The Relation of Cognition to Cerebellar Function in Relapsing-Remitting Multiple Sclerosis

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This thesis is dedicated to the memory of my mother-in-law, Claire Jennings. A wonderful, vibrant woman who cared deeply for so many and had a boundless optimism for life. Your legacy continues to inspire us all.

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The Relation of Cognition to Cerebellar Function in Relapsing-Remitting Multiple Sclerosis: Executive Summary

1.1 Multiple Sclerosis

Multiple Sclerosis (MS) is a common neurological condition in which the body's own immune system attacks cells within the brain and spinal cord. A broad range of signs and symptoms are associated with MS and often linked to the location of damage. As the disease progresses, an accumulation of disability builds placing a substantial burden on individuals, families and society. There is presently no cure for MS; however, several therapies exist that can modify the disease course as well targeting specific symptoms. Therefore, a key priority for intervention and rehabilitation is to offer personalised treatment to every person with MS to minimise disease impact and enhance quality of life.

1.2 Systematic Review

Cognitive impairment affects a significant portion of people with MS and is associated with worse prognosis and functional difficulties. It has become increasing recognised that cerebellar signs and cognitive dysfunction often occur in parallel in Relapsing-Remitting MS (RR-MS). Individuals who show physical signs of cerebellar involvement such as tremor and poor coordination experience greater disease-related impairment and poorer rehabilitation outcomes. Consequently, there is growing interest in the relationship between the cerebellum and cognition in MS.

A Systematic Review was conducted to investigate the contribution of the cerebellum to cognitive performance and other related variables in RR-MS. The aim was to provide a more objective appraisal of the literature and consider the proposed

existence of a distinct cognitive profile for RR-MS patients with cerebellar damage (RR-MSc).

Online literature databases were systematically reviewed for relevant articles. All articles that utilised any neuropsychological outcome measure to examine the relationship between cognition and the cerebellum and met inclusion criteria were included. Data on participants, study characteristics and key findings were extracted and summarised. Study methodology was assessed using a quality rating tool.

A total of 14 studies were included encompassing data from 433 patients. From the demographic information available, case participants were predominately female (73%), had a $\bar{x}$ age of 36.8, disease duration ranged from 2 – 12.1 years, had at least secondary school education, with an Expanded Disability Severity Scale (EDSS) $\bar{x}$ score of 2.0, indicating minimal disability. The most commonly assessed domains of cognition were information processing speed (IPS), verbal memory and verbal fluency. The Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addiction Task (PASAT), both measures of information processing speed; Controlled Oral Word Association Test (COWAT), verbal fluency; and Nine-Hole Peg Test (NHPT), upper limb motor function, were the most frequently used outcome measures. The methodological quality of the studies included was rated as fair to strong.

Several research highlights were considered. The most common and severe cognitive impairments were associated with IPS followed by executive dysfunction and reduced verbal fluency. There was minimal evidence of verbal or visual memory deficits. There was preliminary support for a differential cognitive profile between RR-MS patients

with cerebellar signs (RR-MSc) and those without cerebellar signs (RR-MSnc). The cognitive profile of RR-MSc was associated with further reduced IPS, and more executive dysfunction, however more research was required to substantiate the finding. Cerebellar signs were strongly related to poor performance on motor function tasks. Evidence suggested that the cerebellum does not significantly contribute to fatigue or mood difficulties.

The validity of findings was supported by previous reviews and clinical data from acquired cerebellar lesions. The findings were significant due to an improved characterisation of MS heterogeneity, which has implications for an improved understanding of mechanisms leading to deficits and development of tailored interventions. The field would benefit from an increased number of high quality studies, addressing methodological heterogeneity through stringent inclusion criteria and longer periods of observation to ascertain prognosis of cognitive impairment in RR-MS.

The systematic review concluded that there is substantial evidence to support that the cerebellum contributes to cognitive performance, especially IPS, and motor function. The intricacies of cerebellar-related impairment remain unknown. A common theoretical explanation of the increased cognitive impairment with RR-MSc was that disruption to salient connections or 'loops' between cortical regions and the cerebellum might lead to costly inefficiencies. Further research was warranted to substantiate this theory.

1.3 Empirical Study

The presence of cerebellar signs and cognitive impairment are associated with poor prognosis. As such, it is vital that research efforts focus on developing a clearer measurement of the interrelation of cerebellar cognitive impairment.

The cerebellum forms part of salient cortico-cerebellar loops, which are responsible for a range of functions. It has been proposed that the cerebellum contributes to cognition and motor control through the creation and storage of automated subroutines, enabling precise execution of tasks without the need of feedback or conscious awareness. This results in an increase in task efficiency by acting as a 'shortcut' and frees cortical regions to engage in other tasks. Conversely, cerebellar dysfunction caused by MS pathology reduces efficiency and optimal performance.

Motor planning is the ability to conceive, plan and execute coordinated motor responses. Optimal performance is likely to be dependent on cerebellum integrity and therefore serves as a useful indicator of cerebellar function. Accordingly, inefficient motor planning will be associated with cognitive decline, particularly IPS, as the cerebellum mediates both. The recruitment of RR-MSc and comparing performance on motor planning and cognitive tasks with RR-MSnc offers an opportunity to further elucidate mechanisms.

To calibrate motor planning, the Grooved Peg Test (GPT) - NHPT difference was used to compute a Motor Planning Index (MPI), with the NHPT serving as a control for sensorimotor impairment.

Therefore, the objective of the study was to investigate the longitudinal relation of cognition to cerebellar function in RR-MS, and how changes relate to motor planning and function. The following hypotheses were identified:

1. The baseline cognitive profile of patients with RR-MSc compared with RR-MSnc and HC will be maintained at 1-year follow-up.
2. The performance of patients with RR-MSc on cognitive and motor planning tasks will decline over a 1-year period compared to patients with RR-MSnc and HC, who in turn, will remain stable.
3. Changes in motor planning will be related to changes in information processing speed (IPS) as the cerebellum mediates both.

The study was an extension of a cross-sectional investigation of cognition and motor planning. Participants were recruited from Neurology clinics and assigned to three groups: RR-MSc, RR-MSnc and healthy controls (HC) using a validated self-report cerebellar symptom questionnaire (Tremor and Coordination Scale, TACS). Participants completed a test battery featuring the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), Word List Generation (WLG), Paced Auditory Serial Addition Test (PASAT), Test of Premorbid Function (TOPF), NHPT and GPT. Additional questionnaires included the Fatigue Severity Scale (FSS), Hospital Anxiety and Depression Scale (HADS) and a measure of disability, Expanded Disability Severity Scale (EDSS). The procedure involved participants repeating the test battery with the additional measures of subjective motor function (ABILHAND) and visual acuity (Snellen Pocket Eye Test).

A total of 11 RR-MSc (5 males, $\bar{x}$ age: 41, $\bar{x}$ IQ: 100.9), 17 RR-MSnc (2 males, $\bar{x}$ age: 41, $\bar{x}$ IQ: 106.7) and 9 HC (2 males, $\bar{x}$ age: 37.8, $\bar{x}$ IQ: 107.0) were assessed at baseline and 12 months. No participants were excluded from the study. The drop-out rates were as follows: 3 RR-MSc, 4 RR-MSnc and 21 HC. Reasons for drop out included: declined for personal reasons (10), unable to complete in recruitment window (12) and unable to contact (3).

