loss of co-ordination'. Specifically, they endorsed the statement that *every day* "tremor or loss of coordination problems [force me to modify/prevent me from doing] my daily activities".

A substantial amendment was submitted following saturation of the RR-MSnc group to use the NARCOMS-TACS prior to gaining consent for data collection. It was deemed less intrusive to participants to ask this question outside of informed consent than to unnecessarily inconvenience participants who would not be suitable for allocation to RR-MSc.

2.4.2. Healthy Control Participant Identification

An opportunistic sampling method was used to identify HCs. This included approaching local businesses and through friends and acquaintances of the researcher. HCs were recruited from Cambridgeshire, Greater London and Berkshire. Following identification of potential participants an invitation letter (see *Appendix 8*) was sent and the HC participant information sheet (see *Appendix 9*). All participants contacted the researcher if they wished to be involved, and then an appointment was arranged to gain written informed consent (see *Appendix 10*). Individuals known to the researcher were given the opportunity to complete the assessment at home or in the researcher's home. If participants were not known to the researcher, company buildings, or offices at Royal Holloway, University of London were used. Controls were informed that they were entitled to withdraw at any time without giving a reason, both verbally and on participant information sheets.

All groups were demographically matched for age and gender. Efforts were taken to match pre-morbid intelligence, however the matching process was not successful, and this was statically controlled for. Participants were not matched for employment, as MS patients are much less likely to be employed than those without MS, even at low levels of disability (Schiavolin et al., 2013). According to Weier et al. (2014) patients with cerebellar signs also tend to be older and more physically disabled. Data for healthy controls were collected following saturation of the RR-MSnc group, since there is a larger cohort to select from for the matching process.

2.4.3. Excluded participants

Following identification by the clinical team, ten participants were excluded. Three participants were excluded due to restricted ambulation resulting in an EDSS greater than five. Three participants were excluded due to being over 60 years of age. Two participants were excluded as English was not their first language. Two participants were excluded at telephone screening since they did not score four or more on the NARCOMS-TACS and RR-MSnc group had met saturation. Only one participant not included within the study completed the full battery – which was associated with further information being provided regarding ambulation in a post data-collection discussion.

2.5. Lone Working

Although only participants known to the research team or clinical team were offered home visits, potential risks associated with visiting homes of participants were identified. Thus, the *Camden and Islington NHS Foundation Trust Lone Working*

Policy (September, 2015) was adhered to. Participants not known to the clinical or research team were seen in public buildings (offices or Royal Holloway, University of London).

2.6. Data storage

Participants were allocated an anonymised participant identification number. Participant name and identification number pairings were kept in a separate encrypted and password-protected spreadsheet. Data were also stored in an encrypted and password-protected spreadsheet.

2.7. Power Analysis

Statistical power analysis was carried out to determine the number of participants required to ascertain whether there was an interaction between group membership (RR-MSnc, RR-MSc, HC) and measured variables. The anticipated analyses were to utilise 3x1 one-way ANOVAs for the main dependent variables (pegboard and cognitive test scores) with the independent variable as group membership.

A power analysis was conducted utilising data from Valentino et al. (2009) due to a similarity of design. This study involves a similar clinical population, with the comparison of individuals with RR-MSnc and RR-MSc. Similar inclusion and exclusion criteria were utilised compared to the proposed study. Participants in Valentino et al. (2009) also carried out a cognitive test battery with some similarities (SDMT and semantic fluency tasks).

Within this study, the smallest significant effect-size was $\eta 2 = 0.82$ (for SDMT one-way ANOVA). Therefore, a large effect size of $\eta 2 = 0.8$ (as reported in Cohen, 1992) was utilised for the power calculation.

G*Power (Faul, Erdfelder, Lang & Buchner, 2007) was used for power analysis computations. Input parameters were set as follows: $\alpha = .05$, power = .8, effect size ($\eta 2$) = 0.8, group number = 3, for one-way ANOVA. This demonstrated that 21 individuals would be required per group, a total requirement of 63 participants for an actual power of $\eta 2 = 0.86$.

2.8. Materials

2.8.1. Cognitive Tests

Since motor dysfunction in the MS population is common, especially in those with cerebellar symptoms (Middleton & Strick, 2000), cognitive tests were selected that did not require fine motor control. Short tests were also selected, due to cognitive fatigue within this clinical population. Schwid et al. (2003) demonstrated a reduction in performance of MS participants at the end of testing compared to the beginning, highlighting the requirement for short testing batteries.

Three tests (SDMT, BVMT-R learning trials and CVLT-II learning trials – defined below) in the current battery make up the the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS; Langdon et al., 2012). This was developed by an MS expert consensus group and is considered the gold standard for cognitive screening in

MS. This shows excellent psychometric properties with a sensitivity of 58%, specificity of 86% and accuracy of 75% when compared to the full Brief repeatable battery of neuropsychological tests (BRB-N; Rao & the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990). The final two tests (WLG and PASAT3 – defined below) form part of the BRB-N, considered a sensitive measure of cognitive impairment in MS (Boringa et al., 2001).

2.8.1.1. Symbol digit modalities test (SDMT; Smith, 1982)*:* The SDMT (see *Appendix 11*) is a test of IPS. In this test, symbols are paired with numbers in a nine-item key at the top of the record sheet. The record sheet also contains rows of symbols with their number pairings missing. Individuals are required to vocalise the numbers that correspond to symbols presented within the record sheet as fast as possible. There is an initial practice phase of 10 items to ensure understanding. The total score is the number of correct responses within a 90-second time limit. The oral nature of this test ensures that fine motor skills do not act as a confound. A systematic review demonstrated excellent psychometric properties for the SDMT-oral (Jaywant, Barredo, Ahern, & Resnik, 2016). Parmenter, Weinstock-Guttman, Garg, Munschauer and Benedict (2007) reported good psychometric properties with MS with a sensitivity of 82% and specificity of 60% to cognitive impairment in MS. López-Góngora, Querol, and Escartín (2015) also report good psychometric properties with sensitivity of 78% and specificity of 69% to cognitive impairment in MS. The SDMT demonstrates good test-retest reliability (r = .80) (Smith, 1991), moderate to high concurrent validity, (correlations with WAIS Digit Symbol Coding subtest of r = .62 to r = .91) (Bowler et al., 1992; Hinton-Bayre et al., 1997; Lewandowski; 1984; Morgan & Wheelock, 1992) and good construct validity in MS as it is strongly associated with neuroimaging disease

markers (Christodoulou et al., 2003). It has been demonstrated to be effective at determining cognitive impairment within MS and competently distinguishes between people with MS and healthy controls (Drake et al., 2010; Hughes, Denney & Lynch, 2011; Langdon, 2012; O'Connell, Langdon, Tubridy, Hutchinson & McGuigan, 2015).

2.8.1.2. Word List Generation Task (WLG): Version A. The word list generation task (See *Appendix 12*) is a 90-second semantic fluency task. It assesses spontaneous word generation under a specific category. Within the present study, Version A was utilised which uses 'fruits and vegetables' as the category. Viterbo, Iaffaldano and Trojano (2013) demonstrated on a semantic fluency test that a cut-off of <28 words has a sensitivity of 82% and specificity 66% in discriminating participants with and without cognitive impairment in CIS indicative of MS. Tests of verbal fluency have been associated with neuroimaging markers, particularly associated with atrophy to the anterior and posterior corpus callosum (Bodini et al., 2013; Morrow, Menon, Rosehart, & Sharma, 2017).

2.8.1.3. Paced Auditory Serial Addition Test (PASAT; Gronwall & Sampson, 1974): The PASAT (see *Appendix 13*) is a test of IPS and sustained and divided attention as well as working memory and calculating speed. The researcher provides participants with an audio recording which presents numbers at a rate of one every three seconds. The participant must add this number to the previous number presented. The PASAT has been reported to be aversive (Bosnes, Dahl & Almkvist, 2015; Roman, 1991; Walker et al., 2012) due to pressurised presentation tempos. The PASAT has a three second presentation interval (PASAT3) and a two second presentation interval (PASAT2). Due to the aversive nature, only the PASAT3 was utilised, as this was

deemed sensitive enough within the MS population. Within the MSFC (Multiple Sclerosis Functional Composite) (Fischer, Rudick, Cutter, & Reingold, 1999), only the PASAT3 is used as standard, with an optional two second trial. This has demonstrated good inter-rater reliability (r = .90 to .97) (Solari et al., 2005). Thompson (2000) also reported excellent internal consistency (with split half reliability of r = .96), and good test-retest reliability (r = .92) (Solari et al., 2005). When compared with an extensive working memory test battery, the PASAT was reported to have a 49% sensitivity and 85% specificity for cognitive impairment (Hansen et al., 2015). López-Góngora, Querol, and Escartín (2015) report a sensitivity of 73% and specificity of 59% for the PASAT3 for cognitive impairment. On MRI markers, the PASAT has been associated with lesion volume (Rao et al., 2014) and brain volume loss in MS (Vollmer et al., 2016).

2.8.1.4. California Verbal Learning Task (CVLT-II; Delis, Kramer, Kaplan & Ober, 2000). The CVLT-II (see *Appendix 14*) is a measure of episodic verbal learning and memory. The CVLT-II involves a list of 16 words, within four categories. The experimenter reads aloud the list five times (at a rate of one word per second), and the participant responds with as many words as they can remember. This is conducted over five trials with a maximum score of 16 on each trial. From this, a total score is calculated (maximum 80). This has demonstrated good internal consistency with split-half and α coefficients from α = .83 to .96 for clinical samples (Delis et al., 2000). It also has good predictive validity with regards to employment, good support for construct validity in MS (Stegen et al., 2010). CVLT-II correlates strongly with the CVLT (r = .76) (Delis et al., 2000). It demonstrates good sensitivity to cognitive impairment in MS (Strober et al., 2009) and one paper reported a sensitivity of 61% (Niccolai et al., 2015). Good

test-retest reliability has been demonstrated in general population, (Woods, Delis, Scott, Kramer & Holdnack, 2006), as well as in MS populations (Benedict, 2005; Delis et al., 2000). In accordance with the BICAMS, only the first five trials (learning trials) of the CVLT-II were conducted (Langdon et al., 2012). This reduces the number of cognitive processes involved (Stegan et al., 2010), however aforementioned psychometric properties are inferential since these utilise the other trials (including delayed recall, recognition, and category cued trials) (Langdon, 2012). The CVLT-II has demonstrated good construct validity within the MS population, linked to lesion area, number, and volume on MRI measures (Benedict et al., 2002; Houtchens et al., 2007; Langdon et al., 2012; Mike et al., 2011).

2.8.1.5. Brief Visual Memory Test Revised (BVMT-R; Benedict, 1997): The BVMT-R (see *Appendix 15*) is a test of visual memory. Participants are presented with a set of 2x3 geometric figures for 10 seconds. Following removal of the stimulus sheet, participants are required to draw these shapes accurately in the same position as they appear on the stimulus sheet. This is conducted over three trials. The BVMT-R is scored by allocating one point for accurate drawing and one point for positioning within the matrix (a total of two points for each geometric figure). Each trial has a potential maximum score of 12, and this is conducted over three trials providing an overall score (maximum 36). This test shows good inter-rater reliability ($r > .90$), and good test-retest reliability ($r = .80$) (Benedict, 1997). It demonstrates a 60% sensitivity to cognitive impairment in MS (Niccolai et al., 2015). It has good concurrent validity correlating strongly with measures of explicit memory – e.g. Hopkins Verbal Learning Test ($r = .65$ to $.80$) (Benedict, Schretien, Groniger, Dobraski & Shpritz 1996). It has been demonstrated to be sensitive to impairment with MS Samples (Benedict et al., 2001;

Langdon et al., 2012). In accordance with the BICAMS administration (Langdon et al., 2012) only the learning trials were carried out. Again, this makes discussed psychometric properties inferential, however it provides a 'purer' representation of the cognitive domain of immediate recall visual memory, than if a delayed recall trial was incorporated. Construct validity has been demonstrated as the BVMT-R is significantly associated with neuroanatomical markers and lesion load in MRI scans (Benedict et al., 2002; 2009; Houtchens et al., 2007; Langdon et al., 2012).

2.8.1.6. Test of Premorbid Functioning (TOPF*;* Wechsler, 2011): The TOPF is a brief test to predict premorbid IQ and memory performance (see *Appendix 16*). It consists of 70 words with abnormal grapheme/phoneme translations. Participants read the list, and the number of phonetically correct words provides a raw score. Raw scores, gender, age and years of education are entered into the TOPF premorbid IQ calculator (Wechsler, 2011), which provides an overall premorbid full-scale IQ. O'Carroll (1995) reported that intelligence is correlated with almost all cognitive measures and thus comparison of this to current cognitive tests may be demonstrative of deterioration in a domain from premorbid estimates. Similarly, within the present study utilising the TOPF is important to ensure that groups are matched for premorbid function (thus not over/under emphasising differences). The TOPF shows good test re-test reliability (r = .89 to .95) and high split-half reliability (r = .92 to r = .99) (Wechsler, 2011). It demonstrates concurrent validity with the WAIS-IV verbal comprehension index (r = .75), processing speed index (r = .37) (Wechsler, 2011).

An overview of domains tested by cognitive tests is provided in *Table 1.*

Table 1: Domains assessed by cognitive tests

Cognitive Test	**Domain**
Oral Symbol digit modalities test (SDMT; Smith, 1982)	Information processing speed
Word List Generation Task	Verbal fluency
Paced Auditory Serial Addition Test - three second intervals (PASAT3; Gronwall & Sampson, 1974)	Information processing speed and working memory
California Verbal Learning Task (CVLT-II; Delis, Kramer, Kaplan & Ober, 2000) – learning trials	Immediate verbal recall memory
Brief Visual Memory Test (BVMT-R; Benedict, 1997) – learning trials	Immediate visual recall memory
Test of Premorbid Functioning (TOPF*;* Wechsler, 2011)	Premorbid intellectual functioning estimate

2.8.2. Questionnaires

2.8.2.1. Expanded Disability Status Scale (EDSS Telephone Version; Lechner-Scott et al., 2003): The EDSS (see *Appendix 20*) is a quantitative measure of disability used in MS. Scores on the EDSS range from zero (no disability) to 10 (death due to MS). Typically, a physician ascertains an expanded disability status scale (EDSS; Kurtzke, 1983) score through examination, however Lechner-Scott et al. (2003) validated a telephone-administered standardised interview. Lechner-Scott et al. (2003) showed a strong correlation between telephone and physical examination ($r = .95$). Individuals are only included in the present study with EDSS five or below. If an individual can walk less than 200 meters, then they are excluded as this provides an EDSS greater than five. Scores below this are initially based on the distance an individual can walk without aid or rest. If an individual is defined as unrestricted in ambulation or could walk more than 500 meters without aid, functional system scores are calculated to work out EDSS. To determine functional system (FS) scores, questions were asked regarding symptoms under the following subsections: vision, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, and cerebral functional systems (see *Appendix 20*). For subsections with more than one question, the worst single score was used to determine the FS score.

Frequency of FS scores were used with an FS frequencies table (see *Appendix 21*) to determine EDSS score below 4.5. Permission was granted from Professor Ludwig Kappos (senior author of Lechner-Scott et al., 2003) to utilise the English version of this within the present study. The EDSS has good concurrent validity in RR-MS when using MRI as a disease marker (Kalkers et al., 2001). It has good internal consistency ($\alpha \leq .96$) and test-retest reliability ($r = .87$) (Schäffler et al., 2013). The EDSS has

acknowledged weaknesses in sensitivity to change and aspects of reliability, however, this is the primary measure utilised for disability within MS. Variable inter-rater reliability has been demonstrated (r = .32 to .76), however this was greater for lower EDSS scores (<3.5) – relevant to the present study (Meyer-Moock, et al., 2014). Psychometric properties are given for the physician administered EDSS. However, due to the significant relationship of this with the telephone administered EDSS (Lechner-Scott, 2003) similar psychometrics can be inferred.

2.8.2.2. NARCOMS-Tremor and Coordination Scale (North American Research Committee on MS Registry, NARCOMS-TACS; Marrie & Goldman, 2011): This scale is a single response questionnaire-based measure, comparing current condition to experiences before developing MS. This defines tremor as "the rhythmic shaking of the head, hands or legs" and loss of coordination as "clumsiness or imbalance (e.g. staggering gait or unsteady gait like being drunk)" (Marrie & Goldman, 2011, p119). Responses include 'normal' (0), 'minimal tremor or loss of coordination' (1), 'mild tremor or loss of coordination' (2), 'moderate tremor or loss of coordination' (3), 'severe tremor or loss of coordination' (4), 'total disabling tremor or loss of coordination' (5). Each provides a subsequent descriptor of frequency of tremor or loss of coordination, as well as the impact on changing daily activities. The scale has shown adequate criterion validity (correlation with an external criterion or gold standard measure) for those with an EDSS of 0-6.5. The NARCOMS-TACS correlated with cerebellar functional system score (r = .51) and the 9HPT (r = -.51) as well as hand and mobility domains of the Performance Scales (Marrie & Goldman, 2011). Performance Scales are a validated patient report measure of eight physical and mental domains (Schwartz, Vollmer, Lee & NARCOMS, 1999). Construct validity was adequate, as the

NARCOMS-TACS was moderately to strongly correlated with Performance Scales, EDSS, 9HPT and cerebellar FSS.

2.8.2.3. The Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989): The FSS is a nine-item questionnaire assessing subjective impacts of fatigue on functioning (e.g. motivation, physical functioning, employment) over the past week (see *Appendix 18*). Responses are marked on a seven category Likert scale (1 = strongly disagree; 7 = strongly agree), and a mean response is calculated. Krupp et al. (1989) reported the FSS demonstrated excellent internal consistency ($\alpha = .81$ for people with MS and $\alpha = .88$ within the healthy population) and good test-retest reliability. A difference between people with MS and the general population was found after controlling for depression ($P < .001$) (Armutlu et al., 2007).