The analysis of the results found no significant demographic differences between the groups. Interestingly, there was a significant interaction for EDSS scores indicating the rate of disability grew progressively worse for RR-MSc compared to RR-MSnc ($F(2,34) = 6.49$, $p = .017$). A mixed model ANOVA was used to explore the main effect of group, time and interaction for each of the cognitive and motor measures. There was no significant interaction effect for any test. However, analysis revealed consistent significant group separation on the CVLT-II ($F(2,34) = 8.52$, $p = .001$), SDMT ($F(2,34) = 6.12$, $p = .005$), NHPT ($F(2,34) = 29.11$, $p < .001$), GPT ($F(2,34) = 11.74$, $p < .001$) and MPI ($F(2,34) = 14.19$, $p < .001$) but not for the BVMT-R ($F(2,34) = .387$, $p = .682$). There was a significant effect of time for the BVMT-R ($F(1,34) = 4.74$, $p = .037$) and the CVLT-II ($F(1,34) = 18.83$, $p < .001$). Finally, there was a significant moderate negative correlation between the MPI and IPS. The SDMT was more strongly correlated with motor planning ($r(27) = -.611$, $p < .001$) than the PASAT-3 ($r(27) = -.5$, $p = .002$). There was a weak positive correlation between ABILHAND and NPT ($r(27) = .39$, $p = .017$) and the GPT ($r(27) = .35$, $p = .033$)

In relation to the hypotheses, it was highlighted that the RR-MSc group were significantly outperformed by RR-MSnc and HC groups on all cognitive measures aside from the BVMT-R. There were no significant differences between RR-MSnc and HC groups. The RR-MSc group were characterised by greater impairment on tests of cognition, motor function and motor planning. Contrary to the second hypothesis, the magnitude of group differences remained stable for all groups. Lastly, evidence suggested that the MPI was able to capture the interrelation of cognitive cerebellar damage as indicated by the significant associations with measures of IPS, thus supporting the third hypothesis.

Several limitations were noted. Firstly, patient heterogeneity may have masked true effects. The test battery could have benefited from additional tests for executive dysfunction. The MPI suffered from methodological concerns including the unequal sensorimotor components of the NHPT and GPT which were not accounted for. Results must be considered with caution given the high rate of attrition and the increased likelihood of type II error due to multiple statistical analysis. There was an implication that the study was underpowered to detect certain effects.

It was concluded that RR-MSc may represent a distinct subtype characterised by greater impairment in several domains. These differences were maintained over a year. Furthermore, the findings provide theoretical support that the reduced performance of the RR-MSc group is thought to be related to a reduction in cerebellar function through the loss of subroutines which are considered important for efficiency. The MPI is potentially a promising tool to measure the interrelation of

cerebellar cognitive impairment. The next step is to validate the MPI with an MRI study exploring how it relates to cerebellar lesion load and atrophy. This would ensure that results do not merely reflect the influence of disease severity.

1.4 Integration, Impact and Dissemination

Integration

- To aid integration a clear narrative revolving around the contribution of the cerebellum to cognition and how this related to motor planning was developed and expanded through each thesis component. The underlying intention was always to return the focus to improving the lives of those affected by MS.
- There were several challenges encountered including the practicalities of adding a longitudinal component to a cross-sectional study and encountering issues with attrition.
- Relevant clinical experience on placement, supervision and shared discussions with collaborators and service-user involvement were all useful in overcoming difficulties and integrating the thesis.

Impact

- The proposal that RR-MSc may warrant a distinct subtype has the potential to aid theoretical understanding and enable more tailored interventions for a group associated with poor rehabilitation outcomes.

- Prognostic information of RR-MSc provides greater insight for clinicians and an opportunity for more personalised information, feedback and education for patients and their support network.
- The MPI represents a useful tool for the measurement of interrelation of cerebellar cognitive impairment.
- The research aligns with grassroot campaigns such as the #ThinkHand movement which aims to draw attention to the importance of upper limb function in MS.
- The personal impact of working with people with MS has provided greater insight into living with a chronic condition and knowledge to aid my career as a neuropsychologist.

Dissemination

- For the research to reach a diverse audience, the dissemination strategy focuses on a communication campaign across several channels.
- Proposed dissemination routes include:

    - A plain English summary to research participants and associated clinicians.
    - Approaching national MS organisations, popular blogs (e.g. BartsMS Blog).
    - Submission of an abstract to European Committee for the Treatment and Research in Multiple Sclerosis (ECTRIMS) conference to target a global audience.

- The use of social media to promote the research, increase visibility and generate engagement.
- Submission of systematic review and empirical study to a peer review journal e.g. Multiple Sclerosis and Related Disorders Journal or Multiple Sclerosis Journal.

The Contribution of the Cerebellum to Cognitive Performance and Related Variables in Relapsing-Remitting Multiple Sclerosis: A Systematic Review.

2.1 Abstract

Cognitive impairment is a common and debilitating feature of Multiple Sclerosis (MS). An understanding of the factors that contribute to cognitive deficits remains a key area for research. Given cerebellar damage is associated with poorer disease-related outcomes, there is a considerable amount of interest in role of the cerebellum and the relationship to cognitive performance in MS.

The objective was to conduct a systematic review of all studies published in English that measured the impact of cerebellar damage on cognition in Relapsing-Remitting MS (RR-MS), providing an overview of key findings and an objective evaluation of the content and methodological quality of studies included.

Online literature databases (PubMed, Web of Science, Google Scholar and OVID) were systematically reviewed for relevant articles. All articles that utilised any neuropsychological measure in RR-MS to explore the relationship between cognition and the cerebellum and met inclusion criteria were included. Data on study characteristics and results were extracted and article quality was assessed.

A total of 14 studies were included encompassing data from 433 MS patients. The overall quality of articles was either fair or strong according to a validated test of methodological quality. A review of key data revealed evidence for cerebellar involvement in information processing speed, executive functioning and motor functioning. There was little evidence for cerebellar involvement in other cognitive domains or relation to mood or fatigue symptoms.

There was substantial evidence to support that cerebellar damage adversely affected cognitive performance, particularly regarding information processing speed, although the intricacies of the cerebellar-related cognitive impairment remain elusive. The field would benefit from addressing methodological heterogeneity and increased prevalence of longitudinal studies to ascertain prognosis and interrelation of cerebellar cognitive impairment.

2.2 Introduction

The prevalence of Multiple Sclerosis (MS) in the United Kingdom is increasing (Mackenzie, Morant, Bloomfield, MacDonald, & O'Riordan, 2014). The disease places a substantial burden on individuals, families and society, and as such there is a need for research efforts to focus on the understanding and management of symptoms that impair quality of life (QoL). Cognitive impairment is a common and debilitating feature of MS which is associated with worse prognosis and functional difficulties (Amato et al., 2010; Chiaravalloti & DeLuca, 2008; Langdon, 2011). It has been suggested that the cerebellum plays an important role in cognition (Koziol et al., 2014). Cerebellar damage in MS greatly contributes to disease-related impairment and is associated with poor response to symptomatic treatment and rehabilitation (Langdon & Thompson, 1999; Weier et al., 2015). As a result, there is a considerable amount of interest in the relationship between the cerebellum and cognition in MS. For these reasons, it is important to understand the contribution of the cerebellum to cognitive performance and other related factors in MS.

2.2.1 Multiple Sclerosis

MS is an inflammatory, demyelinating disease of the central nervous system that is characterised by the presence of lesions in the brain and spinal cord, which leads to axonal demyelination (Ransohoff, Hafler, & Lucchinetti, 2015). The damage of myelin results in loss of saltatory conduction and the disease appears to target the myelin and oligodendrocytes before neurons are later lost. The cause of the disease is unknown; although, it is widely considered to involve a combination of environmental

and genetic factors as well as an immune-mediated process (Compston & Coles, 2008; Lobeck, 2002). Typically the disease develops between the ages of 20 – 40 years and women are twice as likely to develop the disease as men (Mackenzie et al., 2014). Based on epidemiologic and genetic data, MS is proposed to be caused by some environmental agent that triggers the disease in susceptible individuals. The trigger is unknown, but likely to be a viral or bacterial infection that occurs in childhood (Male, 2013). The onset of MS can be described as a 'perfect storm', whereby multiple factors combine to create a weakness in the brain and an uncontrolled immune response.

2.2.2 Mechanisms of MS

The precise mechanisms of MS initiation, development and progression remain elusive; however, inflammation and neurodegeneration are both considered to play a key role (Dendrou, Fugger, & Friese, 2015). It has been proposed that early stages of MS begin with the formation of acute inflammatory lesions characterised by breakdown of the blood-brain barrier (BBB) and invading peripheral immune cells (Male, 2013). Migration of autoreactive lymphocytes (T-cells) and macrophages activate various inflammatory processes that cause damage to oligodendrocytes, the cells responsible for support and insulation of axons through the creation of myelin (Compston & Coles, 2008). Damage to the integrity of the axon disrupts communication, leading to a range of clinical signs and symptoms. Although there is variability in terms of the degree of damage to myelin and axons in early stages, there is little overt damage to the brain and spinal cord outside the focal lesions. Moreover, recovery in early stages is possible due to a process of remyelination by which new

myelin sheaths are created; however, this process becomes increasingly inadequate and eventually fails leading to enduring signs and symptoms (Chari, 2007).

It has been suggested that chronic inflammation drives processes that eventually lead to neurodegeneration (Dendrou et al., 2015; Friese, Schattling, & Fugger, 2014). Neuroaxonal injury, due to a cascade of events such as oxidative stress and ionic imbalance combined with a failure of neuroprotective and regenerative mechanisms, culminates in cell death and loss of neuronal activity. This irreversible loss causes brain atrophy and increased functional disability.

2.2.3 Diagnosis and Subtypes

The diagnosis of MS is based on clinical features as there is no one definitive test. The most recent criteria were developed by a panel of experts based on a revision of the McDonald (2001) criteria (Thompson et al., 2018). These criteria are used to confirm or dispute a diagnosis and based on evidence of damage to the central nervous system in time and space, often incorporating magnetic resonance imaging (MRI), and states that neurological disturbance must occur on at least two occasions (lasting more than 24 hours), more than 30 days apart.

Although there are several variations, MS can be broadly divided into three main forms: Relapsing-Remitting MS (RR-MS), secondary progressive MS (SP-MS) and primary progressive MS (PP-MS).

(i) Relapsing-Remitting MS (RR-MS)

The most common subtype, accounting for approximately 85% of MS patients, is the relapsing remitting form (Dendrou et al., 2015). The disease course begins with an episode of neurological dysfunction causing an increase in disability, followed by a remission period and complete or partial recovery. Inadequate recovery leads to residual disability and eventually, disability accumulates with recurrent bouts of relapse and remission over time (Leary, Porter, & Thompson, 2005).

(ii) Secondary Progressive MS (SP-MS)

Out of the 85% of patients with RR-MS, approximately 80% go on to develop the secondary progressive form (Dendrou et al., 2015). The disease pattern is characterised by progressive neurological decline with brain atrophy and increased axonal loss following an initial relapsing course (Leary et al., 2005).

(iii) Primary Progressive MS (PP-MS)

PP-MS accounts for 10 - 15% of the MS population which features a progressive decline from the outset without periods of relapse or remission (Dendrou et al., 2015). The average age tends to be older and comparatively more men are affected (Leary et al., 2005).

2.2.4 Clinical Features

The clinical manifestations of MS are not generally disease specific, instead an overabundance of signs or symptoms can occur affecting cognitive, motor, sensory, visual, and autonomic systems (Compston & Coles, 2008). As such, MS can be defined

as a heterogenous condition and there is considerable diversity in the experience of patients with MS. Conversely, certain features such as Charcot's triad of tremor, nystagmus and dysarthria are distinctive of MS (Weier et al., 2015). Other common symptoms include presentations of fatigue, visual deficits and paresis (Lublin, 2005).

Interestingly, invisible or 'hidden' symptoms of MS including fatigue, pain and cognitive changes were found to be more predictive of subjective health distress than visible symptoms such as tremor and speech difficulties (White, White, & Russell, 2008). In addition, research investigating the lived experiences of people with MS also highlighted the difficulties of these invisible symptoms and the challenges they pose in daily activities (MS Society, 2017).

2.2.5 Cognition

Cognition is the mental action or process of gathering knowledge that is acquired through learning or experience. It encompasses complex skills such as attention, perception, language and reasoning. Some of these skills decrease with normal aging; although, many factors can result in greater than expected cognitive impairment including neurological conditions such as MS (Raz & Rodrigue, 2006). Furthermore, cognitive dysfunction is closely associated with adverse outcomes on a range of daily activities (Chiaravalloti & DeLuca, 2008).

2.2.6 Cognitive Impairment in MS

The study of cognition in MS has increased exponentially over the last two decades due to increased awareness of the profound impact of impaired cognitive functioning. It is estimated that 43% - 70% of patients with MS experience cognitive impairment (Chiaravalloti & DeLuca, 2008). Furthermore, the pattern of cognitive impairment is not uniform: the typical cognitive profile of MS reveals impairments in information processing speed (IPS), memory and executive functioning skills, with relative preservation of verbal skills (Langdon, 2011). Although disease duration is not always associated with cognitive impairment, longitudinal studies have found that cognitive impairment at diagnosis predicts disability progression and poor clinical outcomes (Moccia et al., 2016; Pitteri, Romualdi, Magliozzi, Monaco, & Calabrese, 2016).

Cognitive impairment tends to be progressive with limited evidence of recuperation. One long-term longitudinal study, which followed 50 patients with MS over a 10-year period, found that 26% had mild or moderate impairment at baseline, and by the end of the follow-up period that number had increased to 56% (Amato, Ponziani, Siracusa, & Sorbi, 2001). Correspondingly, those with preserved cognition fell from 74% to 44% by the end of the study. Other short-term longitudinal studies have found similar findings. For example, a recent study evaluated the sensitivity of the Symbol Digit Modalities Test (SDMT) and the Paced Auditory Serial Addition Test (PASAT) to detect cognitive impairment at a 1-year follow-up in RR-MS (López-Góngora, Querol, & Escartín, 2015). At baseline, 27.6% were classified as cognitively impaired, and at 1 year, that increased to 31.6%. The study demonstrated that even relatively short-term longitudinal studies have the potential to detect changes in cognition and replicate the pattern of progression found in longer observations. A further review of

longitudinal studies monitoring cognitive functioning in MS concluded that incipient cognitive decline was the major predictor of further cognitive decline (Amato, Zipoli, & Portaccio, 2006).

Although a range of cognitive domains are impaired in MS, deficits in IPS are considered the most frequent (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004). IPS is defined as the efficiency of cognitive function and often involves working memory. Analysis of MS patient performance on a range of cognitive tests has implied that IPS is the unitary underlying deficit (Langdon, 2011), and therefore forms a valuable component of intact cognitive functioning. The nature of IPS impairment in MS suggests that it relies on the integrity of neural networks - complex interconnections between cortical and deep grey matter structures, supported by white matter projections (G. DeLuca, Yates, Beale, & Morrow, 2015; Ruet et al., 2014). The overarching consensus from research suggests that damage to neural networks would adversely affect cognitive efficiency as measured by IPS.