2.8.2.4. The Hospital Anxiety and Depression scale (HADS; Zigmond and Snaith, 1983): the HADS is a 14-item scale with seven statements measuring anxiety (HADS-A) and seven measuring depression (HADS-D) (see *Appendix 17*). The scale reduces the focus on aspects of anxiety and depression that are common somatic symptoms of illness (sleep disturbance, fatigue, appetite changes). Therefore, it is more specific when assessing anxiety and depression with individuals with long-term conditions such as MS. The HADS has been demonstrated to be more effective than the Beck Depression Inventory-Fast Screen (BDI-FS) at predicting functional outcomes in those with depression in the context of MS (Hanna et al., 2016). Each item is rated 0-3, with higher ratings pertaining to higher symptom severity. The range of the HADS-A and HADS-D is 0-21. HADS-A and HADS-D demonstrate good internal consistency ($\alpha = .82$ and .83 respectively) (Honarmand & Feinstein, 2009). One systematic review

reported that caseness for anxiety and depression was 8/21 with a specificity of 78% and sensitivity of 90% for anxiety, and a specificity of 79% and sensitivity of 83% for depression (Bjelland, et al., 2002). It has also been demonstrated to be sensitive to depression and anxiety in MS (Watson, Ford, Worthington, & Lincoln, 2014). Zigmond and Snaith (1983) provide cut-off scores of 0-7 (normal range), 8-10 (mild range), 11-14 (moderate range), 15-21 (severe range).

2.8.3. Peg Tests

2.8.3.1 Nine-hole peg test (9HPT; Mathiowetz, Weber, Kashman & Volland, 1985)*:* The 9HPT (see *Appendix 22*) This provides a quantification of extremity function and physical disability. It is used as part of the multiple sclerosis functional composite measure (MSFC; Fischer, Rudick, Cutter, & Reingold, 1999) for research and clinical purposes. Participants are required to pick up pegs from the container with one hand and place them in the holes in any order until all holes are filled, subsequently, without pausing removing them one at a time and returning them to the container. This is completed twice for each hand (beginning with the dominant hand). Scores are derived from time taken to complete the task. Solari et al. (2005) report a high inter-rater (r = .84 - .96) and intra-rater (r = .91 - .99) reliability. This measure has very good internal consistency (α = .93) Rasova, Martinkova, Vyskotova and Sedova (2012), and high test-retest reliability (r = .88). Concurrent validity between the EDSS score and 1-year change (r = .27) (Cutter et al., 1999). Poor performances have been demonstrated to be indicative of cerebellar atrophy (Ruet et al., 2014; van de Pavert et al., 2016). This has been widely utilised as a measure of upper extremity tremor (Alusi, Worthington, Glickman, Findley & Bain, 2000; Fox, Bain, Glickman, Carroll & Zajicek, 2000).

2.8.3.2. The Grooved Pegboard Test (GPT; Matthews & Klove, 1964): The test consists of a pegboard with 25 holes (see *Appendix 23*). Canoe-shaped pegs must be precisely oriented and inserted into differentially oriented canoe-shaped holes. This has a high motor planning demand compared to the 9HPT, due to the precise orientation required. First the researcher demonstrates placing five pegs in the top five holes, leaving 20 for the participant to complete. The participant then completes the remaining holes, ensuring that they fill holes sequentially from the opposite side of the board to the hand that they are using, completing a line and then returning to the opposite side from the hand that they are using, until all lines are completed. This is completed once for each hand (beginning with the dominant hand) and a mean score is taken. This tests manipulative dexterity, and requires more motor planning and co-ordination than the 9HPT. It demonstrates marginal/high test-retest reliability within healthy controls (r = .67 to .86) (Dikmen et al., 1999; Levine et al., 2004; Ruff & Parker, 1993). It has modest concurrent validity with relation to tapping speed (Schear & Sato, 1989). Kessler et al. (1991) have demonstrated a weak/modest association with activities of daily living and GPT scores in MS.

2.8.3.3. Motor Planning Index (MPI) The MPI was calculated to provide a measure of motor planning. This was calculated by subtracting the 9HPT time from the GPT time. This procedure is based on subtraction logic (Shoeben, 1982) which suggests that one can subtract time taken to complete a task from time taken to complete a similar task (aside from one critical component) to measure the critical component. Early experimental designs for IPS and attention in MS utilised this construct for calculation of motor programming, and controlled processing speed, amongst other constructs (Kujala, Portin, Revonsuo, & Ruutiainen, 1994; 1995). Difference scores (subtraction

logic) are still commonplace in more recent MS literature (Roth, Denney, & Lynch, 2015). This MPI assumes that the GPT and 9HPT have the same sensorimotor component, and GPT has a greater motor planning element. Assuming this, subtracting 9HPT from GPT will provide an indication of the time of the motor planning component. Criticisms of this index are discussed in *section 4.2.1*.

2.9. Counterbalancing

To experimentally control for order effects on the pegboard tests, counterbalancing procedures were performed, where half of participants for each group performed the 9HPT first and half performed the GPT first. This was to avoid non-specific practice effects, as well as effects of fatigue on performance. Random number sheets were created using SPSS Statistics 21.0 (IBM, 2012). Participants were allocated a random number following group allocation to ensure that counterbalancing was successful for each group.

2.10. Participant information material development

Participant information sheets for MS participants (see *Appendix 5*), were reviewed by a specialist occupational therapist and specialist physiotherapist. Amendments in accordance to their feedback were made.

2.11. Procedure

Participants were informed of the structure of the assessment and the estimated time of 60-90 minutes, and given an opportunity to ask questions. Participants were informed that they would not receive individualised feedback at the end of the session. Participants were informed that they could opt in to receive a summary of the research, by indicating a preference on the consent form (see *Appendix 6* and *Appendix 10*). Written informed consent was gained and participants were informed of their ethical and legal rights.

Demographic information (gender, age, and educational level) was gathered through self-report. Individuals with MS also provided their time since diagnosis through self-report. Closed questions around inclusion/exclusion criteria were also presented before beginning data collection. Questionnaires were administered first. Following administration of questionnaires, MS participants were allocated to RR-MSnc or RR-MSc and were assigned their randomised number 0/1 for counterbalancing purposes. The questionnaires, pegboard tests and cognitive tests were administered in the order demonstrated in *Table 2*.

2.12. Measure administration order

Table 2: Questionnaire, cognitive test and pegboard administration order

Procedure	Tests administered
Questionnaires	1. EDSS Telephone Version
	2. NARCOMS-TACS
	3. FSS
	4. HADS
Pegboard Test 1	5. 9HPT/GPT*
Cognitive Tests	6. TOPF
	7. SDMT
	8. CVLT-II Learning Trials
	9. BVMT-R Learning Trials
Pegboard Test 2	10. 9HPT/GPT*
Cognitive Tests	11. WLG
	12. PASAT3

* order determined by counterbalancing procedure

2.13. Neuropsychological testing

Standardised procedures were adhered to as per individual test guidelines. This allows for replication of the study, comparison of the study findings with other research and a standardised procedure within the present study. This also allowed for comparisons to published norms to determine cognitive impairment within the samples and compare

the samples for generalisability to the population. Testing was completed in one session for all participants, however participants were aware they could request breaks.

Every effort was made to reduce potential distractors within the physical environment, including requesting participants to turn of audio and visual equipment. Where possible participants were requested to sit opposite the researcher at a table. This allowed for standardised presentation of stimulus materials, and standardisation for peg tests (regarding ease of manipulation of materials). A stopwatch was used for timed tasks.

Testing was carried out by the researcher (a trainee clinical psychologist), following demonstration of competence to a Professor of Neuropsychology.

2.14. Analysis

Data were analysed utilising a software package for statistical analysis Statistical Package for the Social Sciences 21.0 (SPSS; IBM Corporation, 2012). All variables were analysed for normality of distribution. Positively skewed data were transformed utilising square root, log10 and inverse transformations successively until normality was sufficient for parametric analyses. Negatively skewed data were transformed utilising reflections of the above, and power transformations (2-4) until normality was sufficient for parametric analyses.

Data were examined to ascertain whether the groups were comparable with regards to gender, pre-morbid intelligence, EDSS and age. A chi-square test was carried out to determine whether groups were matched for gender (as self-defined gender was binary

within the present study). A one-way ANOVA was utilised to ascertain whether the groups differed significantly for pre-morbid intelligence estimates, depression, anxiety and fatigue.

Differences in pre-morbid intelligence estimates resulted in entering them as co-variates within an ANCOVA to statistically control for influence on other variables. A between-groups one-way ANCOVA was utilised to compute differences between cognitive/peg test variables (9HPT; SDMT; CVLT-II learning trials; BVMT-R learning trials; GPT; WLG; PASAT3). Planned contrasts were conducted to look for differences between group means. If data were normally distributed, these would have been conducted utilising post-hoc least significant difference (LSD) tests. However, if data were not normally distributed Games-Howell tests would be utilised in accordance with Field (2013). All statistical analyses used an alpha of (α <.05) for determining significance. The alpha values were not adjusted for multiple corrections for reasons discussed in later sections (see *section 3.2.*). Fisher transformations were utilised to compare strength of correlation coefficients between MPI and cognitive test variables.

3. Results

3.1. Exploratory Data Analysis

All data analysis was carried out using IBM SPSS Statistics 21.0 (2012). The dataset was checked for completeness and there were no missing data. Data was checked for accuracy of scoring by a professor of neuropsychology. Visual inspection and considerations of descriptive statistics demonstrated accurate data entry.

The data were examined to determine whether the assumption of normality was met, required for parametric testing. A cut-off of ±2.58 ($p < .01$) was considered for kurtosis and skew as suggested by Tabachnick and Fidell (2013). Control data were skewed for SDMT and negatively skewed for TOPF. RR-MSnc data were positively skewed for 9HPT and MPI. GPT and MPI were positively skewed for the RR-MSc group (see *Appendix 24*).

Tabachnick and Fidell (2013) suggest using square-root transformations for moderately positively skewed data. The 9HPT was significantly positively skewed for RR-MSnc ($z = 2.73$, $p < .01$). A square-root transformation was carried out on 9HPT scores. For substantially positively skewed data, Tabachnick and Fidell (2013) recommend a logarithmic transformation (Log10). GPT was significantly positively skewed within the RR-MSc group ($z = 3.34$, $p < .01$) and MPI was significantly positively skewed for the RR-MSnc group ($z = 2.79$, $p < .01$) and RR-MSc group ($z = 3.38$, $p < .01$). Data were transformed with a log10 transformation. Skew and kurtosis fell below ±2.58 for

all groups following transformations and thus these met normality assumptions for parametric statistical procedures ($p < .01$) (see *Appendix 24*).

SDMT was significantly positively skewed within the healthy controls (HC) ($z = 3.09$, $p < .01$). These were transformed using a square-root transformation. Following these transformations, data were still minorly skewed ($z = 2.64$ $p < .01$). However, this was deemed normal enough for parametric assumptions ($p < .001$). Premorbid intelligence estimates (pFSIQ) were significantly negatively skewed within HC ($z = -3.81$, $p < .01$). These were transformed using an x^4 transformation, which resulted in minor skew following transformation ($z = -2.62$, $p < .01$). However, these were deemed normal enough for parametric assumptions ($p < .001$). SDMT and pFSIQ transformations were very close to the ±2.58 value for ($p < .01$) and thus normality was assumed (see *Appendix 24*).

3.2. Statistical Analyses

When repeat analyses are required, post-hoc adjustments of the p-value are often implemented. These are designed to reduce the chance of making a type-I error due to familywise error. A criticism of these adjustments is that they are overly conservative (Coolican, 2014; Perneger, 1998) and thus result in type-II error. Within the current study, repeated analyses were required due to the number of cognitive tests and pegboard tests within the battery. Correcting p-values would result in a very stringent p-value. Thus, following recommendations by Perneger (1998), post-hoc adjustments were not implemented, however results should be considered in the context of a raised

propensity for type-I error. Therefore, outputs were presented as least statistical difference (LSD) values.

3.3. Demographic Variables

An overview of descriptive statistics for demographic variables is presented in *Table 3*.

3.3.1. Age

Participants were aged between 23 and 59 (M = 38.96, SD = 10.02). In the HC group ages ranged from 23 to 59 (M = 37.05, SD = 12.39), in the RR-MSnc group ages ranged from 25 – 52 (M = 39.81, SD = 8.05), and in the RR-MSc group ages ranged from 27 – 53 (M = 40.57, SD = 8.88). A one-way independent ANOVA was used to compare mean group ages, which revealed no significant difference between groups ($F(2,53) = .63$, $p = .536$). Age was therefore not considered in subsequent analyses.

3.3.2. Gender

The sample was comprised of 23 males and 33 females, a ratio of 1.43:1 for the full sample and a ratio of 1.69:1 for the MS sample alone. Within groups, the ratio (M:F) of the HC group was (10:11), RR-MSnc was (6:15), RR-MSc was (7:7). Pearson Chi-Square revealed no significant difference in gender between groups ($\chi^2(2) = 2.19$, $p = .335$). Therefore, gender was not considered in subsequent analyses.

3.3.3. Estimated Premorbid IQ

Estimated premorbid IQ (pFSIQ) was calculated with the TOPF scorer programme (Wechsler, 2011). This calculates pFSIQ based on age, gender, TOPF raw score, and years of education. pFSIQ ranged from 79.0 to 127.5 (M = 109.17, SD = 11.28). The HC group pFSIQ ranged from 91.8 to 123.1 (M = 115.34, SD = 7.49), the RR-MSnc group ranged from 79 to 127.5 (M = 109.22, SD = 12.33), and the RR-MSc group from 86.9 to 118.5 (M = 99.83, SD = 7.88).

An independent ANOVA compared the differences between groups in pFSIQ. The three groups differed significantly on pFSIQ scores $F(2,53) = 10.64$, $p < .001$). Levene's test of homogeneity of variance provided a significant result ($F(2,53) = 4.37$ $p = .018$) indicating variance assumptions were not met, and thus planed comparison Games-Howell tests were used. Games-Howell tests demonstrated that the HC group had a significantly higher pFSIQ than the RR-MSc group ($p < .001$). The RR-MSnc also had a higher pFSIQ than the RR-MS ($p = .015$). The RR-MSnc and HC group did not significantly differ ($p = .203$).

Due to the significant difference identified, and the correlation of IQ with all cognitive domains (O'Carroll, 1995) pFSIQ scores will be added as a covariate within subsequent analyses.

3.4. Clinical Variables

An overview of descriptive statistics for clinical variables is presented in *Table 4.*

3.4.1. Symptoms of depression and anxiety

Zigmond and Snaith (1983) report clinically significant cut-offs of HADS-A and HADS-D. Scores are categorised in the normal range (0-7), mild range (8-10) moderate range (11-14) and severe range (15-21). Caseness for anxiety or depression can be defined by scores of less than eight, i.e. those outside of the normal range (Bjelland, et al., 2002).

Scores on the HADS-D ranged from 0 – 14. Within the HC group scores ranged from 0 - 5 (M = 1.24, SD = 1.61) with all participants falling within the normal range (caseness: 0%). Within the RR-MSnc group scores ranged from 0 – 13 (M = 5.19, SD = 3.88), with 16 falling in the normal range, three in the mild range and two in the moderate range (caseness: 24%). Within the RR-MSc group scores ranged from 2 – 14 (M = 7.29, SD = 3.58), with seven in the normal range, five in the mild range and two in the moderate range (caseness: 50%). An independent ANOVA was carried out to compare the differences between groups for HADS-D self-reported scores. This demonstrated a significant difference between groups ($F(2,53) = 17.23$, $p < .001$). Levine's test of homogeneity of variance provided a significant result ($F(2,53) = 6.57$, $p = .003$), indicating variance assumptions were not met, and thus Games-Howell tests were used for planned comparisons. Games-Howell tests demonstrated that the HC group had significantly lower HADS-D scores than the RR-MSnc ($p = .001$) and RR-

MSc group ($p < .001$). The RR-MSc and RR-MSnc group did not differ significantly ($p = .246$).

Scores on the HADS-A ranged from 0 – 16. Within the HC group, scores ranged from 0 – 12 ($M = 4.29$, $SD = 2.88$) with 20 falling in the normal range and one in the moderate range (caseness: 5%). Within the RR-MSnc group scores ranged from 1 – 12 ($M = 6.29$, $SD = 3.61$) with 13 in the normal range, five in the mild range and three in the moderate range (caseness: 38%). Within the RR-MSc group scores ranged from 2 – 16 ($M = 7.43$, $SD = 3.80$), with nine in the normal range, two in the mild range, two in the moderate range and one in the severe range (caseness: 36%). An independent ANOVA was carried out to compare the differences between groups for HADS-A self-reported scores. This demonstrated a significant difference between groups ($F(2,53) = 3.89$, $p = .026$). Planned comparisons demonstrated a significant difference between the HC group and RR-MSc ($p = .01$) but no significant difference between HC and RR-MSnc ($p = .062$) and RR-MSnc and RR-MSc ($p = .335$).

The significant differences found between HC and both MS groups on HADS-D and the HC and RR-MSc on HADS-A are discussed in later sections (see *section 4.1.1*).

3.4.2. Years since diagnosis

Within the MS groups, years since diagnosis ranged from 0.09-22 years ($M = 6.34$, $SD = 6.36$). Within the RR-MSnc group, years since diagnosis ranged from 0.17 to 17 years ($M = 4.79$, $SD = 4.80$). In the RR-MSc group years since diagnosis ranged from 0.09 – 22 years ($M = 8.65$, $SD = 7.78$). An independent t-test was used to compare the years

since diagnosis for the RR-MSnc and RR-MSc groups. Separate variance estimates were used since homogeneity of variance assumptions were not met ($F = 9.24$, $p = .005$). There was no statistically significant difference between the two groups regarding years since diagnosis ($T(20) = -1.66$, $P = .114$). This will not be considered in subsequent analysis.

3.4.3. EDSS Scores

EDSS scores were computed from the verbally administered telephone EDSS (Lechner-Scott et al., 2003). Within the MS groups, EDSS scores ranged from 0 to 5 ($M = 2.24$, $SD = 1.97$). The RR-MSnc group ranged from 0 to 5 ($M = 2.08$, $SD = 1.05$), and the RR-MSc group ranged from 3.5 to 5.0 ($M = 4.50$, $SD = .55$). An independent t-test demonstrated a significantly higher EDSS in RR-MSc than RR-MSnc ($t(33) = -4.95$, $p < .001$). The differences between groups will not be considered within the analysis, and reasons for this discrepancy is discussed in later sections (*see section 4.4.5.5.*).

3.4.4. Fatigue

Total score was calculated from the FSS responses and the mean response was calculated. Individuals who scored FSS < 4 were considered to have no fatigue, those scoring FSS 4-5 were within the borderline range, and those with FSS > 5 were considered to be fatigued. In the HC group FSS scores ranged from 1.11 to 4.56 (M = 2.45, SD = 1.05), with three individuals meeting the borderline range for fatigue. In the RR-MSnc group FSS scores ranged from 1 to 6.56 (M= 4.19, SD = 1.55), with three individuals meeting the borderline range for fatigue, and 9 individuals meeting clinically significant fatigue. In the RR-MSc group FSS scores ranged from 2.67 to 6.67 (M = 5.11, SD = 1.39), with two individuals meeting the borderline range for fatigue, and 8 individuals meeting the clinically significant range for fatigue. An independent ANOVA was carried out to compare the differences between groups for FSS mean self-reported scores. This demonstrated a significant difference between the group ($F(53,2) = 18.22$, $p < .001$). Planned comparisons demonstrated significant differences between the HC group, RR-MSnc ($p < .001$) and RR-MSc ($p < .001$). There was no significant difference between RR-MSnc and RR-MSc ($p = .052$). The impact of the differences in fatigue between the HC group and MS participants will be discussed in *section 4.1*.

3.4.5. NARCOMS-TACS Criterion Validity

It is essential to consider the criterion validity of the NARCOMS-TACS, as this is the sole measure used for identification of cerebellar symptoms for group allocation. A similar procedure to Marrie and Goldman (2011) was used to ascertain the criterion validity of the NARCOMS-TACS for the current study. This used Spearman's rank

correlations with casewise deletion. There were moderate to strong positive correlations between NARCOMS-TACS and 9HPT ($r = .61$, $p < .001$), GPT ($r = .53$, $p < .001$), MPI ($r = .44$, $p < .001$), and EDSS ($r = .81$, $p < .001$). This demonstrates adequate criterion validity of the NARCOMS-TACS to the peg tests and motor planning index. The 9HPT is widely utilised as a measure of upper limb tremor (Alusi et al., 2000; Fox et al., 2000). This is of interest as the previous validation only had three percent of individuals reported severe tremor (Marrie & Goldman, 2011). Using Fishers transformation on the correlation coefficients, there is no significant difference between the strength of the correlations (9HPT vs GPT: $z = .12$, $p = .90$; 9HPT vs MPI: $z = .36$, $p = .71$; GPT vs MPI: $z = .24$, $p = .81$).

Table 3: Descriptive statistics for demographic variables

		Gender	Age		Years Education		Employment	Premorbid IQ	
	N	M:F	$\bar{x}$ (SD)	Range	$\bar{x}$ (SD)	Range	F:P:U:S*	$\bar{x}$ (SD)	Range
HC	21	[10]:11	37.05 (12.39)	23 - 59	17.29 (2.45)	11 - 21	20:1:0:0	115.34 (7.49)	91.80 - 123.10
RR-MSnc	21	6:15	39.81 (8.05)	25 - 52	16.57 (3.09)	11 - 22	12:7:2:0	109.22 (12.33)	79.00 - 127.50
RR-MSc	14	7:7	40.57 (8.88)	27 - 53	13.86 (2.07)	12 -19	5:1:7:1	99.83 (7.88)	86.90 - 118.50

**F: Full time; P: Part time, U: Unemployed, S: Extended sick leave*

Table 4: Descriptive statistics for clinical variables

	Years since diagnosis		EDSS		NARCOMS		FSS		HADS-D		HADS-A	
	$\bar{x}$ (SD)	Range	$\bar{x}$ (SD)	Range	$\bar{x}$ (SD)	Range	$\bar{x}$ (SD)	Range	$\bar{x}$ (SD)	Range	$\bar{x}$ (SD)	Range
HC	-	-	-	-	-	-	2.45 (1.05)	1.11-4.56	1.24 (1.61)	0–5	4.29 (2.88)	0–12
RR-MSnc	4.79 (4.80)	0.17-17.00	2.98 (1.05)	0–5	0.81 (0.75)	0 - 2	4.19 (1.55)	1.00-6.56	5.19 (3.88)	0–13	6.29 (3.61)	1–12
RR-MSc	8.65 (7.78)	0.09-22.00	4.50 (0.55)	0-5	4.14 (0.36)	4 - 5	5.11 (1.39)	2.67–6.67	7.29 (3.58)	2–14	7.43 (3.80)	2-16

3.5. Cognitive Tests

ANCOVAs covarying pFSIQ were conducted for cognitive tests between the three groups. Descriptive statistics are provided for each cognitive test in *Table 5*. ANCOVA F values, as well as significance values (p = .05) are provided for ANCOVAs and planned comparisons in *Table 6*. The ANCOVAs revealed statistically significant differences for the CVLT-II ($F(3,52) = 3.42$, $p = .002$), the BVMT-R ($F(3,52) = 2.93$, $p = .004$), the PASAT3 ($F(3,52) = 12.89$, $p < .001$), and the SDMT ($F(3,52) = 7.81$, $p < .001$) whilst statistically controlling for pFSIQ. No significant differences were found in the WLG ($F(3,52) = 2.55$, $p = .07$). Planned comparisons for the CVLT-II revealed a significant difference between HC and RR-MSc ($p = .01$), and between RR-MSnc and RR-MSc ($p = .008$) but no significant difference between HC and RR-MSnc ($p = .85$). Planned comparisons for BVMT-R revealed a significant difference between HC and RR-MSc ($p = .038$) but no significant difference between HC and RR-MSnc ($p = .40$) or between RR-MSnc and RR-MSc ($p = .11$). Planned comparisons for PASAT3 revealed significant differences between HC and RR-MSc ($p = .0.13$) and between RR-MSnc and RR-MSc ($p = .047$) but not between HC and RR-MSnc ($p = .37$). Planned comparisons for SDMT demonstrated significant differences between HC and RR-MSnc ($p = .038$), between HC and RR-MSc ($p < .001$) and between RR-MSnc and RR-MSc ($p = .025$).

Table 5: Descriptive statistics for cognitive tests

	HC		RR-MSnc		RR-MSc	
	M (SD)	*Range*	*M (SD)*	*Range*	*M (SD)*	*Range*
SDMT	59.52 (9.62)	48-88	51.57 (10.80)	23-73	42.07 (11.50)	21-62
CVLT-II	50.14 (8.71)	35-64	49.91 (11.51)	32-72	40.14 (9.43)	22-58
BVMT-R	26.14 (6.16)	11-34	23.62 (8.11)	8-33	18.21 (9.74)	6-30
WLG	28.33 (5.70)	20-44	27.52 (5.47)	19-36	23.64 (5.06)	14-30
PASAT3	50.33 (7.39)	34-60	45.67 (8.92)	24-56	35.43 (11.55)	17-54
SDMT Sqrt	7.69 (0.60)	6.93-9.38	7.14 (0.79)	4.8-8.54	6.43 (0.92)	4.58-7.87

Table 6: ANCOVA and planned comparisons for cognitive tests

	ANCOVA		Post Hoc Tests (Least Significant Difference)		
	ANCOVA F	*Significance*	*HC vs RR-MSnc*	*HC vs RR-MSc*	*RR-MSnc vs RR-MSc*
CVLT-II	3.42	.024*	.85	.01*	.008*
BVMT-R	2.93	.042*	.40	.038*	.11
WLG	2.55	.070	.83	.12	.13
PASAT3	12.89	< .001*	.37	.013*	.047*
SDMT Sqrt	7.81	< .001*	.038*	< .001*	.025*

3.6. Pegboard Tests

ANCOVAs covarying pFSIQ were conducted for the pegboard tests between the three groups. Descriptive statistics for pegboard tests are provided in *Table 7*. The motor planning index (MPI) was computed by subtracting the 9HPT from the GPT as described in the methodology. *Figure 1* demonstrates a box plot of the MPI, demonstrating graphically the differences in means, as well as presenting the interquartile range. This was compared with ANCOVAs covarying pFSIQ between the groups. F values, as well as significance values ($p = .05$) are provided for ANCOVAs and planned comparisons in *Table 8*. The ANCOVAs revealed significantly significant differences between groups on the 9HPT ($F(3,52) = 20.04$, $p < .001$), GPT ($F(3,52) = 20.15$, $p < .001$), and the MPI ($F(3,52) = 16.75$, $p < .001$). Planned comparisons revealed statistically significant differences on the 9HPT between HC and RR-MSnc ($p = .01$), between HC and RR-MSc ($p < .001$) and between RR-MSnc and RR-MSc ($p < .001$). Planned comparisons revealed statistically significant differences on the GPT between HC and RR-MSnc ($p = .001$), between HC and RR-MSc ($p < .001$) and RR-MSnc and RR-MSc ($p < .001$). Planned comparisons revealed statistically significant differences on the MPI between HC and RR-MSnc ($p = .001$), between HC and RR-MSc ($p < .001$) and between RR-MSnc and RR-MSc ($p < .001$).

Table 7: Descriptive Statistics for pegboard tests

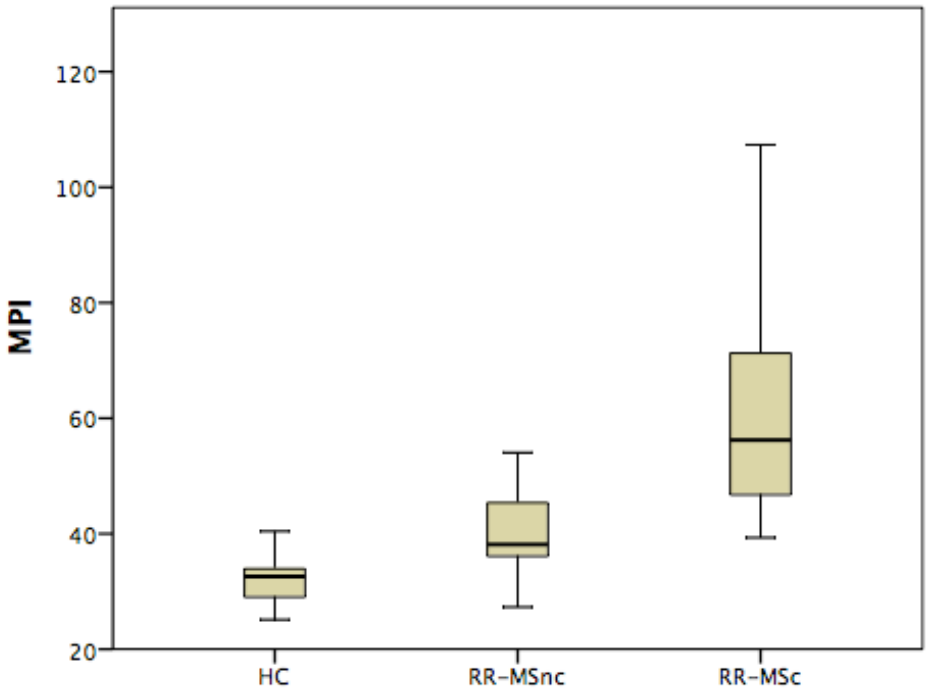
	HC		RR-MSnc		RR-MSc	
	M (SD)	*Range*	*M (SD)*	*Range*	*M (SD)*	*Range*
9HPT	19.12 (2.00)	15.83-22.77	22.29 (4.01)	17.63-33.75	28.95 (5.09)	21.71-37.18
GPT	51.67 (5.34)	43.36-62.10	65.92 (16.75)	45.25-103.81	94.61 (32.98)	66.79-186.02
MPI	32.55 (4.27)	25.13-40.42	43.63 (14.11)	27.30-82.09	65.66 (29.81)	39.32-148.84
9HPT Sqrt	4.37 (0.23)	3.98-4.77	4.70 (0.41)	4.20-5.81	5.36 (0.47)	4.66-6.10
GPT Log10	1.71 (0.04)	1.64-1.79	1.81 (0.10)	1.66-2.02	1.96 (0.13)	1.82-2.27
MPI Log10	1.51 (0.06)	1.40-1.61	1.62 (0.13)	1.44-1.91	1.79 (0.16)	1.59-2.17

Table 8: ANCOVA and planned comparisons for pegboard tests

	ANCOVA		Post Hoc Tests (Least Significant Difference)		
	ANCOVA F	*Significance*	*HC vs RR-MSnc*	*HC vs RR-MSc*	*RR-MSnc vs RR-MSc*
9HPT Sqrt	20.04	< .001*	.01*	< .001*	< . 001*
GPT Log10	20.15	< .001*	< .01*	< .001*	< .001*
MPI Log10	16.75	< .001*	< .01*	< .001*	< .001*

3.6.1. Motor planning index

Figure 1: Motor planning index boxplot



3.7. Defining cognitive impairment

A cognitive impairment index was created for each participant. The index was computed utilising a similar procedure to previous published neuropsychological studies (e.g. Camp et al., 2005). Data were compared with published neuropsychological norms. SDMT, CVLT-II learning trials, BVMT-R learning trials, and PASAT3 utilised UK norms from Orchard, Giovannoni and Langdon (2013). WLG utilised Dutch norms from Boringa et al. (2001) as no UK norms are available. Participants were assigned a cognitive impairment grade for each cognitive test based on the number of standard deviations they fell below the published norm. Individuals were assigned grade zero if the score was greater than or equal to the published norm, a grade of one if the score was less than one standard deviation below the mean, a grade of two if the score was between one standard deviation and two standard deviations between the mean, and a grade of three if the score was more than two standard deviations below the mean. HC cognitive impairment index ranged from 0-9 ($M = 4.19$, $SD = 2.44$), RR-MSnc from 0-12 ($M = 5.86$, $SD = 3.77$) and RR-MSc from 2-15, RR-MSnc and RR-MSc ($M = 9.07$, $SD = 3.91$). A one-way ANOVA demonstrated a significant difference between groups ($F(53,2) = 8.85$, $p < .001$). Planned comparisons revealed significant differences between HC and RR-MSc ($p < .001$) and RR-MSnc and RR-MSc ($p = .008$). No significant difference was found between HC and RR-MSnc.

'Failure' on a test was defined as 1.5 standard deviations below the published norm as fitting with BICAMS recommendations (Langdon et al., 2012). 'Failing' three tests was considered widespread cognitive impairment. *Table 9* provides the frequency and

proportion of individuals 'failing' each cognitive task, and the frequency and proportion of individuals with widespread cognitive impairment.

Table 9: Frequency of failed tests

	HC (%)	RR-MSnc (%)	RR-MSc (%)
SDMT	0 (0%)	5 (24%)	10 (71%)
CVLT-II	8 (38%)	8 (38%)	9 (64%)
BVMT-R	4 (19%)	6 (29%)	8 (57%)
WLG	9 (43%)	10 (48%)	9 (64%)
PASAT3	1 (5%)	3 (14%)	6 (43%)
Widespread cognitive impairment	1 (5%)	6 (29%)	8 (57%)

As data was compared with published norms for creation of cognitive impairment index, pFSIQ was not entered as a covariate within the analysis. Within the utilised published norms the estimated pFSIQ (derived from TOPF) was (M = 110.45, SD = 8.48) for people with MS and (M = 111.03, SD = 8.75) for HCs. This is equivalent to the pFSIQ for HC and RR-MSnc within the current study (HC: M = 115.34, SD = 7.49; RR-MSnc M = 109.22, SD = 12.33), however RR-MSc (M = 99.83, SD = 7.88) appeared to have a lower premorbid IQ than the utilised data. Due to this, it could it could be argued that the RR-MSnc group would have less impairment than the RR-MSc group because of a higher cognitive reserve associated with higher pFSIQ and thus less cognitive impairment.

3.8. Sample representativeness

Table 10 compares published norms mean MS scores for SDMT, CVLT-II learning trials, BVMT-R learning trials, PASAT3 (Orchard, Giovannoni & Langdon, 2013) and WLG (Boringa et al., 2001) with mean MS scores from the present study (combining RR-MSnc and RR-MSc). No normative data was present for WLG. MS mean scores showed a high level of similarity to MS norms.