2.2.7 Effect of Cognitive Impairment on Daily Living

Several studies indicate that MS patients with cognitive deficits are compromised in many everyday activities including impaired social functioning (G. DeLuca et al., 2015) and continued employment (Honarmand, Akbar, Kou, & Feinstein, 2011). Evidence also suggests that poor QoL measures are associated with cognitive deficits (Cutajar et al., 2000). However, this finding has not always been replicated (Baumstarck-Barrau et al., 2011). After accounting for multiple predictors, a study by Benedict et al (2005) found QoL was most strongly predicted by measures of depression, whereas cognitive

impairment predicted vocational status. The overwhelming message is that intact cognitive functioning is important for activities of daily living.

2.2.8 Other Factors Contributing to Cognition

There are several factors that have the potential to affect neuropsychological test interpretation. For example, research has consistently demonstrated a negative association between depression and cognitive functioning in MS (Arnett, Barwick, & Beeney, 2008). Depression symptomatology in MS has been linked with reduced performance on measures of IPS, visual memory and executive functions (Morrow, Rosehart, & Pantazopoulos, 2016; Portaccio, 2016). Many of these deficits resemble the cognitive profile described above and thus highlights the challenge in disentangling contributions to performance. In addition, premorbid ability and fatigue have also been identified as factors that may influence performance (Benedict et al., 2002). Within this context, it is important these potentially confounding variables need to be considered when reviewing studies of cognition in MS.

2.2.9 Organisation of the Cerebellum

The cerebellum occupies the posterior cranial fossa and attached to the brain stem by the superior, middle and anterior cerebellar peduncles; thereby providing multiple connections to various regions of the brain (Roostaei, Nazeri, & Sahraian, 2014). It consists of two cerebellar hemispheres, separated by the vermis, and divided into three lobes: anterior, posterior and flocculonodular. Each lobe is considered to have

distinct functions. The cerebellum encompasses almost 80% of the total brain neurons, yet only represents 10% of the intracranial space (Herculano-Houzel, 2010).

2.2.10 Cerebellar Function

The cerebellum plays a vital role in many aspects of human behaviour and it is widely accepted that the function of the cerebellum is to integrate, regulate, and coordinate motor processes. However, converging evidence has demonstrated the importance of the cerebellum for other functions, including participation in a variety of cognitive functions (Koziol et al., 2014; Roostaei et al., 2014). For example, neuroimaging research has shown that different regions of the cerebellum form distinct cortico-cerebellar circuits with specific areas of the cerebral cortex as well as cerebellar involvement in higher-order cognitive processes (e.g. executive functions) (Balsters, Laird, Fox, & Eickhoff, 2014; Middleton & Strick, 1994; Stoodley & Schmahmann, 2010).

Further evidence to imply a role for the cerebellum in cognition is demonstrated in the cerebellar cognitive affective syndrome (CCAS) (Schmahmann & Sherman, 1998). The syndrome is characterised by acquired focal lesions and sequalae can include cognitive impairment such as executive dysfunction, impaired working memory, and visuospatial deficits, as well as personality and affective changes. Furthermore, a topographical distinction between anterior and posterior lobe damage has been proposed, with the latter being associated with changes in cognition (Stoodley & Schmahmann, 2010). From an anatomical and functional viewpoint, evidence suggests that the cerebellum is integrated into various neural networks, and consequently,

damage of either the cerebellum or related areas can affect a multitude of brain functions.

2.2.11 Role of the Cerebellum in MS

MS often has a predilection for the cerebellum. A broad range of clinical signs and symptoms of MS arise from lesions within the cerebellum and associated areas such as tremor, gait ataxia and poor coordination of voluntary movements (Weier et al., 2015). To exemplify, the role of the cerebellum in motor function is aptly demonstrated by performance on motor tasks such as the Nine-hole Peg Test (NHPT), which relies on cerebellar integrity. Research has found MS patients with higher cerebellar lesion load and increased atrophy performed worse on the NHPT compared with controls without cerebellar damage (van de Pavert et al., 2016). It is estimated that 11% of MS patients report cerebellar symptomatology as the predominant disease feature (Rot, Ledinek, & Jazbec, 2008). Furthermore, a large-scale study of patient relapses found that cerebellar relapse accounted for approximately 10% of all relapses (Kalincik et al., 2014). Undoubtedly, the cerebellum in MS contributes to a range of networks, in part due to the numerous connections to other parts of the central nervous system. Unfortunately though, cerebellar signs also tend to be more persistent and contribute to poorer outcomes (Amato & Ponziani, 2000).

Given the importance of the cerebellum in MS, there has been a growing interest in the contribution of the cerebellum to cognition. Syndromes such as CCAS and the cerebellar topographical organisation indicate cerebellar damage in MS is likely to contribute to cognitive impairment. This premise has also been supported by recent

studies of cognition in MS patients. For example, Weier et al (2014) demonstrated a significant association between cerebellar lesion and atrophy with Paced Auditory Serial Addition Task (PASAT) and Symbol Digit Modalities Test (SDMT), both measures of IPS. However, this finding has not always been replicated (Cerasa et al., 2013). Instead, Cerasa et al concluded that cognitive impairment was related to grey matter atrophy in specific cortical regions connected to the cerebellum. Despite their different conclusions, both studies highlight a role of the cerebellum in cognition and the importance of the integrity in cortico-cerebellar circuits.

Several theories have attempted to explain how the cerebellum participates in cognition. A recent consensus paper described the cerebellum as being critical for the modulation of sensorimotor and cognitive functions by way of multiple cortico-cerebellar loops, controlling diverse streams of information underlying a wide range of functional domains (Koziol et al., 2014). It is considered that the presence of these functionally distinct cortico-cerebellar loops disencumber cortical regions by reducing the cognitive load, so that attention can focus on higher cognitive tasks such as motor planning or reasoning (Balsters et al., 2014; Stoodley, 2012).

Of particular interest is a model describing the role of the cerebellum as having the ability to encode internal models of mental representations (Ito, 2008). An internal model is a neural representation of the external world (Ito, 2012). Accordingly, during tasks such as voluntary movement, the cerebellum can develop and hold a representation of information developed in the motor cortex during motor acquisition and use the internal model to perform precise movement without external feedback

or even conscious awareness. Support for the model is underpinned by clinical observations of normal control subjects and patients with cerebellar dysfunction (Koziol et al., 2014), however the model remains contentious.

There is a growing literature indicating cerebellar involvement in cognition in MS, however whether cerebellar involvement represents a distinct cognitive profile in MS remains unknown. In addition, the specificities of any relationship are not fully determined. As such, there is justification for a systematic review to investigate the contribution of the cerebellum to cognitive functioning and other-related variables in MS.

2.3 Summary and Objectives

Cognitive impairment is a common and debilitating feature of MS; therefore, it is important research efforts focus on understanding factors that contribute to cognitive deficits. It has previously been established that damage to the cerebellum in MS is associated with disease-related impairment and poorer rehabilitation outcomes. Consequently, there is growing interest in the relationship between the cerebellum and cognition in MS. The aim of this review is to measure the impact of cerebellar damage on cognition and other-related variables in MS. The review will pay attention to whether there is a specific cognitive profile for MS patients with cerebellar damage, which in turn, may have implications for differential treatment responses. Furthermore, if any relationship exists, the review will elucidate the nature of the relationship based on proposed mechanisms. Although several phenotypes of MS exist, the systematic review will predominately focus on RR-MS, the most common pattern of progression.

The objective is to conduct a systematic review of all studies published in English that investigated the relationship between cerebellar function and cognitive performance and other related variables such as fatigue in RR-MS. The review will also evaluate the content and methodological quality of the studies included. To the author's knowledge, this is the first systematic review to adopt the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to explore the influence of cerebellar involvement on the cognitive performance of RR-MS.

2.4 Method

2.4.1 Literature Search

To identify relevant studies, a literature search was conducted across four online literature databases and trial registers (PubMed, Web of Science, Google Scholar and OVID) between the 25th – 28th August 2017 using the search terms in Table 1. Previous meta-analyses, systematic reviews and leading journals investigating the role of cerebellum in cognition with MS patients were also searched.

Table 1 *Search terms used for literature review*

Search terms	*"multiple sclerosis" OR "relapsing-remitting multiple sclerosis"* *AND* *"cognitive deficits" OR "cognition" OR "cognitive impairment" OR "cognitive dysfunction" OR "memory" OR "information processing" OR "attention" OR "executive functioning"* *AND* *"Cerebellar damage" OR "cerebellar dysfunction" OR "cerebellum damage" OR "cerebellar impairment" OR "cerebellum*"*

2.4.2 Eligibility Criteria

The inclusion criteria for the studies in the present review were published, peer-reviewed in English language measured the impact of cerebellar function to cognitive performance in individuals with RR-MS with no age limit. Evidence of cerebellar involvement was verified through the presence of lesions in the cerebellum as demonstrated by neuroimaging techniques or the use of validated clinical assessment measures that were indicative of cerebellar damage (e.g. Cerebellar Functional System

Score, Kurtzke, 1983). No date restriction was applied. No restrictions were placed on the type or presence of a control group. Studies were included if sufficient data were available for analysis (unavailable information was requested from authors and included if obtained) and the number of participants in any condition was required to be more than 5 at any given point. Studies that pooled individuals with other types of MS (e.g. PP-MS) were excluded unless separate data for individuals with RR-MS were provided.

Studies were required to have used at least one neuropsychological outcome measure. All primary and secondary neuropsychological outcomes that measured performance of different cognitive abilities or non-cognitive outcomes (e.g. fatigue or mood) were included. Each study was independently screened, selected for inclusion and data extracted by one author (JC). Any ambiguity with data collection was resolved through discussion with another researcher (DL).

2.4.3 Study Selection

All articles gathered during the literature search were assessed for eligibility. Irrelevant articles were excluded based on the title and abstract, and duplicates removed before those remaining were subject to a full-text review independently by one reviewer (JC) and verified by another (DL). In total, 14 articles met the inclusion criteria for data extraction (see Fig. 1).

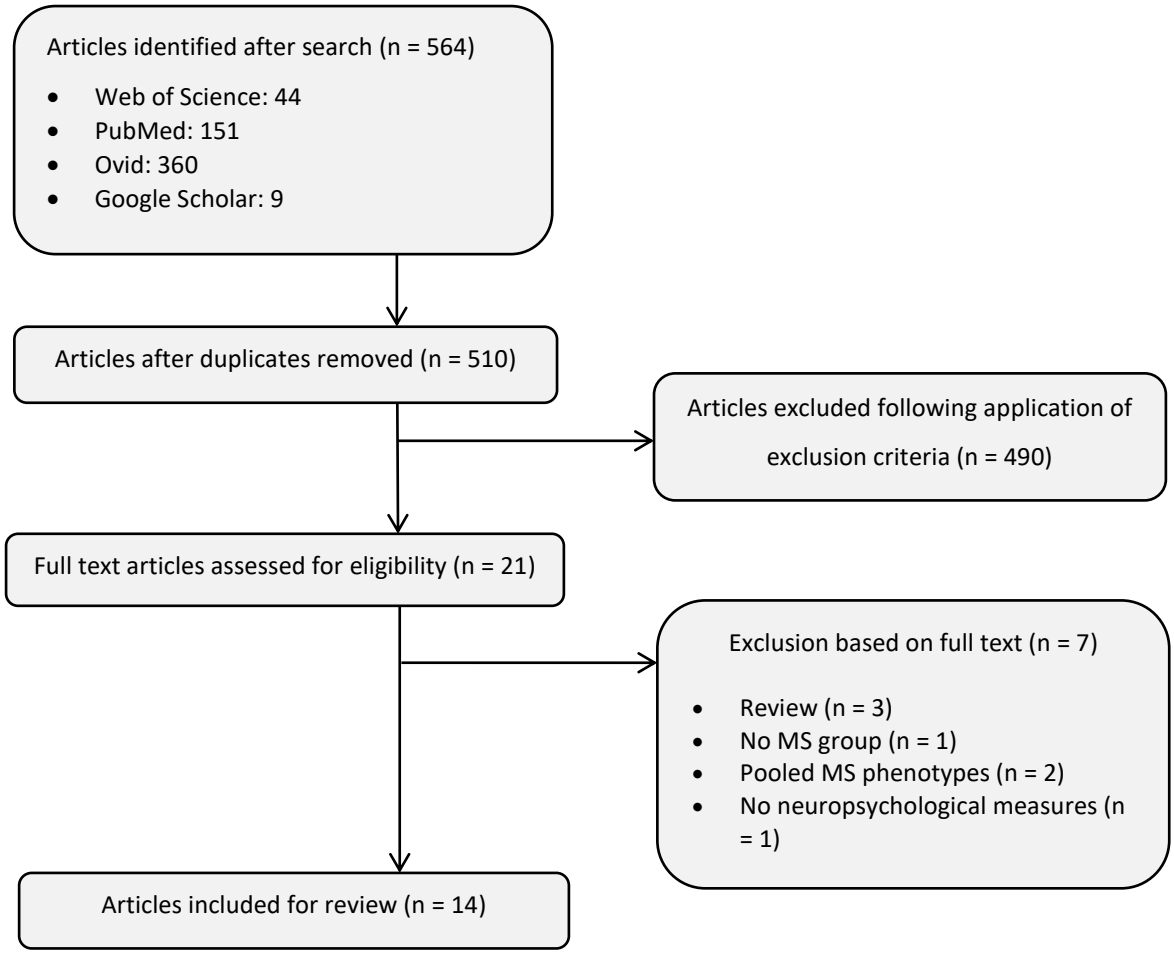

Figure 1 PRISMA Flow chart of the study selection process

2.4.4 Data Extraction

The following information was extracted from the final 14 articles:

- Characteristics of study participants: means and standard deviations (SD) for age, gender, level of education, MS phenotype, disease duration and Expanded Disability Status Scale (EDSS) when stated, were independently extracted.
- Characteristics of each study: the design and methodology were recorded. Information about the nature of the investigation and theories of underlying mechanisms was also noted.

- Outcome measures: the use of any neuropsychological outcome measure or other related-variable was recorded.
- Key findings: in relation to the objective of understanding the contribution of the cerebellum to cognitive impairment in MS, all relevant clinical, neuroimaging and neuropsychological findings were extracted and summarised.