Table 10: Descriptions of published norms and current study data

	Mean (SD) HC norms[1]	Mean (SD) HC[2]	Mean (SD) MS norms[1]	Mean (SD) RR-MS[2]
SDMT	62.2 (9.8)	59.52 (9.62)	47.8 (14.0)	47.77 (11.89)
CVLT-II Learning trials	55.9 (12.4)	50.14 (8.71)	47.3 (12.4)	46.00 (11.64)
BVMT-R Learning trials	27.6 (5.0)	26.14 (6.16)	21.4 (6.9)	21.46 (9.07)
PASAT 3	50.5 (8.7)	50.33 (7.39)	42.6 (13.8)	41.57 (11.13)
WLG	26.3 (6.1)	28.33 (5.70)	-	25.97 (5.58)

[1]Boringa et al. (2001); Orchard, Giovannoni and Langdon, (2013)

[2]Current Study: Combined RR-MSnc and RR-MSc scores

Due to the relatively small MS sample size (n = 35) and control sample size (n = 21), it is of importance to consider whether the sample is typical of the population. By comparing the sample means with published norms (*Table 10*) we can infer that the current study has a relatively typical sample of the population.

3.9. Association between motor functioning and cognitive function

To test the associations between motor planning and cognitive function, partial correlations (covarying pFSIQ) were carried out between MPI and all cognitive variables. Partial correlations were carried out between SDMT and MPI whilst controlling pFSIQ. Higher scores on the SDMT were significantly associated with reduced MPI whilst controlling for pFSIQ ($r(53) = -.55$, $p < .001$), demonstrating a strong negative correlation. r^2 values were calculated to demonstrate the amount of variance shared by SDMT and MPI whilst controlling for pFSIQ, indicating 30% ($r^2 = .30$) of MPI variance was shared with SDMT. Partial correlations were carried out between PASAT3 and MPI. Higher scores on the PASAT3 were significantly associated with reduced MPI whilst controlling for pFSIQ ($r(53) = -.33$, $p = 013$), demonstrating a moderate negative correlation. 11% of PASAT3 variance was shared with MPI ($r^2 = .11$). Partial correlations were carried out between BVMT-R and MPI ($r(53) = -.44$, $p < .001$) demonstrating a moderate negative correlation. 19% of BVMT-R variance was shared with MPI ($r^2 = .19$). Partial correlations were carried out between CVLT-II and MPI ($r(53) = -.35$, $p = .01$), demonstrating a moderate negative correlation. 12% of CVLT-II variance was shared with MPI ($r^2 = .12$). Partial correlations were carried out between WLG and MPI whilst controlling for pFSIQ ($r(53) = -.18$, $p = .18$) indicating no significant correlation. 3% of the variance of WLG variance was shared with the MPI ($r^2 = .03$).

For the hypothesis that motor planning is associated with IPS to be tested, one must compare the correlations between IPS and MPI as well as IPS and the pegboard tests, as a significantly stronger correlation should be noted between MPI/GPT than 9HPT.

Partial correlations were carried out between SDMT and PASAT3. *Table 11* presents the correlation coefficients and statistical significance of these.

Table 11: Correlations of IPS with motor function and planning

	SDMT		PASAT3	
	r	**p**	**r**	**p**
9HPT	-.60	< .001*	-.44	.001*
GPT	-.61	< .001*	-.38	.004*
MPI	-.58	< .001*	-.33	.013*

Fisher transformations were computed to ascertain whether there was a statistically significant difference between correlation coefficients. For the SDMT, there was no significant difference between correlations coefficients for 9HPT v GPT ($z = -.13$, $p = .90$), GPT v MPI ($z = -.26$, $p = .79$) or 9HPT v MPI ($z = -.13$, $p = .89$). For the PASAT3, there was no significant difference between correlation coefficients for 9HPT v GPT ($z = -.38$, $p = .70$), GPT v MPI ($z = -.26$, $p = .79$), or 9HPT v MPI ($z = -.64$, $p = .52$). This suggests that information processing speed is not contributing more to the motor planning index than motor function.

3.10. Summary

The findings of the analysis demonstrated that all groups were successfully matched on age and gender. Groups were not matched for premorbid IQ and consequently this was entered as a covariate into subsequent analyses. Regarding clinical variables, MS

groups were matched for years since diagnosis. However, HC showed significantly fewer symptoms of depression than both MS groups and HC showed significantly fewer symptoms of anxiety than RR-MSnc. HC also demonstrated significantly fewer symptoms of fatigue than both MS groups. MS groups were not matched for EDSS scores. Regarding cognitive tests, HC significantly outperformed RR-MSc on all cognitive tests other than the WLG. HC significantly outperformed RR-MSnc only on SDMT. RR-MSnc significantly outperformed RR-MSc on SDMT, CVLT-II and PASAT3. The cognitive impairment index significantly differentiated RR-MSc from HC and RR-MSnc, but not HC from RR-MSnc. More than twice the frequency of widespread cognitive impairment was noted in the RR-MSc group than RR-MSnc group. On the tests of motor function and motor planning HC significantly outperformed RR-MSnc and RR-MSc, and RR-MSnc outperformed RR-MSc. There was a significant negative moderate-strong correlation between the SDMT, PASAT3, CVLT-II and BVMT-R and MPI. However, there were no significant differences between the strengths of the correlations for the MPI, GPT and 9HPT with measures of IPS.

4.0. Discussion

Significant research has demonstrated that a substantial proportion individuals with MS have cognitive impairment, which impacts on quality of life and daily functioning. The most significant deficits are with IPS. Some research has begun to consider cognitive profiles of RR-MSc. Research has also demonstrated a link with the cerebellum and motor function and motor planning. The present study aimed to consider differences between the cognitive profiles of individuals with RR-MSnc and RR-MSc, and consider how these relate to motor planning and function.

4.1. Hypothesis 1: RR-MSc will have a different cognitive profile to RR-MSnc and HC, demonstrated by worse performances on tests examining IPS, verbal memory, visual memory and verbal fluency

Groups significantly differed on all neuropsychological variables other than the WLG. Significant differences were only found between HC and RR-MSnc on SDMT. RR-MSnc significantly outperformed RR-MSc on CVLT-II, SDMT and PASAT3, but not the BVMT-R. HC significantly outperformed RR-MSc on all tests aside from WLG. This supports the notion that there is a difference in the cognitive profile between groups, and supports *Hypothesis 1* aside from differences in verbal fluency.

Age, gender and premorbid IQ are known to impact scores on cognitive tests. Within the current study, groups were matched for age and gender, and premorbid IQ was statistically controlled for. There was no significant difference between the two MS

groups in years since diagnosis. Therefore, these variables cannot account for the differences.

The HC group significantly differed in self-reported symptoms of fatigue from the MS groups (which did not significantly differ from each other). The lack of a significant difference between the two MS groups furthers the notion that cerebellar dysfunction does not contribute to the development of fatigue (Weier et al., 2014). Within the RR-MSnc group 43% met the clinically significant range for fatigue and 57% in the RR-MSc group, whereas no HCs fell in this range. Within the general population, most individuals with MS report clinically significant fatigue (Minden et al., 2006; Weiland et al., 2015). There have been mixed findings regarding the effects of self-reported fatigue on cognition, with some studies reporting significant impacts (Diamond, Johnson, Kaufman & Graves, 2008; Krupp & Elkins, 2000; Rotstein, O'Connor, Lee, & Murray, 2012; Weinges-Evers et al., 2010) and others reporting no significant difference (Beatty et al., 2003; Bol, Duits, Hupperts, Verlinden, & Verhey, 2010; Hanken, Eling & Hildebrandt, 2015; Johnson, Lange, DeLuca, Korn & Natelson, 1997; Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009; Niino et al., 2014; Parmenter, Denney, & Lynch, 2003; Paul et al., 1998). Overall, it appears that self-reported fatigue is not linked with objective cognitive performance. Thus, fatigue is unlikely to account for the difference in cognitive profile between the three groups.

The HC group also significantly differed in self-reported symptoms of depression from the MS groups (whom did not significantly differ from each other). 0% of HC, 24% of RR-MSnc and 50% of RR-MSc met caseness for depression. The HC group significantly differed in self-reported symptoms of anxiety from the RR-MSc group,

but not the RR-MSnc group. However, the two MS groups did not significantly differ from each other. Five percent of HC, 38% of RR-MSnc and 36% of RR-MSc met caseness for anxiety. These raised rates of common mental illness are representative of the MS population (Boeschoten et al., 2017). Depression and anxiety have been demonstrated to affect cognition in MS (Arnett, Higgonson, & Voss, 1999; Arnett, Higginson, & Randolph, 2001; Arnett et al., 1999; 2008; Bruce, Hancock, Arnett & Lynch, 2010; Chiaravolloti & Deluca, 2008; Figved et al., 2008; Golan et al., 2017; Goretti et al., 2014; Hanssen, Beiske, Landrø & Hessen, 2014; Lubrini et al., 2016; Morrow, Rosehart & Pantazopoulos, 2015; Niino et al., 2014, Raimo et al., 2016; Thornton & Raz, 1997). However, it was not possible to statistically control for these variables using ANCOVA as this would significantly reduce the power of the analysis and increase the likelihood of type-II error.

The prevalence of depression and anxiety is higher in the MS population than in the general population (Boeschoten et al., 2017) as is fatigue (Minden et al., 2006; Weiland et al., 2015). Therefore, it can be considered part of the clinical syndrome of MS, rather than just noise or error variance, and thus extricating these statistically as a covariate would reduce meaningful variance (Miller & Chapman, 2001). Overall therefore it appears that there are significant differences in cognitive tests likely associated with meaningful differences in cognitive function between HC, RR-MSnc and RR-MSc.

When all variables were considered simultaneously, utilising a cognitive impairment index incorporating published norms, there was a significant difference found between RR-MSc and RR-MSnc (as well as HC). This is indicative of a different cognitive profile. However, it is possible that pFSIQ may have added a confound between RR-

MSc and RR-MSnc, as the RR-MSnc had a greater pFSIQ and thus a greater cognitive reserve and this was not controlled for in the cognitive impairment index due to comparison with other data. However, differences in pFSIQ were only minimal (Orchard, Giovannoni & Langdon, 2013). When considering widespread cognitive impairment ('failure' on three or more cognitive tests) 57% of individuals met widespread cognitive impairment within the RR-MSc group, compared to 5% in the HC and 29% in RR-MSnc. This is indicative of a differing cognitive profile between the two MS groups characterised by greater widespread cognitive impairment within the RR-MSc group, and RR-MSnc being more associated with specific deficits.

Overall, the present research indicates that HC, RR-MSnc and RR-MSc differ on cognitive test performance, and that RR-MSc and RR-MSnc have a different cognitive profile.

4.1.1. Interpretation

4.1.1.1. Information processing speed

The highest significant difference between groups was found on the SDMT followed by the PASAT3, both established tools for measuring IPS in MS. An expert committee deemed the SDMT to be the most reliable, valid and sensitive screening test to cognitive impairment in MS for routine clinical use (Langdon et al., 2012). It is widely reported that SDMT performance is impaired in those with MS (Drake et al., 2010; Forn, Belenguer, Parcet-Ibars & Ávila, 2008; Hughes, Denney & Lynch, 2011; López-Góngora, Querol & Escartín, 2015; O'Connell, Langdon, Tubridy, Hutchinson &

McGuigan, 2015), and in the present study SDMT was the only cognitive test that significantly differentiated RR-MSnc from HC. It demonstrated a high sensitivity with 71% of RR-MSc 'failing' SDMT, and 24% of RR-MSnc 'failing' SDMT, and a high degree of specificity with 0% of control participants 'failing' SDMT. Thus, it can be concluded that in the present study RR-MSnc had slower IPS than HC, and RR-MSc had slower IPS than RR-MSnc.

However, the PASAT3 did not differentiate RR-MSnc from HC. Previous research has found PASAT to be moderately sensitive to cognitive impairment in MS (Hansen et al., 2015; López-Góngora, Querol, & Escartín, 2015). This non-significant finding may be due to multiple factors. In MS studies, the SDMT has been shown to not be necessarily predictive of PASAT performance (Weier et al., 2014; Williams, O'Rourke, Hutchinson, & Tubridy, 2006). This is because SDMT and PASAT may represent somewhat different, albeit overlapping, cognitive domains (Costa, Genova, DeLuca, & Chiaravalloti, 2016; Weier et, 2014), for instance, the PASAT includes a significant working memory component, as well as IPS. This additional working memory component may impair RR-MSc due to the cerebellum's role in the articulatory control system (see *section 4.1.1.2.*). Construct contamination is common in all tests designed to assess IPS (Chiaravalloti, Christodoulou, Demaree, & DeLuca, 2003). This is demonstrated by differing neuroanatomical correlates with cognitive tests on neuropsychological research involving neuroimaging. For instance, Yu et al. (2012) report that the SDMT was more sensitive to white matter tract damage in MS than the PASAT, and had stronger associations with markers of cerebral and cerebellar markers. Similarly, Damasceno, Damasceno and Cendes (2014) report that SDMT was associated with intracortical lesions, and the PASAT with cerebellar leukocortical

lesions. Similarly, Weier et al. (2014) suggests that PASAT performance is primarily linked to cerebellar and whole brain atrophy. The RR-MSnc group therefore are likely to have less impairment on PASAT than RR-MSc, and this pattern was recognised in the current study (with 43% of RR-MSc 'failing' the PASAT compared to 14% of RR-MSnc). This might be associated with the fact that the SDMT is considered a purer indicator of IPS than PASAT, which represents IPS, attention and working memory domains.

However, this may also be associated with the fact that three participants within the control group met the ceiling for PASAT3, thus reducing the difference between HC and MS groups. Future studies should consider utilising the PASAT2 to avoid this ceiling effect. The PASAT3 is easier than PASAT2, the latter being more irksome for participants, and thus PASAT2 was not included due to the distress this can cause to participants. However, this may have resulted in a loss of meaningful variance and sensitivity.

Within the current study, RR-MSnc performed significantly better than RR-MSc on the PASAT3 and SDMT. This supports previous research demonstrating this difference (Bozzali et al., 2013; Cerasa et al., 2012; Damasceno, Damasceno & Cendes, 2014; Moroso et al., 2017; Ruet et al., 2014; Valentino et al., 2009; van de Pavert et al., 2016; Weier et al., 2014). Most of these studies utilised neuroimaging methods, aside from one who utilised the 9HPT as indicative of cerebellar dysfunction (Ruet et al., 2014).

Overall, these findings are indicative of impairments in attention and IPS in individuals with RR-MSnc, and a further impairment in those with RR-MSc (including

impairments in attention and working memory). This fits with previous empirical evidence in this area. At a brain level, the cerebellum has five times more neurons than the entire cerebral cortex (Herculano-Houzel, 2009), which makes the its functions especially vulnerable to slowed information processing speed. Reductions are also likely associated with disruption to corticocerebellar networks which rely on the integrity of several subcortical structures including the cerebellum (Ceresa et al., 2013; Forn et al., 2008; Valentino et al., 2009). This results in recruitment of compensatory networks rather than from cerebellofrontal networks, the latter associated with fastest task responses (Ruet et al., 2014). Thus a plausible theoretical explanation may be associated with reduced IPS in RR-MSc from a lack of optimisation and automation of cognitive functions associated with the cerebellum (Bonnet et al., 2010), which has been linked to grey matter loss in Vermis II (Moroso et al., 2017). Thus, this is a possible demonstration of 'cognitive compensation failure' (Bonnet et al., 2010). This is further considered in later sections (*see section 4.3)*.

4.1.1.2. Memory

The findings of the present study demonstrate significant differences between HC and RR-MSc, and RR-MSnc and RR-MSc on CVLT-II learning trials, a well-established verbal memory task. This indicates more significant impairment in verbal memory in RR-MSc compared to the other two groups.

These findings are supported by neuroimaging findings by van de Pavert et al. (2016) who found associations with grey matter cerebellar lesion load in MS and reduction of visual and verbal immediate and delayed memory recall (shown on The Adult Memory

and Information Processing Battery; AMIPB; Coughlan & Hollows, 1985). Many previous studies did not find an association with cerebellar signs and the verbal memory domains using the Rey Auditory Verbal Learning Test (Ceresa et al., 2013; Valentino et al., 2009) or selective reminding task (Ceresa et al., 2012), and some did not assess verbal memory domains (Moroso et al., 2017). The findings from the present study suggest that use of CVLT-II, a highly sensitive measure to verbal memory decline in MS (Langdon et al., 2012) should be incorporated into neuropsychological batteries for clinical examination and research. However, with the BICAMS cut-off ($\bar{x}$ -1.5SD), 38% of the HC group 'failed' the task, suggesting a reduced specificity of the measure. Thus, this should be utilised in conjunction with a broader battery, such as the BICAMS (Langdon et al., 2012).

HCs performed significantly better on BVMT-R learning trials (visual memory) than RR-MSc. There was no significant difference between RR-MSc and RR-MSnc on BVMT-R. However, quite a substantial difference between means was recognised in RR-MSnc and RR-MSc, and more than twice as many RR-MSc 'failed' the BVMT-R compared to RR-MSnc. Thus, it is likely that the planned comparison between the two groups was underpowered (n = 35) for significance to be found.

Cerebellar atrophy and lesions have been associated with reduction of immediate (and delayed) visual and verbal memory within MS demonstrated on the ROCFT and AMIPB (Ceresa et al., 2013; van de Pavert et al., 2016). However, no significance was demonstrated on the spatial recall test (SPART) (Ceresa et al., 2012). Some studies did not include visual memory within their battery (Moroso et al., 2017). Findings from the present study corroborate most studies within the area, that RR-MSc demonstrate a

reduction in visual memory compared to HC. The BVMT-R demonstrates a high level of sensitivity (Langdon et al., 2012) and is quicker to administer than the ROCFT and AMIPB – thus it is recommended that this is incorporated into clinical practice and research. However, it is possible that a lengthier examination such as the ROCFT and AMIPB may have demonstrated difference between RR-MSnc and RR-MSc.

It is possible that these visual and verbal memory deficits could be associated with reduced registration of information (the acquisition hypothesis) (DeLuca et al., 1998; DeLuca, Leavitt, Chiaravalloti & Wylie, 2013; Gmeindl & Courtney, 2012; Langdon, 2010), implicating IPS. Differences between RR-MSc and RR-MSnc in verbal memory may also be associated with damage to the cortico-subcortical circuitry involved in the articulatory control system, specifically associated with the posterior part of the cerebellum (Ceresa et al., 2013; Chen & Desmond, 2005; Desmond et al., 2003). The articulatory control system sub-vocally rehearses information from the phonological loop which maintains auditory working memory and supports long-term memory consolidation. Thus, damage to this process may impair verbal memory.

No significant difference was found between HC and RR-MSnc for the CVLT-II or BVMT-R. This does not fit previous findings, and these are gold-standard screening tests for cognitive impairment within MS (Langdon et al., 2012). One of the most sensitive tests to cognitive decline in MS is SDMT (Langdon et al., 2012), and the power calculation was based on the effect size from SDMT (Valentino et al., 2009). Thus, it is possible that a larger sample would be required to detect differences in CVLT-II and BVMT-R between HC and RR-MSnc. For example, a moderate effect size was reported for all memory domains within a large meta-analysis (n = 3891)

(Prakash, Snook, Lewis, Motl & Kramer, 2008). The lack of significance within the current study may also be associated with the high premorbid IQ (and thus cognitive reserve) of the RR-MSnc group discussed in later sections (see *section 4.4.1.*). It may also be associated with the removal of RR-MSc from the RR-MSnc group, which may make the RR-MSnc group atypical of the MS population due to reduced heterogeneity.

4.1.1.3. Verbal Fluency

There was no significant difference between groups in WLG. This does not replicate previous findings for verbal fluency tests in RR-MS (Bodini et al., 2013; Hynčicová et al., 2017; Morrow, Menon, Rosehart, & Sharma, 2017; Viterbo Iaffaldano & Trojano, 2013). Similarly, this does it replicate findings for greater impairment in RR-MSc than RR-MSnc (Ceresa et al., 2012; Valentino et al., 2009), who demonstrated significant impairments in the COWAT (Valentino et al., 2009) and WLG (Ceresa et al., 2012). This may be associated with a lack of statistical power, discussed in later sections (see *section 4.4.7.*). However, within all groups many individuals 'failed' the WLG. This is potentially suggestive of the lack of specificity of the WLG to cognitive impairment in RR-MS.

4.1.1.4. Widespread cognitive impairment

The cognitive impairment index provides evidence against the notion that when cognitive domains are considered simultaneously there is no association with cerebellar symptomology and cognitive impairment (Daams et al., 2016). This demonstrated significantly greater global impairment in RR-MSc than RR-MSnc, but was unable to

differentiate RR-MSnc and HC. Widespread cognitive impairment ('failure' on three or more tests) was recognised in 5% of HC, 29% of RR-MSnc and 57% of RR-MSc. These findings taken together are suggestive of a cognitive subtype associated with cerebellar pathology, which supports most research within this area (Ceresa et al., 2012; Ceresa et al., 2013; Valentino et al., 2009).

4.1.2. Summary

The present findings support previous research demonstrating that cerebellar symptomology may indicate a distinct clinical subtype of RR-MS, involving more severe and widespread cognitive impairment (Ceresa et al., 2012; Ceresa et al., 2013; Valentino et al., 2009). Overall, there are significant differences between the cognitive profiles of RR-MSnc, RR-MSc, and HC. HC demonstrated less impairment than individuals with MS on measures of IPS, and RR-MSc showed greater impairment than RR-MSnc. HC also performed better on a verbal memory test than both MS groups, and on a measure of visual memory than RR-MSc. Cerebellar symptomology was associated with the most significant cognitive impairment in these domains. There was a much greater proportion of individuals with RR-MSc to have widespread cognitive impairment (57%) compared to RR-MSnc (29%) and HC (5%). These findings are possibly associated with the 'universal cerebellar transform', suggesting that cerebellar damage would result in impairment across the domains (Koziol et al., 2014; Schmahmann, 2004). However, domain specific involvement of the cerebellum has also been discussed. These findings support current research within RR-MSc, and provide clinical and research implications of utility of the BICAMS and PASAT3 as sensitive and timely measures of cognitive function within this population. Overall, the

null hypothesis that there are no significant differences between the cognitive profile of the three groups can be rejected.

4.2. Hypothesis 2: Individuals with RR-MSc will perform worse than RR-MSnc and HC on tasks of motor planning

The hypothesis that individuals with RR-MSc will perform worse than RR-MSnc and HC on tasks of motor planning was supported by the findings. Groups significantly differed on the test of motor function (9HPT), the test of motor function and planning (GPT) and the motor planning index (9HPT - GPT). HC performed these tasks significantly faster than RR-MSnc who performed significantly faster than RR-MSc. As with *hypothesis 1* – age, gender and premorbid IQ cannot account for these differences.

Low mood has been demonstrated to have an impact on motor function within MS (Maier et al., 2015). Maier et al. (2015) correlates BDI with 9HPT (as well as cognitive function), however causality cannot be determined. It could be that maladjustment to fine motor impairment has resulted in depression. Alternatively, it could be that psychomotor retardation, a common symptom of depression (F32, ICD-10; WHO, 1992) could account for the difference. As with *hypothesis 1*, this variance is considered meaningful, and thus included within the analysis. The two MS groups did not differ significantly in depression scores. Self-reported fatigue has also been demonstrated to impact on motor function, independently of depression, EDSS and other clinical variables (Golan et al., 2017). This is part of the clinical picture of MS and there is no significant difference between the MS groups. However, it is possible that the impact

of mood and fatigue have accentuated differences between HC and MS groups within the present study.

Previous research has supported the present findings of worsened performance on motor function within RR-MSc (Weier et al., 2014). However, to the authors knowledge, this is the first demonstration of reduced motor planning performance within RR-MSc. Overall, the null hypothesis that there is no difference between RR-MSc and RR-MSnc and HC on tasks of motor planning can be rejected.

4.2.1. Interpretation

There are several criticisms of the MPI. MPI was calculated by subtracting the 9HPT from the GPT. This is based on subtraction logic (Shoeben, 1982). This assumes that task difficulty is additive – however it could be that the additional demands between the basic task and the more complex task could be mentally computed simultaneously (partly or wholly) with the basic task.

Within the current study, both peg tests involve coordination of perceptive, visuospatial and motor functions. The 9HPT is a test of sensorimotor function requiring round pegs to be placed in round holes. The GPT has higher motor planning demands because each peg must be precisely oriented when it is placed in one of the canoe-shaped holes of differing orientations. Therefore, the difference between timed performance on the two tests gives an indication of how the increased motor planning demands affect GPT performance of the three different groups. For subtraction logic to create an accurate MPI, the GPT and 9HPT would have to have the same sensorimotor component.

However, there are some differences between the experimental conditions. The 9HPT and GPT may vary in difficulty because the former has nine holes and the latter 20 holes (and five holes that the experimenter demonstrates with). Thus, the GPT has a larger field of operations, with more target holes to compute movement vectors for. Thus, it has additional motor planning complexity. This poses a rationale for the subtractive method for HC, as the difference between the 9HPT and GPT is the additional time required for healthy controls for extra motor planning demands. However, there is an additional sensorimotor loading on the GPT, as one is required to rotate the pegs which uses more dexterity and fine motor coordination than the 9HPT where one simply places cylindrical pegs within the holes (without considering orientation). This additional complexity may pose more difficulty in task completion for those with cerebellar symptoms due to expected motor/visual sequelae. Similarly, in the 9HPT, individuals are required to remove the pegs and return them to the container, once all the holes have been filled. This results in 18 manipulations of pegs (nearly equivalent to the GPT 20 manipulations) however, it requires less dexterity and fine motor control to remove pegs than place them.

There are also subtle differences in task complexity. For instance, in the 9HPT, participants can place pegs in any order, whereas in the GPT individuals must fill the holes sequentially from the opposite side of the board to the hand they are using for each row. This adds an executive function differential. Binétray et al. (2016) considered these differences using a line crossing-off task. In one condition participants crossed out lines horizontally from left to right then right to left (an optimised form of visual exploration) (T2) and in the other condition from left to right, then starting from left and moving right on the next line (writing habit) (T1) (Binétray et al., 2016). T1 was

associated with more cognitive processes including executive compensatory processes of inhibiting crossing at the end of one line, and beginning again at the left side of the next line (Binétray et al., 2016). T1 speed was correlated with a composite test involving executive functions, flexibility and information processing speed, whereas T2 was not (Binétray et al., 2016). Within the current study, this suggests greater cognitive involvement when additional rules are set for order of filling holes for the GPT (such as in T1), compared to allowing intuitive and ecological completion in the 9HPT. This is of specific importance as this may add further deficits to the RR-MSc group as they may have more difficulty generating automatic processes (such as those required for the GPT/T1/writing) (Bonnet et al., 2010), as well as having more cognitive impairment for the added cognitive demands on the GPT.

For these considerations, it would be beneficial to manufacture a new pegboard with 20-holes (with the same layout, peg weight, visual field, completion instructions) as the GPT but without the key-slots which require planning to orient. However, the value of utilising the standard 9HPT and GPT is that they are available and can be utilised by any research group. Consequently, if deemed clinically informative, the MPI could be calculated by most healthcare organisations.

The findings demonstrate that RR-MS groups have poorer fine motor function and these difficulties are significantly worsened in those with cerebellar symptoms. This corroborates previous research showing a link with cerebellar lesions and atrophy and motor dysfunction, commonly on the 9HPT (Damasceno, Damasceno & Cendes, 2014; Ruet et al., 2014; van de Pavert et al., 2016; Weier et al., 2015a). Significant difference between RR-MSnc and HC may be associated with minor cerebellar dysfunction, or

reduced IPS which impacts the more demanding aspects of the GPT more than the 9HPT.

Despite the methodological considerations with MPI, the findings provide early support for a link between motor planning and RR-MSnc, which is exacerbated in RR-MSc. To the author's knowledge, this is the first study in MS to demonstrate that RR-MSc perform worse with motor planning than RR-MSnc. More research with fewer methodological concerns is required within this area.

For effective motor control, humans must be able to anticipate musculo-skeletal inputs, CNS latency and response dynamics, based on experience (Herreros, Arsiwalla & Verschure, 2016; Herreros & Verschure, 2013), which are stored as subcortical representations/models in the cerebellum. The cerebellum works to create mental bodily representations based on predictions of sensory inaccuracies (Koziol et al., 2014; Ramnani, Toni, Josephs, Ashburner, & Passingham, 2000; Shadmehr & Krakauer, 2008;), which are incorporated with prospective memory for sensory predictions (D'Angelo, 2011; Spencer & Ivry, 2009). These representations can be mentally manipulated to suit the task of navigating vectors and attuning the peg to fit within the hole of the GPT (computing this by incorporating significant amounts of information of state estimation and movement predictions, amongst other information). Thus, inefficiencies of the cerebellum to create subcortical representations will result in impaired motor planning (Ito, 1969; 2008). It is likely that for this reason, individuals with cerebellar damage have reduced cognitive predictive abilities for motor actions and planning (Pezzulo, 2008). For HC completing the GPT and 9HPT, forward models (Ito, 2008) combining internal cerebellar information with CNS information will create a plan/model which results in efficient and accurate movements. It is likely that within

the present study, the inefficiencies in this process for individuals with RR-MSc resulted in significantly greater differences in motor function (9HPT) and motor planning (9HPT - GPT) than HC and RR-MSnc.

4.3. Hypothesis 3: Differences in motor functioning will be related to cognitive function, most significantly IPS

To test this hypothesis, MPI was used to operationalise motor functioning. When controlling for pFSIQ, a strong significant negative correlation was observed between SDMT and MPI and moderate significant negative correlation between PASAT3 and MPI. The r^2 variances demonstrating 30% shared variance for SDMT and MPI, and the 11% shared variance for PASAT3 and MPI demonstrating an association of IPS to MPI. Significant moderate negative correlations were also recognised on the CVLT-II and BVMT-R. 12% of CVLT-II variance, and in 19% of BVMT-R variance was shared with MPI. There was no significant correlation between WLG and MPI. These findings support the notion the differences in motor functioning are related to cognitive function, aside from WLG. SDMT, the most utilised measure of IPS in MS, showed the strongest correlation with MPI. Thus the null hypothesis that there is no relation of motor functioning to cognitive function can be rejected.

However, the existence of a specific link of motor planning to IPS was hypothesised. *Table 11* demonstrates that there is a link between motor planning (GPT/MPI) and IPS (PASAT3/SDMT) but also demonstrates a significant association between sensorimotor function (9HPT) and IPS. There was no significant difference between the strengths of these correlations. This suggests that there may not be a specific link

between IPS and MPI but instead suggests cerebellar damage may be associated with simultaneous decline in motor function, planning and cognition.

4.3.1. Interpretation

The results from the present study demonstrate an association between motor functioning and planning and cognitive tests (aside from WLG). This association appears to indicate that cognitive dysfunction occurs simultaneously with motor dysfunction from the onset of RR-MSc, supporting previous research in the area (Ruet et al., 2014; Weier et al., 2014). This cognitive decline appears to be global in nature, (spanning IPS, working memory, and visual and verbal memory domains), however it should be noted that several cognitive domains were not fully considered, including language functions, visuospatial functions and executive functions.

This global decline is likely associated with the 'universal cerebellar transform' which would hypothesise cross-domain impairment (Koziol et al., 2014; Schmahmann, 2004) as the cerebellum is acting as an 'oscillation dampener' to optimise performance (Koziol et al., 2014; Schmahmann, 2004). This suggests that the cerebellum acts to modulate arrays of cognitive and sensorimotor information to create congruous and efficient behaviours (Koziol et al., 2014; Schmahmann, 2004). Conversely damage to the cerebellum as in RR-MSc would result in dissonance and inefficient processing which would be universal in nature, resulting in global cognitive decline.

It was hypothesised that the RR-MSc group would display further deficits in verbal fluency as individuals with cerebellar cognitive affective syndrome demonstrate verbal

fluency deficits (e.g. mutism or telegraphic speech) (Koziol et al., 2014). However, within the present study, this was not demonstrated. Further research into the role of executive functions and language functions in RR-MSc is required.

It was hypothesised that the recognised deficits in IPS, which support previous research (Damasceno, Damasceno & Cendes, 2014; Weier et al., 2014) would be associated with motor planning (independently of function). This was due to the consideration that reductions in IPS may be attributable to the same structures (at a brain level) and models (at a neuropsychological level) as motor planning. Thus, it was thought that disruption in these areas would result in a reduction in automation of cognitive functions and result in inefficiencies of information processing (Rocca et al., 2012; Ruet et al., 2014). This hypothesis was supported by fMRI studies demonstrating increased cerebellar activation in rapid cognitive processes in HC but not in those with MS (Bonnet et al., 2010; Genova et al., 2009; Moroso et al., 2017; Rocca et al., 2012).

However, within the present study a unique contribution of IPS to motor planning was not found, and instead equivalent correlations between motor planning and motor function were recognised with IPS (*see Section 3.9*). This indicates that IPS may simply be associated with motor function, as opposed to a specific relationship to motor planning. This discrepancy between the present findings and MRI data may be associated with insufficient statistical power as a relatively small sample was utilised within the present research (see *section 4.4.7*). Also, perhaps recruitment of compensatory cortical areas shown in RR-MSc (Bonnet et al., 2010; Ruet et al., 2014) is effective in completion of neuropsychological tests, but a saturation effect of cognitive load on the cerebral areas compensating for cerebellar damage may be

recognised in more ecologically valid examinations where domains are not considered in relative isolation of each other. More research is required in this area.

4.4. Limitations

4.4.1. Sample representativeness

The overall female to male ratio for all participants was 1.43:1 and 1.69:1 for MS participants alone, marginally lower than the population prevalence. Prevalence data suggests that the incidence of MS in the general population is 2.35-2.40:1 (Ahlgren, Odén, & Lycke, 2011; Mackenzie, Morant, Bloomfield, MacDonald, & O'Riordan, 2014). It is possible that this sample may have overemphasised male characteristics.

The mean age of the sample groups ranged from 37.05-39.81. Within the general population, the mean age of onset is around 30 years of age (Rejdak, Jackson & Giovannoni, 2010). Progression and stability of disability in EDSS is heterogeneous (Cree et al., 2016; Hughes et al., 2012). However, in one large prospective study, only 11% of patients reached EDSS 6 at a median time of 16.8 years (Cree et al., 2016). Thus, this sample may be more representative of a younger MS population. This may provide under estimates of motor impairment as motor decline is more rapid in older populations (Roy et al., 2016).

Estimated premorbid IQ group means were 115.34 for HC, 109.22 for RR-MSnc and 99.83 for the RR-MSc. Significant differences between the groups on this variable resulted in premorbid IQ being added as a covariate into analyses. In the general

population, 50% of individuals fall between IQ 90-109 (25-74th percentile) (Wechsler, 2014). Thus, the sample has a higher average IQ than expected within the general population. This may have resulted in an underestimate of cognitive deficits as higher premorbid functioning (cognitive reserve) reduces the rate of cognitive decline associated with brain atrophy in MS (Nunnari et al., 2016; Sumowski et al., 2009).

Visual inspection of mean scores for the present sample, and mean published norms (Orchard, Giovannoni & Langdon, 2013, Boringa et al., 2001) shown in *Table 10,* appear to demonstrate similarity between MS norms and MS observed scores, as well as HC norms and mean HC. This suggests that the current sample is representative of the wider population regarding cognitive strengths and weaknesses of healthy and MS populations. However, there are some differences between sampling methods and samples of these two studies discussed later (see *section 4.4.4*).