2.4.5 Assessment of Study Quality

The Effective Public Health Practice Project (EPHPP) was used to assess study methodological quality (Thomas, Ciliska, Dobbins, & Micucci, 2004). The tool utilises a 6-item scale (selection bias, study design, confounders, blinding, data collection method and withdrawal and dropout) to provide an overall quality rating. Two authors independently rated each study (JC & DL). If a study scored a weak rating in each domain, the study would be excluded from the systematic review. The EPHPP tool was selected due to strengths in inter-rater reliability and suitability for systematic reviews (Armijo-Olivo, Stiles, Hagen, Biondo, & Cummings, 2012).

2.5 Results

2.5.1 Study Quality

The quality of each study was evaluated regarding certain methodological aspects and summarised in Table 2. The overall quality of each study included in the review was strong, with only three studies scoring a fair quality rating (Cerasa et al., 2012, 2013; Rocca et al., 2012). It was noted that most studies did not provide information on blinding procedures, increasing the risk of detecting and reporting bias. In contrast, all studies scored a strong rating on data collection methods indicating that all outcome measures used were reliable and valid. No studies were excluded based on the quality rating.

Table 2 *Quality ratings for studies included in the systematic review*

Lead Author and Year	Selection Bias	Study Design	Confounders	Blinding	Data Collection Method	Withdrawals and Dropout	Overall Quality Rating
Cerasa, 2012	Fair	Strong	Strong	Fair	Strong	Weak	***Fair***
Cerasa, 2013	Strong	Strong	Strong	Fair	Strong	Weak	***Fair***
Cirillo, 2015	Fair	Strong	Fair	Fair	Strong	Strong	***Strong***
D'Ambrosio, 2017	Strong	Strong	Strong	Fair	Strong	Strong	***Strong***
Damasceno, 2014	Strong	Strong	Strong	Fair	Strong	Strong	***Strong***
Fartaria, 2017	Strong	Fair	Strong	Fair	Strong	Strong	***Strong***
Kolb, 2014	Strong	Strong	Strong	Fair	Strong	Strong	***Strong***
Lesage, 2010	Strong	Strong	Strong	Fair	Strong	Strong	***Strong***
Rocca, 2012	Strong	Strong	Strong	Weak	Strong	Strong	***Fair***
Romascano, 2015	Strong	Strong	Strong	Fair	Strong	Strong	***Strong***
Ruet, 2014	Strong	Strong	Strong	Fair	Strong	Strong	***Strong***
Valentino, 2009	Strong	Strong	Strong	Fair	Strong	Strong	***Strong***
Weier, 2014	Fair	Fair	Strong	Fair	Strong	Strong	***Strong***
Weier, 2016	Strong	Strong	Strong	Fair	Strong	Strong	***Strong***

Overall quality rating: Strong = no weak ratings; Fair = one weak rating; Weak = two or more weak ratings

2.5.2 Study Participants

The total amount of case group patients from all studies was 433. The sample size for each study was variable, ranging from 20 to 60 patients in the case group. All studies applied formal criteria to meet the diagnosis of RR-MS including the revised McDonald criteria (Polman et al., 2011). Two studies investigated paediatric populations (Cirillo et al., 2016; Weier et al., 2016), reporting a similar average age, although differing ranges of disease duration. The rest of the studies investigated adult populations, with an average age of 38.6 years within the case group. Except for Kolb et al (2014), all

studies provided a ratio of male/female, which indicated an average of 74% in favour of female patients which reflects wider prevalence rates. The lack of reporting in patient's years of education precluded mean calculations, although the available data suggested most patients had at least secondary school education. There was disparity regarding disease duration of the case adult patients, ranging from an average mean per study of 2 to 12.1 years. When reported, the average EDSS score was 2.0, indicating that case participants tended to report minimal disability. However, there was a wide range of EDSS across studies (0 to 7.5), which would suggest there was diversity across patients. Furthermore, four studies used RR-MS with cerebellar signs (RR-MSc) as the MS phenotype of interest. Two of those studies (Cerasa et al., 2012, 2013) used structural MRI as part of the criteria for defining RR-MSc, whereas the other two studies used evidence of cerebellar symptoms as indicated by an EDSS cerebellar functional systems score. Finally, two studies provided no details of a clear inclusion or exclusion criteria (Romascano et al., 2015; Weier et al., 2014), whereas the others provided at least a reference to inclusion criteria. Overall, the case participants were a largely heterogenous group involving predominately adult females with minimal disability with clear evidence of RR-MS.

Nearly all studies employed a control group. The control group participants were either healthy controls matched on certain variables (n = 8) or RR-MS patients without cerebellar signs (RR-MSnc) (n = 4). It is difficult to comment further on the methodological quality and adequacy of the control groups given the disparity between studies as well as incomplete data provided. The available demographic information reflects similar characteristics of the case group.

2.5.3 Study Methods

The most common study design was controlled clinical trial often incorporating the use of neuroimaging techniques. No studies employed a randomised control design.

2.5.4 Neuropsychological Measures

Table 3 summarises the 19 different neuropsychological measures utilised to measure cognitive performance. A range of specific cognitive domains were tested, with information processing speed the most commonly investigated domain. The tests most commonly used were (in order): SDMT, PASAT (both measures of IPS) and COWAT (verbal fluency). There was evidence that several studies employed the use of a recommended test battery such as the Brief International Cognitive Assessment for MS (BICAMS) (Langdon et al., 2012). No studies reported any follow-up data for any outcome measure.

Table 3 *Brief description of specific neuropsychological outcome measures used by studies from the systematic review*

Neuropsychological Outcome Measures	Domain	Brief Description	Study (Lead author)
California Verbal Learning Test	Verbal Memory	Participants repeat a list of 16 unrelated words over five different trials. After each trial, the participant is asked to recall as many words as possible.	Kolb, 2014
Computerised Speed Cognitive Test	Processing Speed and Attention	The test uses a digit/symbol substitution task. Participants are required to record digits that correspond to symbols presented on the computer screen.	Ruet, 2004
Controlled Oral Word Association Test	Verbal fluency	Participants generate as many words in three one-minute naming trials from a given letter or category.	Ceresa, 2012; Ceresa, 2013; Fartaria, 2017; Romascano, 2015; Ruet, 2004; Valentino, 2009
Digit Span	Working Memory	Sequence of digits is read aloud. Subjects asked to immediately recall digits in the correct order. If correct, a sequence with an additional digit is presented.	Kolb, 2014; Ruet, 2004
Judgement of Line Orientation	Visuospatial Skills	The test measures a participant's ability to match the angle and orientation of lines in space to provide an indication of visuospatial skills.	Ceresa, 2012; Ceresa, 2013; Valentino, 2009
Mini-Mental State Examination	General Cognition	A 30-point questionnaire used to estimate severity of cognitive impairment including orientation and memory functions.	Ceresa, 2012; Ceresa, 2013
Modified Card Sorting Test	Executive Function	A shortened version of the Wisconsin Card Sorting Test. The participant tasked with matching cards without guidance; however, participant is told whether a particular match is right or wrong.	Ceresa, 2013; Valentino, 2009