Many of the control participants were known by the researcher. This may have impacted on test performance by affecting state anxiety or creating performance effects.

4.4.2. Group Allocation

One limitation of the present study was the use of the self-report NARCOMS-TACS questionnaire for group allocation. It is possible that this lacks specificity, as those in the RR-MSc group had higher EDSS scores and perhaps this group were not reporting primary cerebellar symptomology but instead this was associated with more global atrophy which resulted in cerebellar symptoms.

The NARCOMS-TACS demonstrated adequate criterion validity with the EDSS cerebellar functional system score (EDSS<6.5) (Marrie & Goldman, 2011). It demonstrated good criterion validity within the current study with strong correlations with 9HPT, an established measure of upper arm tremor (as well as GPT and MPI). However, it would be more valid to utilise imaging methods to recognize cerebellar atrophy or lesions. This would also avoid a binary grouping, instead being able to consider lesion load or T2-Weighted MRI based cranial volume measurements. This would allow for correlational analysis.

Within the current study, there were moderate to strong correlations between NARCOMS-TACS and 9HPT, GPT, MPI and EDSS demonstrating a coherent data set despite small numbers and indicating good criterion validity of NARCOMS-TACS.

4.4.3. Assessment Environment

All MS participants were assessed within their own homes. Control participants were assessed within their own homes, their place of work, or within the home of the researcher. This may have resulted in differences in state anxiety during testing.

Whilst all efforts were taken to standardise testing, some confounds may have been introduced by differential environmental factors, particularly with differences between the groups assessment locations. Auditory and visual distractions as well as interruptions could not be fully controlled. The PASAT involves audio recordings, played through speakers which may have been affected by ambient noise. Participants were also tested at different times of the day, which may have resulted in confounds

between participants associated with fatigue and alertness. However, if this was standardised, there may be group differences between HC and MS participants as fatigue may impact individuals with MS at different times of day to HC (Powell, Liossi, Schlotz, & Moss-Morris, 2017).

4.4.4. Cognitive impairment index

There are some limitations of the cognitive impairment index. The standardisation sample for BICAMS tests plus PASAT3 (Orchard, Giovannoni & Langdon, 2013) utilised a mixed phenotype MS group (76% RR-MS) with some progressive phenotypes, which was compared to the present study which only included RR-MS. This may have resulted in greater levels of cognitive impairment in the normal data associated with progression of the disease (Amato, Zipoli & Portaccio, 2006; Calabrese et al., 2009; Planche, Gibelin, Cregut, Pereira, Clavelou, 2016). However, individuals with RR-MSc were purposefully selected by the clinical team towards the end of data collection, and exclusively selected by the researcher following RR-MSnc saturation. Thus, the current study likely has a greater proportion of RR-MSc. This may have resulted in greater cognitive impairment in the current group compared to published norms. Further research should be carried out to gain normal data on BICAMS for different subcategories of RR-MS. Additionally, the WLG utilised Dutch norms. Cultural and linguistic factors may reduce the generalisability of these norms to the present study.

4.4.5. Clinical factors introducing variance

4.4.5.1. Speech/dysarthria

It is possible that RR-MSc participants had more dysarthria. Dysarthria and 'scanning speech' are common in those with cerebellar signs (Poser & Brinar, 2001; Schmahmann, 2004; Weier et al., 2015a). Dysarthria may have reduced test scores that require rapid oral motor responses (Arnett, Smith, Barwick, Benedict & Ahlstrom, 2008; Smith & Arnett, 2007). Within the current study these include the WLG, SDMT, PASAT3 and CVLT-II. One experimental study compared 50 MS patients with 50 healthy controls utilising a regression analysis to determine the variance explained by a dysarthria, measured on a reliable and valid oral motor speed task (SDMT: 6-10%; PASAT 2-4%; naming task 7-11%) (Arnett et al., 2008). This demonstrates a slight, but significant contribution of objective articulation speed deficits on cognitive test performance. This may result in an overestimate of cognitive impairment within the RR-MSc group. Further studies should formally assess dysarthria. However, though dysarthria was not formally evaluated in participant selection, no significant dysarthria was noted for any participants during the assessment.

4.4.5.2. Visual disorders and processing

Visual symptoms such as acuity disturbances and nystagmus may also add additional confounds to results. Visual difficulties are one of the most common symptoms of MS (Costa, Genova, DeLuca, & Chiaravalloti, 2016; Qureshi, Beh, Frohman, & Frohman, 2014). Costa et al. (2016) report that these are easily assessed objectively, however

informal and subjective evaluations are commonplace in MS IPS literature, such as within the current study. These subjective ratings may have reduced the replicability of the present study. One study examined the effects of mild visual acuity disturbances in RR-MS who subjectively reported adequate vision (Bruce, Bruce, & Arnett, 2007). This study demonstrated that even mild visual acuity disturbances can account for a significant amount of the variance (13%) on a battery of visual attention (including the SDMT). Nystagmus is a common in MS and is associated with cerebellar dysfunction (Iyer et al., 2015; Kutzelnigg et al., 2007; Tornes, Conway, & Sheremata, 2014; Weier et al., 2015b). For clarity and acuity of vision, stimuli must be steadily held as retinal images (particularly in the fovea) (Stahl, Plant, & Leigh, 2002). This requires corrective eye movements and ability to suppress unwanted eye movements, as well as compensatory eye movements from a vestibule-ocular reflex responding to head movements (Stahl, Plant, & Leigh, 2002). Nystagmus therefore results in acuity disturbances, which impairs performance in cognitive tests with visual requirements (Bruce, Bruce & Arnett, 2007). Within the present study, this is likely to impact BVMT-R and SDMT. This is also likely to impact sensorimotor aspects of the peg tests. Assuming both peg tests have the same sensorimotor requirements, both tests should be equally affected and thus the MPI would remain unaffected. Further studies should formally assess visual function.

Individuals with MS may have reduced visual processing capacity beyond ocular-motor disturbances. Recognition of a limitation of temporal processing within the visual system has been recognised in a recent study (Lopes Costa et al., 2016). These have been shown to impact on cognitive tests including the SDMT (Lopes Costa et al., 2016). Within the present study we assume that RR-MSc and RR-MSnc have the same visual

processing abilities, however we cannot exclude the possibility that visual processing was different between groups. Further research within this area is required.

4.4.5.3. Medication

Within the present study, individuals were excluded if they received steroid treatment in the previous two months. No further information was gathered regarding current medical treatment or adherence. Some evidence has suggested that DMTs may have benefits on cognitive performance (Barak & Achiron, 2002; Fischer et al., 2000; Langdon, 2012; Patti et al., 2010; 2012; 2013; Paty & Li, 1993). It is possible that differential medical treatments and adherence between participants, could add additional confounds.

4.4.5.4. Comorbidities

Within the present study, individuals were excluded if they had any pre-existing diagnosed mental health difficulties, epilepsy or substance misuse disorders. However, screens for premorbid pathologies such as attention deficit hyperactivity disorder (ADHD) and dyslexia were not screened for. These could add confounds into the current findings, and these are commonly overlooked within MS research (Costa, Genova, DeLuca, & Chiaravalloti, 2016).

4.4.5.5. Level of disability

EDSS is the most common method of quantifying disability within MS, but it disproportionately reflects locomotion. Within the current study, individuals were excluded if they were unable to walk without aid or rest for more than 200 meters (as this is the limit for EDSS 5). Higher scores on EDSS (4.5 – 5) are associated with restricted ambulation without aid (between 200 meters and 500 meters). Since cerebellar damage in MS is associated with physical symptoms which may impair ambulation such as ataxia, tremor and loss of coordination (Middleton & Strick, 2000; Schmahmann, 2004; Weier et al., 2015a) it is likely that RR-MSc will have higher EDSS scores. This was found by de Groot et al. (2009) who demonstrated that impairment of the cerebellar tract was associated with an EDSS of more than 4.5. Significant differences were found between the RR-MSnc and RR-MSc groups for EDSS, however this was not included in the analysis as this was considered descriptive of realistic clinical differences between RR-MSnc and RR-MSc.

4.4.6. Cognitive Battery

Some limitations associated with the neuropsychological test battery were recognised. The battery was selected due to the sensitivity and specificity to cognitive impairment in MS. A relatively brief battery was used as fatigue is common in MS, and to minimise inconvenience caused to the participants. Three out of five cognitive tests were those from the BICAMS (Langdon et al., 2012). The final two tests (WLG and PASAT) are included in the BRB-N (Rao & the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990). The utility of internationally recognised tests of

cognition in MS, such as the BICAMS, allows for comparison across studies (Costa, Genova, DeLuca, & Chiaravalloti, 2016).

A ceiling effect, was reached on the PASAT3 where three HCs achieved the top score. This may have resulted in an underestimation of differences between the HC group and MS groups increasing the likelihood of type-II error. Including the PASAT2 would have increased the ceiling on this test. However, although all individuals engaged fully with the PASAT3, some reported finding it aversive. This fits with published literature regarding the testing process (Bosnes, Dahl & Almkvist, 2015; Roman, 1991; Walker et al., 2012). Therefore, adding a faster tempo task may not have provided benefits to outweigh the ethical costs.

Including further tests of executive function could allow for more clarity in the cognitive profile of RR-MSc. Significant research has demonstrated deficits in executive functions in MS, however no 'typical profile' has been recognised (Chiaravalloti & DeLuca, 2008). By considering a heterogeneous definition of MS, with considerations of differing phenotypes, a typical profile may emerge. For instance, for RR-MSc, Ceresa et al. (2012) implicated frontocerebellar connections in executive functions, and grey matter cerebellar higher lesion load has been demonstrated to reduce performance on the Stroop (Clausi et al., 2009; Trennery, 1989; van de Pavert et al., 2016). Including an array of executive function tasks including Delis-Kaplan Executive Function System (D-KEFS) colour/word interference and Tower of London Task (Delis, Kaplan, & Kramer, 2001), Brixton spatial anticipation task and Hayling Sentence completion task (Burgess & Shallice, 1997) could begin to develop these profiles.

The battery incorporates both visual and verbal tasks (learning trials for CVLT-II and BVMT-R), which are recommended by the BICAMS (Langdon et al., 2012). However, the current battery lacks memory presented within context, or with delayed recall. Including subtests from the AMIPB (Coughlan & Hollows, 1985) or Weschler Memory Scale (Wechsler, 2009) could provide information in these areas. Also, to provide clarity over whether memory difficulties are associated with dysexecutive memory profiles (recall difficulties) or rapid-forgetting/assimilation difficulties, the battery should include a recognition trial. Similarly, to more effectively disentangle IPS and attentional processes, specific attention tasks could be incorporated, such as the Test of Everyday Attention (TEA; Robertson, Nimmo-Smith, Ward, & Ridgeway, 1994). This could provide useful information for rehabilitation.

4.4.7. Statistical power

The present study had a sample of 56 participants, falling below the recommended minimum of 63. This was associated with difficulties recognised by clinical teams in finding individuals with RR-MSc who had an EDSS score of five or below. The initial power calculation was based on group differences for SDMT in Valentino et al. (2009), utilising an effect size of $\eta 2 = 0.80$. Within the current study, the observed effect size for SDMT was $\eta 2 = 1.06$. This means that the actual power within that analysis for SDMT was .91 indicating an adequately powered study for this variable.

However, for the non-significant variable within the analysis (WLG), the effect size was $\eta 2 = 0.92$ (still a large effect size). The actual power within the analysis for WLG is .77, indicating a marginally underpowered study. It is possible that the study was not

adequately powered to detect a significant effect for this cognitive task (type-II error). Increasing the sample size may have found significance for this variable. Effect sizes are reported in *Appendix 25* and are deemed adequate.

A decision was made not to remove statistical outliers from the analysis, as the clinical population covers a broad range of disability. Including these outliers in the analysis allows for retention of clinically relevant variance, however may still cause statistical problems, such as an over-estimation of effect. The groups were not balanced equally (21:21:14) meaning that for the RR-MSc group (n = 14), there may have been a greater impact of outliers on the data.

A significant number of analyses were carried out to test the three hypotheses. Least significant difference tests were utilised as post-hoc adjustments to the p-value can be criticised for being overly conservative (Coolican, 2014; Perneger, 1998). With the current test battery, which assessed an array of domains, these were considered too conservative. Therefore, results should be interpreted with caution due to increased likelihood of familywise error (increased risk of type-I error).

4.5. Clinical Implications

The current study demonstrated significant differences, in cognitive domains of RR-MSc and RR-MSnc which are evident from early in the disease course. This suggests that cerebellar symptomology defines a distinct cognitive subtype associated with more severe and widespread cognitive impairment. This provides prognostic information for cognition, motor-planning and function for individuals with recognised cerebellar

lesions and atrophy. Differential levels of cognitive impairment between RR-MSc and RR-MSnc is indicative that RR-MSc will have worse prognosis (Amato et al., 2010). This can be useful for a systemic understanding of the likely difficulties that an individual may have, or may encounter with disease progression. Thus, appropriate treatment planning and life decisions (e.g. employment or driving) can be considered at an early stage.

The present study demonstrated that those with RR-MSc have significantly reduced IPS compared to RR-MSnc. They also seem to demonstrate further memory impairments than are expected within the general population. This finding could support neurologists in identifying patients who may benefit from a neuropsychological examination and subsequent rehabilitation. For example, one paper suggested that early intervention for cognitive impairment in MS may prove effective, through strengthening cognitive reserve by engaging patients in regular mentally stimulating activities following early identification (Sumowski, 2015). Considering individuals diagnosed with MS with cerebellar damage as high-risk for cognitive decline may allow for early intervention in cognitive decline. There is still substantial debate over the effectiveness of cognitive rehabilitation in MS (Filippi & Rocca, 2013), though some studies have demonstrated benefits of this within MS for memory, executive functions, attention, IPS and verbal fluency (Amato et al., 2014; Chiaravalloti, Moore, Nikelshpur, & DeLuca, 2013; Mattioli et al., 2010; Pedullà et al., 2016). Adjustments of cognitive task difficulty based on performance and impairment was demonstrated to be beneficial (Pedullà et al., 2016), and therefore identification of different cognitive profiles in the current study would allow for tailored rehabilitation packages based on phenotype.

The demonstrated reduction in motor function and planning for those with cerebellar symptoms is of significant clinical importance. Individuals with MS have exacerbated fluctuations in fatigue and strength (Powell, Liossi, Schlotz, & Moss-Morris, 2017). Thus, more cerebellar function is required to incorporate these changes to create internal models for effective motor planning. Cerebellar damage therefore can be very debilitating for individuals with RR-MS. Within neurorehabilitation teams, understandings of the interrelations of these cognitive functions and physical rehabilitation techniques would be imperative in designing effective therapeutic exercises and goal planning for physical therapy modalities. Examples of difficulties that individuals may experience at a macro level include state estimation for rehabilitation of ataxic gait or ability to 'transfer' from one place to another. At a micro level these could include compensatory eye movements to maintain retinal images (Frens & Donchin, 2009).

It may be that the GPT is more sensitive to cerebellar symptom presentation and change than the 9HPT. Within the current study, the range of the GPT (range = 142.66) which was much greater than the 9HPT (range = 21.35). This increased spread of participants may increase the sensitivity of the measure to dysfunction. There was no significant difference in strength of correlations with NARCOMS, however this may be associated with the ranking of scores for non-parametric comparisons, due to only having five possible NARCOMS scores.

At present, the clinical usefulness of the MPI is yet to be determined. The initial data is promising, however further research must be conducted to establish psychometric properties. *Figure 1* demonstrates a reasonable overlap of scores and thus it might be

difficult to categorise what counts as a motor planning deficit. It may be that age-based norms may be required to find clinically meaningful cut-offs, as motor decline occurs more rapidly in older populations (Roy et al., 2016). However, a larger sample would be required to analyse this. Further research should be conducted within this area as this could provide a quantification of motor planning impairment, from which an understanding of potential life restrictions and disability can be derived. This may have safety planning implications, for instance when used in conjunction with driving assessment batteries, or implications for rehabilitation.

The study has also demonstrated criterion validity for the NARCOMS for individuals with more significant cerebellar symptoms than in the previous validation (Marrie & Goldman, 2011). This demonstrated moderate to strong associations for 9HPT, GPT and MPI. This may be a more efficient way of rating people with cerebellar dysfunction, which can be conducted over the telephone or by MS nurses as opposed to face-to-face examinations by physicians trained in the EDSS.

The association of cognition and motor planning, indicative of a universal cerebellar transform that spans domains of cognition has clinical implications. A day-to-day example incorporating both cognition and automation of motor actions is driving. Thus, it may be indicated to consider cognitive assessments spanning all domains, as well as motor planning in assessments of driving proficiency for those with RR-MSc.

4.6. Future Research

A follow up study, or longitudinal study, exploring the differences in cognitive profile and motor function and planning may provide a greater understanding into differential prognosis in RR-MSnc and RR-MSc. One paper demonstrated sensitivity of the SDMT and PASAT to cognitive decline in individuals with RR-MS within one year (López-Góngora, Querol, & Escartín, 2015). For this reason, a one-year follow up of the present study is being conducted within the research department.

It may also be beneficial to assess differences in executive dysfunction in RR-MSc and RR-MSnc. Research has demonstrated impacts of MS pathology on executive functions, however no typical profiles have been recognised (Chiaravalloti & DeLuca, 2008). It is possible that by considering further subtypes of MS, including RR-MSc, profiles of executive dysfunction may emerge.

Further research with a larger sample may provide a greater understanding of the relationship between IPS and MPI. Increased statistical power would facilitate the use of regression models.

The current study focused on individuals with RR-MS with relatively low levels of disability (EDSS five or less). Consideration of motor planning and function, and the interrelation of this to cognition within PPMS, SPMS, or PRMS for those with and without cerebellar lesions or atrophy may provide a further understanding of the involvement of the cerebellum in MS. It may also be of interest to consider those with a CIS with damage located within the MS to examine these phenomena. Considerations

of treatment approaches for these recognised subgroups of MS may also warrant interesting findings.

Future research could explore similar hypotheses whilst defining RR-MSc with neuroimaging techniques. Variables such as lesion load or T2-Weighted MRI based cranial volume measurements, would allow for more accurate diagnosis of those with cerebellar symptomology, which does not rely on self-report. It would allow for correlational analysis, thus considering individuals on a continuum rather than as binary groups. This would also provide further information associated with the topographical organisation of the cerebellum (e.g. anterior cerebellum and motor control and posterior with cognitive processes).

Further research should be conducted to consider the clinical usefulness of the MPI, with generation of age matched norms to derive meaningful cut-offs.

4.7. Conclusions

The study aimed to explore the differences in the cognitive profile and motor planning and function within MS. The cerebellum is a predilection site for atrophy and therefore RR-MSc is common. Previous research has associated RR-MSc with more significantly impaired cognitive function and motor function than in RR-MSnc. Within the present study, comparisons between RR-MSnc, RR-MSc and HC revealed more significant cognitive impairment in RR-MSc than RR-MSnc and HC in IPS, visual memory and verbal memory. RR-MSc demonstrated more widespread cognitive impairment than those without cerebellar symptoms. Individuals with RR-MSc also performed worse in

peg tests examining extremity function. Furthermore, they demonstrated more difficulty on a MPI, which aimed to isolate time spent on motor planning from sensory-motor aspects of peg tests.

To the authors knowledge this is the first empirical study examining motor planning within RR-MSc. The study provided early support for the hypothesis that individuals with RR-MSc perform worse than RR-MSnc on tests of motor planning. Theoretically the reduction in performance in RR-MSc may be associated with reduced cerebellar functionality to create subcortical representations/models of motor functions. These incorporate a wide range of sensory and cognitive information which can be reproduced with minimal cognitive input and allocation of attention. Without this functionality, less efficient and more noisy CNS inputs are relied upon for motor actions and planning, thus reducing speed and accuracy.

Research outside of MS has suggested that the cerebellum provides similar models for cognitive processes, and cerebellar dysfunction can result in global cognitive impairment. Within the present study there were moderate to large correlations between memory domains, IPS and the MPI. This cross-domain association of motor planning and function to cognitive function may be associated with the 'universal cerebellar transform' suggestive that the cerebellum acts as an 'oscillation dampener' to coordinate an array of inputs of cognitive and motor functions into consistent, coordinated and timely response.

These findings have significant implications for provision of prognosis within a highly heterogeneous disorder. It also provides considerations for differential rehabilitation

approaches for individuals with RR-MSc, for whom rehabilitation is usually less effective. These findings contribute the understanding that the role of the cerebellum extends beyond the motor domain. Further research should focus on methodological considerations of the present study, broader assessment of cognitive domains, the clinical utility of the MPI, as well as differential treatment approaches for RR-MSnc and RR-MSc.

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Appendices

Appendix 1: HRA Proportionate Review Confirmation of Ethical Approval (dated 28/04/16)

NHS
Health Research Authority

South Central - Hampshire A Research Ethics Committee
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0207 104 8046
Fax:

28 April 2016

Mr Jonathan Hinchliffe
Department of Clinical Psychology, Royal Holloway, University of London
Egham
Surrey
TW20 0EX

Dear Mr Hinchliffe

Study title:	**Cognition in multiple sclerosis**
REC reference:	**16/SC/0165**
Protocol number:	**N/A**
IRAS project ID:	**196840**

Thank you for your letter of 28th April 2016, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Mrs Maxine Knight, nrescommittee.southcentral-hampshirea@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

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.

Conditions of the favourable opinion

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

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

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

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

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

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

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

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" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity insurance]		
Instructions for use of medical device [Pegboard Tests]		
IRAS Checklist XML [Checklist_16032016]		16 March 2016
IRAS Checklist XML [Checklist_28042016]		28 April 2016
Letters of invitation to participant [Invitation letter MS]	V1.2MS	28 April 2016
Letters of invitation to participant [invitation letter controls]	V1.2HC	28 April 2016
Non-validated questionnaire		
Other [Lone worker policy C&I]		
Other [REC Response cover letter]		28 April 2016
Participant consent form [Participant Consent form MS]	V1MS	11 February 2016
Participant consent form [Participant Consent form controls]	V1HC	11 February 2016
Participant consent form [Participant Consent form MS]	V1.2MS	28 April 2016
Participant consent form [Participant Consent form controls]	V1.2HC	28 April 2016
Participant information sheet (PIS) [Information sheet controls]	V1.2HC	28 April 2016
Participant information sheet (PIS) [Information sheet MS]	V1.2MS	28 April 2016
REC Application Form [REC_Form_16032016]		16 March 2016
REC Application Form [REC_Form_28042016]		28 April 2016
Research protocol or project proposal [Study protocol]	V1	04 March 2016
Research protocol or project proposal [Study protocol]	V1	04 March 2016
Summary CV for Chief Investigator (CI) [Summary CV for Chief Investigator]	V1	05 March 2016
Summary CV for supervisor (student research) [Academic supervisor CV]	V1	18 February 2016
Validated questionnaire [HADS]		
Validated questionnaire [FSS]		
Validated questionnaire [EDSS by phone]		
Validated questionnaire [NARCOMS registry: tremor and coordination scale]		
Validated questionnaire [TOPF: Test of Premorbid Function]		
Validated questionnaire [SDMT: Symbol Digit Modalities Test]		
Validated questionnaire [PASAT: Paced Auditory Serial Addition Task]		
Validated questionnaire [COWAT: Controlled Oral Word Association Test]		
Validated questionnaire [CVLT-II: California Verbal Learning Task]		
Validated questionnaire [BVMT-R: Brief Visual Memory Test]		

Statement of compliance

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

After ethical review

Reporting requirements

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

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

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

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

16/SC/0165	**Please quote this number on all correspondence**

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

Yours sincerely

pp

Dr Simon Kolstoe
Chair

Email: nrescommittee.southcentral-hampshirea@nhs.net

Enclosures: *"After ethical review – guidance for researchers"*

Appendix 2: Ashford and St Peter's R&D: Letter of access (Dated 17/10/16)

Jonathan Hinchliffe
Trainee Clinical Psychologist
Department of Clinical Psychology
Royal Holloway, University of London
Egham,
Surrey,
TW20 0EX

St Peter's Hospital
Guildford Road
Chersey
Surrey
KT16 0PZ

Tel 01932 872000
Web: www.ashfordstpeters.nhs.uk

Date: 17th October 2016

Dear Jonathan

Letter of Access for Research at ASPH

Study title:	**Cognition in multiple sclerosis**
IRAS project ID:	**196840**
REC reference:	**16/SC/0165**

This letter confirms your right of access to conduct research through **Ashford & St Peter's Hospitals NHS Foundation Trust** for the purpose and on the terms and conditions set out below. This right of access commences on **17th October 2016** and ends on **21st September 2017** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at **Ashford & St Peter's Hospitals NHS Foundation Trust** has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to **Ashford & St Peter's Hospitals NHS Foundation Trust** premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through **Ashford & St Peter's Hospitals NHS Foundation Trust**, you will remain accountable to your employer **Royal Holloway, University of London** but you are required to follow the reasonable instructions of **Dr Martha Wrigley, R&D Manager** in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with **Ashford & St Peter's Hospitals NHS Foundation Trust** policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate **with Ashford & St Peter's Hospitals NHS Foundation Trust** in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on **Ashford & St Peter's Hospitals NHS Foundation Trust** premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Where required by law, your HEI employer will initiate your Independent Safeguarding Authority (ISA) registration, and thereafter, will continue to monitor your ISA registration status via the on-line ISA service. Should you cease to be ISA-registered, this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity. You MUST stop undertaking any regulated activity.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

Ashford & St Peter's Hospitals NHS Foundation Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that the organisation(s) accept no responsibility for damage to or loss of personal property.

This letter may be revoked and your right to attend the organisation(s) terminated at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of the organisation(s) or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you MUST stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

If your circumstances change in relation to your health, criminal record, professional registration or suitability to work with adults or children, or any other aspect that may impact on your suitability to conduct research, or your role in research changes, you must inform the organisation that employs you through its normal procedures. You must also inform the nominated manager in each participating organisation.

We wish you well with your research. If you need any support or information, please do not hesitate to contact the Trust R&D Department:
Freda Gomes- R&D Support Manager on Tel: 0193-272-3349, E: Freda.Gomes@asph.nhs.uk or Dr Martha Wrigley- R&D Manager on Tel: 0193-272-3302, E: Martha.Wrigley@asph.nhs.uk

Ashford and St. Peter's Hospitals NHS
NHS Foundation Trust

Yours sincerely,

Freda Gomes
R&D Support Manager
E-Mail: Freda.Gomes@asph.nhs.uk

Copy to: Prof Dawn Langdon, Professor of Neuropsychology, Director of Health and Medicine, RHUL
Dr Isaac John, Deputy Director of R&D, ASPH
Dr Martha Wrigley, R&D Manager, ASPH
HR Office, ASPH
HR Department of the substantive employer

R&D
Research & Development
"Aspiration for Innovation"

Appendix 3: Ashford and St Peter's R&D Letter of Permission (Dated 17/10/16)

Ashford and St. Peter's Hospitals NHS
NHS Foundation Trust

Research & Development Department

R&D Ref: 2016JH01SP

Jonathan Hinchliffe
Trainee Clinical Psychologist
Royal Holloway, University of London

St Peter's Hospital
Guildford Road
Chertsey
Surrey
KT16 0PZ
Tel: 0193-272-3534
Fax: 0193-272-2841

Date: 17th October 2016

Dear Johnathan,

Letter of NHS Permission at ASPH

Full Study Title:	**Cognition in multiple sclerosis**
IRAS Project ID:	**196840**
REC Ref:	**16/SC/0165**

Thank you very much for submitting your study for R&D review. I am very pleased to inform you that the Director of R&D has approved your study and the R&D office has no objection to your proceeding with this study. However, the R&D Office would highly appreciate to receive final report of your study and any dissemination(s) from this work.

Please make sure you are using the latest version of all documents and are following the latest procedures.

We wish you success with your research!

If you wish to discuss further, please do not hesitate to contact me.

Scale document down

Yours sincerely,

Research & Development
"Aspiration for Innovation"

Freda Gomes
R&D Support Manager
E-Mail: Freda.Gomes@asph.nhs.uk

Cc:
Prof Dawn Langdon, Professor of Neuropsychology, Director of Health and Medicine, RHUL
Dr Isaac John, Deputy Director of R&D, ASPH
Dr Martha Wrigley, R&D Manager, ASPH

Appendix 4: St Georges Approval for PIC inclusion

St George's University of London

St George's University Hospitals NHS
NHS Foundation Trust

St George's Joint Research & Enterprise Office (JREO)
Ground Floor, Hunter Wing, St George's University of London,
Cranmer Terrace, Tooting, London SW17 0RE

13th January 2017

Dear Dr David Barnes (MS)

RE: **IRAS ID 196840_ Confirmation of Capacity and Capability at St George's University Hospitals NHS Foundation Trust**

SHORT PROJECT TITLE: Cognition in multiple Sclerosis
REC Reference: 16/SC/0165
JREO Reference: PIC16.0017
IRAS project ID: **196840**
Sponsor: Royal Holloway University of London
Local Collaborator/Principal Investigator: Dr David Barnes (MS)

This email confirms that St George's University Hospitals NHS Foundation Trust has the capacity and capability to deliver the above referenced study as a PIC. Please find attached our agreed Statement of Activities as confirmation.

The documents reviewed and approved were those specified in the HRA approval EMAILdated 13/01/2017 the protocol version approved is version 1.3 dated 18/11/2016.

The Governance team of the JREO is constantly looking for ways to improve the service that we offer to our researchers. If you could please take a moment of your time and complete a brief feedback survey we would be grateful. The link is www.surveymonkey.com/s/RCNMRC9. Thank you for taking the time to complete this form, your feedback is very valuable to us.

Please contact the JREO if you require any further guidance or information on any matter mentioned above. We wish you every success in your research.

Best wishes,

Debbie Rolfe

Carbon Copy: (Sponsor)Royal Holloway University of London

JREODOC0104 HRA APPROVAL LETTER/EMAIL v1 26/04/2016

Appendix 5: MS Participant Information Sheet

Study Title: Cognition in Multiple Sclerosis

Ethics Committee Reference Number:

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve. **A member of the research team will go through the information sheet with you, discuss the information and answer any questions you have**.
We'd suggest this should take about 15-20 minutes. Please feel free to talk to others about the study if you wish.

Part 1 tells you the background/purpose of the study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Please ask us for more information if anything is unclear.

Research Sites
1) Participants homes
2) St. Peter's Hospital - Guildford Road, Chertsey, Surrey, KT16 0PZ

Questions about the research can be directed to:
The Principal Investigator: Jonathan Hinchliffe
Department of Clinical Psychology, Royal Holloway University of London, Egham, Surrey, TW20 0EX
Tel: 01784 414012
Email: Cerecog@live.rhul.ac.uk
Alternatively, feel free to ask any questions to your consultant neurologist (Dr. Khaled Abdel-Aziz, Dr. David Barnes or Dr. Jan Coeberghe).

Complaints procedure

If you have any concerns or questions about any aspects of the study, please contact the principal investigator (Jonathan Hinchliffe) who will endeavour to answer your questions.

If you remain unhappy and wish to make a formal complaint, you can do this by contacting Professor Dawn Langdon
Department of Psychology, Royal Holloway University of London, Egham, Surrey, TW20 0EX
Email: d.langdon@rhul.ac.uk

Part 1

Background to the project
Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system. It affects 100,000 people in the UK and individuals are typically diagnosed between 20-40 years of age. There are a number of physical symptoms of multiple sclerosis such as fatigue, visual problems, muscle weakness, spasm, pain and difficulties with balance. 50-60% of individuals also experience cognitive impairment (changes in thinking abilities).

Purpose of the research
The purpose of the study is to compare the cognitive profile (strengths and weaknesses in thinking skills) of individuals with MS to those who do not have MS. The study will be particularly looking at how certain physical symptoms relate to different profiles of thinking skills. This has clinical and theoretical implications, increasing the understanding of the effects of multiple sclerosis, as well as creating an ability to differentially diagnose individuals. This will then allow professionals to best support people to compensate for difficulties they experience and increase the quality of life of individuals with multiple sclerosis.

Who can take part?
You are eligible to take part if you are between 18 and 60 years of age, and you have a diagnosis of relapsing remitting multiple sclerosis. To take part, you must have been born and educated in England. We will be unable to include you if you have experienced a relapse or major medication change in the last two months. We will also not be able to include you if you are currently abusing drugs or alcohol, if you have a significant psychiatric condition or have another neurological condition. If you are unsure that any of these apply to you, please discuss it with the chief investigator.

Do I have to take part?
No. Your participation is completely voluntary. Non-participation will not affect clinical care.

How do I take part?
If you agree to take part, someone will go through the information sheet with you and you will be asked to sign a consent form. A member of the research team will then

contact you to discuss your participation and arrange a time to meet and complete the research. It can take two hours or more to complete all the tasks. It is possible that these tasks could cause you to become fatigued. Please bear in mind that you are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive or your legal rights.

What will I have to do if I take part?
You will initially be asked to complete a number of questionnaires, and then to complete a number of tests. These will measure various areas of cognition including verbal fluency, processing speed, attention, working memory, verbal learning, memory, premorbid IQ, dexterity and extremity function. Some of these tests may be challenging.

Where will I have to go and for how long?
The researcher may see some participants in their own homes or at St Peter's Hospital. Participation will take about 2 hours and can usually be completed in one session with breaks if you need them.

When will I give consent to take part in the research?
Following reading through this information sheet, the researcher will provide more information and answer any questions that you may have. When you, and the researcher, feel fully satisfied that you have all the information you require to make an informed decision, consent will be sought. At this point, you will be asked to sign the consent form. No assessments will take place before informed consent is gained.

Part 2

What are the potential benefits of taking part?
Whilst there may be no personal benefits to participating, the information you give could greatly contribute to improvements in the availability of cognitive testing for people with MS.

What are the potential disadvantages of taking part?
It is possible that you may feel fatigued whilst carrying out the tests. Should this happen, please let Jonathan Hinchliffe know, and we can take a break or complete the tests on another occasion.

Will my participation be kept confidential?
We will follow ethical and legal practice to ensure that all information you provide to us, and the results from your tests will be kept strictly confidential. Some parts of your medical records and data collected will be looked at by the principal investigator, their academic supervisor and specific members of the clinical team at Ashford and St Peter's Hospital. All data will be coded anonymously and stored securely.

We will not let your GP know that you are taking part in the study. However, if a member of the research team feels you would benefit from discussing the study or your general well-being with your GP or your neurology team they may advise you to do so.

The overall results of the study will be made public in a completely anonymous form ensuring that no participants can be identified.

The only time we would consider breaking confidentiality is if you disclose information that makes the researcher concerned for your safety or that of someone else. We would then do our best to discuss options available to you and ourselves in terms of informing other people.

What will happen to my results after the study?
All your information will be stored anonymously. Analysis of the information obtained will be completed on a computer by the principal investigator based at Royal Holloway, University of London. The paper copies of the results will be stored in a secure filing

cabinet at Royal Holloway University of London for 3 years for audit purposes. At which point all data will be disposed of following confidential disposal procedures.