Neuropsychological Outcome Measures	Domain	Brief Description	Study (Lead author)
Paced Auditory Serial Addition Test 3	Processing Speed	The examiner presents numbers every three seconds (recorded for standardisation), and the participant must add this number to the previous number presented.	Ceresa, 2012; D'Ambrosio, 2017; Damasceno, 2014; Kolb, 2014; Lesage, 2010; Romascano, 2015; Ruet, 2004; Fartaria, 2017; Weier, 2014
Rey Auditory-Verbal Learning Test	Verbal Memory	Participants repeat a list of 15 unrelated words over five different trials. Another list of 15 unrelated words are given and the client must again repeat the original list of 15 words and then again after 30 minutes.	Ceresa, 2013; Valentino, 2009
Rey-Osterrieth Complex Figure Test	Spatial Memory	Participants asked to reproduce a complicated line drawing, first by copying it freehand, and then drawing from memory.	Ceresa, 2013; Valentino, 2009
Selective Reminding Test - Long term storage, consistent long term retrieval, delayed recall	Verbal Memory	Task requires participant to recall a list of 12 unrelated words over a number of trials. Words not recalled are presented again in subsequent trials until participant correctly recalls all 12 words on three consecutive trials, or until 12 trials have been completed.	Ceresa, 2012; Cirillo, 2015; Fartaria, 2017; Romascano, 2015; Ruet, 2004
Spatial Recall Test - immediate recall, delayed recall	Visual Memory	Participants are required to reproduce patterns from a checkboard over three learning trials.	Ceresa, 2012; Romascano, 2015; Ruet, 2004; Fartaria, 2017
Stroop Test	Executive Function	A measure of a participant's ability to name colours of different stimuli within a timed paradigm	Ceresa, 2012; Rocca, 2012; Ruet, 2004
Symbol Digit Modalities Test	Processing Speed	In this test, symbols are paired with numbers. Following a practice phase, participants are required to record numbers that correspond to figures presented within the test-sheet.	Ceresa, 2012; Ceresa, 2013; Cirillo, 2015; D'Ambrosio, 2017; Damasceno, 2014; Kolb, 2014; Lesage, 2010; Romascano, 2015; Fartaria, 2017; Valentino, 2009; Weier, 2014; Weier, 2016

Neuropsychological Outcome Measures	Domain	Brief Description	Study (Lead author)
Trail Making Test	Executive Function	The task requires participants to 'connect the dots' in two parts, firstly numerically and secondly, alphanumerically	Cirillo, 2015; Weier, 2016;
Verbal and Spatial Reasoning Test	Verbal Reasoning	Using a multiple-choice format, participants are required to complete six sections of inductive reasoning problems	Lesage, 2010
Wechsler Abbreviated Scale of Intelligence - subtests (Vocabulary, Similarities)	IQ	A test of general cognitive ability, made up of several subtests measuring various cognitive abilities. Combined the subtests provide an estimate of a Full-Scale Intelligence quotient (FSIQ). Subtests can be used to provide an estimate of other abilities such as verbal comprehension.	Cirillo, 2015; Lesage, 2010; Weier, 2016

2.5.5 Other Variables

Table 4 summarises the 8 non-neuropsychological outcome measures. The most commonly tested area was motor function, with 6 of the studies using the NHPT. Interestingly, no studies investigated subjective Quality of Life. In addition, Table 2 indicates that 12 studies investigated the role of the cerebellum using neuroimaging techniques including structural MRI. A review of the key findings indicated that lesion load and cerebellar volume were most often assessed.

Table 4 *Brief description of other outcome measures used by studies from the systematic review*

Outcome Measure	Domain	Brief Description	Study (Lead author)
Nine-Hole Peg Test	Motor Function	The test consists of a board with 9 holes. Pegs must be inserted and removed as quickly as possible, providing quantification of extremity function and physical disability.	Cirillo, 2015; D'Ambrosio, 2017; Damasceno, 2014; Lesage, 2010; Romascano, 2015; Weier, 2014
Antisaccade Task	Visual Motor Function	The task involves the recording of saccade eye movement as participant is required to inhibit the reflexive saccade to a stimulus.	Kolb, 2014
Beck Depression Inventory	Mood	Participants answer a 21-question multiple-choice self-report inventory to measure severity of depression.	Ceresa, 2012
Beery Visual Motor Integration	Visual Perception	Identifies significant difficulties in integrating or coordinating visual perceptual and motor (finger and hand movement) abilities.	Weier, 2016
Fatigue Scale for motor and cognitive fatigue	Fatigue	The test uses a Likert-type 5-point scale on a 20-item questionnaire to measure fatigue on two subscales (mental and physical fatigue).	Romascano, 2015; Weier, 2014
Fatigue Severity Scale	Fatigue	A 9-statement measure of fatigue that allows for discrimination with depression. Participants rate how much they endorse these from 1-7 (1 strongly disagree, to 7 strongly agree).	Lesage, 2010
Grooved Pegboard test	Motor Function	The test consists of a pegboard with 25 holes. Pegs must be inserted into randomly positioned holes at the correct orientation, due to a key on the side of pegs.	Weier, 2016
Hospital Anxiety and Depression Score	Mood	A 14-item scale with seven statements measuring anxiety and depression. The scale reduces the focus on aspects of anxiety and depression that are common somatic symptoms of illness.	Fartaria, 2017; Lesage, 2010; Romascano, 2015

2.5.6 Important Findings

The salient findings from each study are reported in Table 5. Overall, there was evidence of cognitive impairment in patients with RR-MS, specifically in the domains of IPS and executive functions. Furthermore, nearly all studies indicate support for the

contribution of the cerebellum to cognitive performance as well as support for a differential cognitive profile between RR-MS patients with cerebellar symptoms and those without cerebellar symptoms. In addition, findings also showed strong evidence of cerebellar involvement in tests of motor function. Although there was limited information, it does not appear that the cerebellum contributes significantly to mood or fatigue symptoms.

2.5.7 Attention and Information Processing Speed

Patients with evidence of cerebellar signs demonstrated deficits on measures of attention and IPS. This was observed in studies that compared IPS performance to a healthy control group (Cerasa et al, 2012; Damasceno et al, 2014; Kolb at al, 2014; Weier et al 2016), although this finding was not always consistent (Lesage et al, 2010; Romascano et al, 2015). In addition, three studies that compared performance to those with RR-MS without cerebellar damage also indicated evidence of IPS deficits (Cerasa et al 2013; Valentino et al, 2009; Weier et al, 2014).

2.5.8 Executive Function

Focal tests of executive function including verbal fluency demonstrated some evidence of deficits in patients with cerebellar damage. Several studies reported lower performance on the WLG, Stroop and TMT-B tests when compared to either healthy controls or RR-MSnc (Ceresa et al, 2012; Ceresa et al, 2013; Fartaria et al 2017; Rocca et al, 2012; Valentino et al 2009; Weier et al 2016). In contrast, two studies did not

report any differences in executive functioning (Romascano et al 2015; Ruet et al 2004).

2.5.9 Memory

There was minimal evidence to suggest that the cerebellum contributes to either verbal or non-verbal memory. Several studies indicated that there was no difference between patients with cerebellar signs and healthy controls or RR-MSnc on a range of memory tasks (Ceresa et al, 2012; Romascano et al 2015; Ruet et al 2004; Valentino et al 2009). Only one study found a significant difference on performance on spatial memory, but not verbal memory (Ceresa et al, 2013). Two studies fail to provide sufficient information to infer any differences on memory tests (Cirillo et al 2015; Kolb et al, 2014).

2.5.10 Motor Function

There was strong evidence to indicate cerebellar involvement in motor function. Nearly all studies that included motor functioning as a measure, typically the NHPT, demonstrated that cerebellar signs resulted in poorer performance (e.g. Cirillo et al, 2015; Romascano et al, 2015; Weier et al, 2014). Furthermore, cerebellar lesion load and volume were repeatedly found to predict performance (e.g. D'Ambrosio at al, 2017; Damasceno et al, 2014; Lesage et al, 2010).