The overall findings of the study will be published in a scientific paper or peer reviewed journal. The data will also be incorporated into the doctoral thesis of the principal investigator. Findings may also be distributed through voluntary organisations such as the MS Society and presented at appropriate scientific conferences.
If you would like a summary of the study's findings please indicate this on the consent form.

What will happen if I want to withdraw from the study?
You can decide you no longer wish to take part at any point. Following your request to withdraw from the study, all the data collected from you will be destroyed. This will not affect the standard of care you receive or your legal rights.

Should you give consent and later lose capacity to do so we will include your data in the study unless you indicate otherwise on the consent form.

Who is organising the research?
The principal investigator is a Trainee Clinical Psychologist (Jonathan Hinchliffe), who is conducting the research as part of his doctorate in clinical psychology. The research will be supervised by a Professor of Neuropsychology (Professor Dawn Langdon) and is sponsored by Royal Holloway University of London. Three consultant neurologists (Dr. Khaled Abdel-Aziz, Dr David Barnes and Dr Jan Coeberghe) are collaborators in the study.

A Research Ethics Committee (REC) has approved this study. RECs are independent groups of people who protect your interests by reviewing all research undertaken in the NHS.

Appendix 6: MS Consent Form

Ashford and St. Peter's Hospitals NHS
NHS Foundation Trust

Consent Form

Study Title: Cognition in multiple sclerosis
Name of principal investigator: Jonathan Hinchliffe
Participant reference number:
Ethics Committee Reference Number: 16/SC/0165

	Please initial to confirm
1. I confirm that I have read and understand the information sheet for the above study dated Information Sheet: 28.04.16 V1.2MS	
2. I have had the opportunity to consider the information, ask questions and have received adequate answers.	
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
4. Where it is relevant to my taking part in this research, I understand that relevant sections of my medical notes and data collected during the study may be looked at by the research team and responsible individuals from the NHS Trust. I give permission for these individuals to have access to my records.	
5. I give permission for data already collected to be retained for the purposes of the research if I lose capacity to consent to taking part whilst the study is ongoing.	
6. I would like to receive group feedback about the overall results of the study. I understand this will be sent once the study is complete in late 2017. I give permission for my address to be held by the above named researcher until the end of the research to facilitate this.	
7. I agree to take part in the above research study.	

_____ Date: _____
Name of participant

_____ Date: _____
Name of person taking consent

Consent form: 28.04.16 V1.2MS

Appendix 7: MS Invitation Letter

Jonathan Hinchliffe (BSc Hons, MSc, PGDip)
Department on Clinical Psychology
Royal Holloway, University of London
Egham
Surrey
TW20 0EX

Dear Sir/Madam,

This letter provides an outline of a research project that you may wish to take part in: '*Cognition in Multiple Sclerosis'*. The project aims to look at strengths and weaknesses in the thinking skills of individuals with multiple sclerosis, and to compare these with those who do not have multiple sclerosis.

Background: Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system. It affects 100,000 people in the UK and individuals are typically diagnosed between 20-40 years of age. 50-60% of individuals experience cognitive impairment (changes in thinking abilities).

Purpose: To compare the cognitive profile (strengths and weaknesses in thinking skills) of individuals with MS to those who do not have MS. The study will be particularly looking at how certain physical symptoms relate to different profiles of thinking skills. This has clinical and theoretical implications, increasing the understanding of the effects of multiple sclerosis, as well as creating an ability to differentially diagnose individuals. This will then help professionals to best support people to compensate for difficulties they experience and increase the quality of life of individuals with multiple sclerosis.

Who is conducting the research? Jonathan Hinchliffe (Trainee Clinical Psychologist, 01784 414012) is the principal investigator for the research. This research will be submitted as part of his doctoral thesis (Doctor in Clinical Psychology) and is sponsored by Royal Holloway University of London. Taking part is entirely voluntary and whether you participate, or do not participate, will have no impact on your care at Ashford and St. Peter's Hospitals. Jonathan's contact details are located on the bottom of this letter.

What is involved? Involvement in the study will take less than two hours. You will be invited to meet with Jonathan Hinchliffe, either at your own home or at St. Peter's

Hospital. You will initially be asked to complete a number of questionnaires, and then to complete a number of tests. Some of these tests may be challenging, but most people find them enjoyable.

What happens next? If you are interested in taking part in the study, please contact Jonathan Hinchliffe on the contact details below. A more detailed information sheet can be provided on request, and you are welcome to discuss participation in the study with the neurology team or with Jonathan. If you are not interested in taking part then you do not need to take any further action. Your details will remain confidential and we will not attempt to contact you regarding this research again.

What if I change my mind? You can withdraw from the study at any time, without providing a reason for doing so. At this point any existing information that you have given will be removed.

Thank you very much for taking the time to consider taking part in this research project.

Yours sincerely,

Jonathan Hinchliffe
Trainee Clinical Psychologist / Principal Investigator
Tel: 01784 414012
Email: Cerecog@live.rhul.ac.uk

Appendix 8: HC Invitation Letter

Jonathan Hinchliffe (BSc Hons, MSc, PGDip)
Department on Clinical Psychology
Royal Holloway, University of London
Egham
Surrey
TW20 0EX

Dear Sir/Madam,

This letter provides an outline of a research project that you may wish to take part in: '*Cognition in Multiple Sclerosis'.* The project aims to look at strengths and weaknesses in the thinking skills of individuals with multiple sclerosis, and to compare these with those who do not have multiple sclerosis.

Background: Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system. It affects 100,000 people in the UK and individuals are typically diagnosed between 20-40 years of age. 50-60% of individuals experience cognitive impairment (changes in thinking abilities).

Purpose: To compare the cognitive profile (strengths and weaknesses in thinking skills) of individuals with MS to those who do not have MS. This has clinical and theoretical implications, increasing the understanding of the effects of multiple sclerosis, as well as creating an ability to differentially diagnose individuals. This will then help professionals to best support people to compensate for difficulties they experience and increase the quality of life of individuals with multiple sclerosis.

Who is conducting the research? Jonathan Hinchliffe (Trainee Clinical Psychologist) is the principal investigator for the research. This research will be submitted as part of his doctoral thesis (Doctor in Clinical Psychology) and is sponsored by Royal Holloway University of London. Taking part is entirely voluntary and whether you participate, or do not participate, will have no impact on your care at Ashford and St. Peter's Hospitals. Jonathan's contact details are located on the bottom of this letter.

What is involved? Involvement in the study will take less than two hours. You will be invited to meet with Jonathan Hinchliffe, either at Royal Holloway University of London or other appropriate venues. You will initially be asked to complete a number of questionnaires, and then to complete a number of tests. Some of these tests may be challenging, but most people find them enjoyable.

What happens next? If you are interested in taking part in the study, please contact Jonathan Hinchliffe on the contact details below. A more detailed information sheet can be provided on request, and you are welcome to discuss participation in the study with the neurology team or with Jonathan. If you are not interested in taking part then you do not need to take any further action. Your details will remain confidential and we will not attempt to contact you regarding this research again.

What if I change my mind? You can withdraw from the study at any time, without providing a reason for doing so. At this point any existing information that you have given will be removed.

Thank you very much for taking the time to consider taking part in this research project.

Yours sincerely,

Jonathan Hinchliffe
Trainee Clinical Psychologist / Principal Investigator
Tel: 01784 414012
Email: Cerecog@live.rhul.ac.uk

Appendix 9: HC Participant Information Sheet

Study Title: Cognition in Multiple Sclerosis

Ethics Committee Reference Number:

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve. **A member of the research team will go through the information sheet with you, discuss the information and answer any questions you have**.
We'd suggest this should take about 15-20 minutes. Please feel free to talk to others about the study if you wish.

Part 1 tells you the background/purpose of the study and what will happen to you if you take part.
Part 2 gives you more detailed information about the conduct of the study.

Please ask us for more information if anything is unclear.

Research Sites

1) St Peter's Hospital
2) Royal Holloway University of London - Department of Clinical Psychology, Royal Holloway University of London, Egham, Surrey, TW20 0EX

Questions about the research can be directed to:
The Principal Investigator: Jonathan Hinchliffe
Department of Clinical Psychology, Royal Holloway University of London, Egham, Surrey, TW20 0EX
Tel: 01784 414012
Email: Cerecog@live.rhul.ac.uk

Complaints procedure

If you have any concerns or questions about any aspects of the study, please contact the principal investigator (Jonathan Hinchliffe) who will endeavour to answer your questions.

If you remain unhappy and wish to make a formal complaint, you can do this by contacting

Professor Dawn Langdon
Department of Psychology, Royal Holloway University of London, Egham, Surrey, TW20 0EX
Email: d.langdon@rhul.ac.uk

Part 1

Background to the project
Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system. It affects 100,000 people in the UK and individuals are typically diagnosed between 20-40 years of age. Cognitive impairment (changes in thinking abilities) is recognised in 50-60% of individuals. In order to understand the pattern of difficulties people with MS have in thinking we must compare them to healthy individuals.

Purpose of the research
The purpose of the study is to compare the cognitive profile (strengths and weaknesses in thinking skills) of individuals with MS to those who do not have MS. This has clinical and theoretical implications, increasing the understanding of the effects of multiple sclerosis, as well as creating an ability to differentially diagnose individuals. This will then allow professionals to best support people to compensate for difficulties they experience and increase the quality of life of individuals with multiple sclerosis.

Who can take part?
You are eligible to take part if you are between 18 and 60 years of age. To take part, you must have been born and educated in England. We will not be able to include you if you are currently abusing drugs or alcohol, if you have a significant psychiatric condition or have a neurological condition that may affect your thinking skills. If you are unsure that any of these apply to you, please discuss it with the chief investigator.

Do I have to take part?
No. Your participation is completely voluntary.

How do I take part?
If you agree to take part, someone will go through the information sheet with you and you will be asked to sign a consent form. A member of the research team will then contact you to discuss your participation and arrange a time to meet and complete the research. It can take two hours or more to complete all the tasks. It is possible that these tasks could cause you to become fatigued. Please bear in mind that you are free to withdraw at any time, without giving a reason.

What will I have to do if I take part?
You will initially be asked to complete a number of questionnaires, and then to complete a number of tests. These will measure various areas of cognition including verbal fluency, processing speed, attention, working memory, verbal learning, memory, premorbid IQ, dexterity and extremity function. Some of these tests may be challenging, but most people find them enjoyable.

Where will I have to go and for how long?

The researcher may participants at St Peter's Hospital or at Royal Holloway University of London. Participation will take about 2 hours and can usually be completed in one session with breaks if you need them.

When will I give consent to take part in the research?
Following reading through this information sheet, the researcher will provide more information and answer any questions that you may have. When you, and the researcher, feel fully satisfied that you have all the information you require to make an informed decision, consent will be sought. At this point, you will be asked to sign the consent form. No assessments will take place before informed consent is gained.

Part 2

What are the potential benefits of taking part?
Whilst there may be no personal benefits to participating, the information you give could greatly contribute to improvements in the availability of cognitive testing for people with MS.

What are the potential disadvantages of taking part?
It is possible that you may feel fatigued whilst carrying out the tests. Should this happen, please let Jonathan Hinchliffe know, and we can take a break or complete the tests on another occasion.

Will my participation be kept confidential?
We will follow ethical and legal practice to ensure that all information you provide to us, and the results from your tests will be kept strictly confidential. All data will be coded anonymously and stored securely.

The overall results of the study will be made public in a completely anonymous form ensuring that no participants can be identified.

What will happen to my results after the study?
All your information will be stored anonymously. Analysis of the information obtained will be completed on a computer by the principal investigator based at Royal Holloway, University of London. The paper copies of the results will be stored in a secure filing cabinet at Royal Holloway University of London for 5 years for audit purposes. At which point all data will be disposed of following confidential disposal procedures.

The overall findings of the study will be published in a scientific paper or peer reviewed journal. The data will also be incorporated into the doctoral thesis of the principal investigator. Findings may also be distributed through voluntary organisations such as the MS Society and presented at appropriate scientific conferences.

If you would like a summary of the study's findings please indicate this on the consent form.

What will happen if I want to withdraw from the study?
You can decide you no longer wish to take part at any point. Following your request to withdraw from the study, all the data collected from you will be destroyed.

Should you give consent and later lose capacity to do so we will include your data in the study unless you indicate otherwise on the consent form.

Who is organising the research?

The principal investigator is a Trainee Clinical Psychologist (Jonathan Hinchliffe), who is conducting the research as part of his doctorate in clinical psychology. The research will be supervised by a Professor of Neuropsychology (Professor Dawn Langdon) and is sponsored by Royal Holloway University of London. Three consultant neurologists (Dr. Khaled Abdel-Aziz, Dr David Barnes and Dr Jan Coeberghe) are collaborators in the study.

A Research Ethics Committee (REC) has approved this study. RECs are independent groups of people who protect your interests by reviewing all research undertaken in the NHS.

Appendix 10: HC Consent Form

Ashford and St. Peter's Hospitals NHS
NHS Foundation Trust

Consent Form

Study Title: Cognition in multiple s§clerosis
Name of principal investigator: Jonathan Hinchliffe
Participant reference number:
Ethics Committee Reference Number: 16/SC/0165

	Please initial to confirm
1. I confirm that I have read and understand the information sheet for the above study dated Information Sheet: 28.04.16 V1.2HC.	
2. I have had the opportunity to consider the information, ask questions and have received adequate answers.	
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
4. I give permission for data already collected to be retained for the purposes of the research if I lose capacity to consent to taking part whilst the study is ongoing.	
5. I would like to receive group feedback about the overall results of the study. I understand this will be sent once the study is complete in late 2017. I give permission for my address to be held by the above named researcher until the end of the research to facilitate this.	
6. I agree to take part in the above research study.	

R&D Research & Development "Aspiration for Innovation"

_____ Date: _____
Name of participant

_____ Date: _____
Name of person taking consent

Appendix 11: Symbol Digit Modalities Test (SDMT)

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Appendix 12: Word List Generation – Version A (WLG)

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Appendix 13: Paced Auditory Serial Addition Test (PASAT)

[Removed from online version]

Appendix 14: California Verbal Learning Task II (CVLT-II**)**

[Removed from online version]

Appendix 15: Brief Visual Memory Test – Revised (BVMT-R)

[Removed from online version]

Appendix 16: Test of Premorbid Functioning (TOPF)

[Removed from online version]

Appendix 17: Hospital Anxiety and Depression Scale (HADS)

[Removed from online version]

Appendix 18: Fatigue Severity Scale (FSS)

[Removed from online version]

Appendix 19: NARCOMS: Tremor and coordination Scale (TACS)

[Removed from online version]

Appendix 20: EDSS Telephone Version – Reproduced with permission from Professor Ludvig Kappos (Senior Author)

[Removed from online version]

Appendix 21: EDSS Functional System Convertor

[Removed from online version]

Appendix 22: Nine-hole peg test instructions (9HPT)

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Appendix 23: Grooved pegboard test instructions (GPT)

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Appendix 24: Skewness and Kurtosis Calculations and Transformations

(Page 1)

Variable	HC		RR-MSnc		RR-MSc	
	Skewness	Kurtosis	Skewness	Kurtosis	Skewness	Kurtosis
FSS	1.80	-0.50	-1.24	-0.67	-0.80	-1.07
HADS-D	2.16	0.22	0.91	-0.79	0.06	-0.73
HADS-A	1.33	1.07	0.57	-1.07	1.56	0.83
9HPT	-0.08	-0.64	2.73*	1.48	0.65	-1.00
SDMT	3.09*	1.71	-0.80	1.43	-0.29	-0.68
Premorbid IQ	-3.81*	2.10	-0.84	0.45	1.11	1.13
CVLT-II	-0.40	-1.02	0.67	-0.87	-0.03	0.21
BVMT-R	-2.12	0.71	-1.59	-0.72	0.00	-1.30

Scores <±2.58 meet criteria for normal distribution ($p < .01$)
* Scores >±2.58 (must be transformed)

(Page 2)

Variable	HC		RR-MSnc		RR-MSc	
	Skewness	Kurtosis	Skewness	Kurtosis	Skewness	Kurtosis
GPT	0.82	-0.83	2.17	0.59	3.34*	1.89
MPI	0.64	-0.83	2.79*	1.26	3.38*	1.92
WLG	2.20	1.30	0.05	-1.05	-0.72	-0.78
PASAT	-0.69	-0.73	-1.63	0.26	0.10	-0.90
Age	2.06	-0.81	-0.11	-1.02	0.14	-0.98
Years since diagnosis	N/A	N/A	2.35	0.79	0.29	-1.01

Scores <±2.58 meet criteria for normal distribution ($p < .01$)
* Scores >±2.58 (must be transformed)

Skew and Kurtosis z-scores for Transformed Variables

	Transformation	HC		RR-MSnc		RR-MSc	
		Skewness	Kurtosis	Skewness	Kurtosis	Skewness	Kurtosis
9HPT	Square Root	-0.29	-0.67	2.29	1.21	0.49	-1.01
SDMT	Square Root	2.64*	1.46	-2.00	1.81	-0.78	-0.52
GPT	Log 10	0.62	-0.94	1.41	-0.48	2.30	1.24
MPI	Log 10	0.26	-0.83	1.66	0.41	2.09	1.09
TOPF	X^4	-2.62*	1.41	0.65	-0.90	2.52	1.78

* Scores >±2.58

Appendix 25: Effect Sizes

	Effect size f	Effect size d
SDMT	1.06	3.19
CVLT-II	0.86	2.59
BVMT-R	0.97	2.90
WLG	0.92	2.76
PASAT	0.96	2.89
9HPT	0.97	2.91
GPT	0.98	2.94
MPI	0.98	2.94