2.5.11 Mood

It was harder to infer the prevalence of mood difficulties from the results in part due to the limited number of studies that investigated the domain. Of the studies that included a mood outcome measure, two studies found no evidence significant mood difficulties in individuals with cerebellar signs (Ceresa et al, 2012; Fartaria et al 2017), one study found individuals with RR-MS had significantly higher rates for trait anxiety, depression compared to control, however this was not correlated with cognitive performance (Lasage et al, 2010), and one study found a significant difference in depression symptoms between patients with MS compared to controls, however it appears scores were not clinically significant (Romascano et al, 2015). Therefore, there is minimal support that the cerebellar is involved in difficulties with affect.

2.5.12 Fatigue

All three studies that measured fatigue indicated higher rates of fatigue in individuals with RR-MS (Lasage et al, 2010; Romascano et al, 2015; Weier et al, 2014). Only one study found individuals with cerebellar signs had higher rates of fatigue than those without (Weier et al, 2014). However, differences were not correlated with cerebellar volumes. The results suggest the cerebellum does not substantially contribute to fatigue. In contrast, fatigue is likely to contribute to cognitive performance.

Table 5 *Characteristics and main findings of studies included in the systematic review*

Study	Study Type	Objective	Case Group	Control Group	Main Findings
Cerasa, 2012	Case-Control with MRI	To investigate the influence of cerebellar signs in RR-MS on specific cerebellar-cortical circuits	Type = RR-MSc n = 12 ratio = 83% age = 38.7 ± 13.5 Edu = 12.5 (5-16) Dur = 98.4 ± 62.6 (months) EDSS = 3 (1.5-4)	Type = RR-MSnc n = 15 ratio = 73% age = 35.6 ± 7.1 Edu = 13 (8-7) Dur = 93.1 ± 69.2 (months) EDSS = 2 (2-4)	There were no significant differences in performance on any neuropsychological tests between patients with RR-MSc and RR-MSnc. The presence of significant impaired performance was only in relation between RR-MSc and HC on measures of IPS (SDMT) and executive functioning (Stroop test), and both MS groups and HC on WLG. Cerebellar lesion load did not correlate with any neuropsychological outcome.
Cerasa, 2013	Case-Control with MRI	Investigation of neuroanatomical abnormalities in RR-MSc and RR-MSnc	Type = RR-MSc n = 12 ratio = 83% age = 38.9 ± 8.7 Edu = 13 (5-17) Dur = 12.1 ± 8.7 EDSS = 2.5 (1-4) FSS = 4 ± 1.1	Type = RR-MSnc n = 14 ratio = 79% age = 38.6 ± 8.5 Edu = 13 (95-17) Dur = 8.8 ± 4.4 EDSS = 2 (1.5-4.5) FSS = 3.7 ± 1.6	Patients within the RR-MSc group exhibited poorer performance on IPS (SDMT), verbal fluency (COWAT) and spatial memory tests (ROCFT) compared to RR-MSnc and HC. Within the RR-MSc group, grey matter volume loss in the frontal and temporal cortical areas were significantly correlated with performance on the SDMT and COWAT respectively.
Cirillo, 2015	Case-Control with MRI	Investigation of functional connections of the cerebellar dentate nuclei in paediatric RR-MS patients and correlations with clinical, cognitive and structural MRI measures	Type = RR-MS n = 48 ratio = 65% age = 14.9 (8.1-17) Edu = N/R Dur = 1.7 (0.1-8.1) EDSS = N/R	Type = HC n = 27 ratio = 59% age = 15.2 (8.5-17) Edu = N/R	8 of the RR-MS patients were found to be cognitively impaired - defined as an abnormal performance on ≥ 3 tests of the Brief Neuropsychological Battery for Children (Portaccio et al, 2009). No further information is provided regarding the nature of the cognitive impairments. RR-MS patients who were cognitively impaired showed a widespread reduction in functional connections between the dentate nucleus and regions within the parietal, frontal and temporal lobes compared to both HC and cognitively preserved RR-MS patients. More generally comparisons between RR-MS patients and HC indicated functional connectively is influenced by disease duration and lesion volume.

Study	Study Type	Objective	Case Group	Control Group	Main Findings
D'Ambrosio, 2017	Case-Control with MRI	To investigate the contribution of cerebellar sub-regions to motor and cognitive performance in different phenotypes of MS using MRI	Type = RR-MS n = 52 ratio = 65% age = 43.3 ± 11.2 Edu = 13.8 ± 3.7 Dur = 8.2 (0-34) EDSS = 2 (1-6)	Type = HC n = 32 ratio = 43% age = 39.6 (8.4) Edu = 16.9 ± 2.6	There was a significant difference between RR-MS and SP-MS on SDMT performance, which was largely accounted for by the SP-MS group. No comparisons of cognitive performance on SDMT and PASAT-3 were made with HC. There were no significant differences in cerebellar volume between RR-MS and HC. When MS phenotypes were pooled, lower posterior cerebellar volume and brain lesion volume predicted poor cognitive performance.
Damasceno, 2014	Case-Control with MRI	To investigate the cerebellar grey matter pathology in RR-MS on clinical and cognitive functioning	Type = RR-MS n = 42 ratio = 76% age = 30.52 ± 6.6 Edu = 13.69 ± 1.83 Dur = 6.4 ± 4.94 EDSS = 2.5 (0-4)	Type = HC n = 30 ratio = 77% age = 29.52 ± 7.52 Edu = 15.18 ± 0.77	The presence of cerebellar lesions was found in 53.8% of the RR-MS sample. A high burden of leukocortical lesions resulted in poorer performance on the PASAT-3 whereas greater volumes of intracortical lesions resulted in poorer performance on the SDMT. More generally, the RR-MS group performed significantly worse on the NHPT, PASAT-3 and SDMT when compared to HC after controlling for years of education.
Fartaria, 2017	Case with MRI	The investigation of cerebellar pathology using ultra-high-field MRI and the contribute of MRI metrics to clinical and cognitive performance in RR-MS	Type = RR-MS n = 20 ratio = 75% age = 34.9 (21-46) Edu = N/R Dur = 36.5 ± 21.8 (months) EDSS = 1.5 (1-2)	No control group	Cerebellar lesion characteristics measured by superior MRI metrics established a significant correlation between a visual memory task (SRT - delayed recall) as well as motor performance (NHPT). No other correlations were found with cognitive measures within the Brief Repeatable Battery of Neuropsychological Tests, which included both the PASAT-3 and SDMT using images acquired at superior MRI.

Study	Study Type	Objective	Case Group	Control Group	Main Findings
Kolb, 2014	Case-Control with MRI	Investigation of the relationship between saccadic eye movements using an antisaccade paradigm and neurological abnormalities, cerebral damage and cognitive dysfunction in patients with RR-MS	Type = RR-MS n = 24 ratio = N/R age = 47 (25-63) Edu = N/R Dur = 6 (2-18) EDSS = 3 (1-6)	Type = HC n = 24 ratio = N/R age = 41 (30-62) Edu = N/R	Individuals with RR-MS performed worse than matched controls on an antisaccade paradigm, there was a significant negative correlation between the amount of antisaccadic errors and performance on IPS tests (PASAT-3 and SDMT). The number of antisaccadic errors was also significantly associated with cerebellar damage. The authors suggest that the cerebellar contributes to occular motor deficits in RR-MS and saccadic paradigms provide a surrogate measure of cognitive impairment.
Lesage, 2010	Case-Control with MRI	To investigate whether the cerebellar cortex plays a role in cognitive performance using functional MRI	Type = RR-MS n = 19 ratio = 79% age = 41.7 (29-55) Edu = N/R Dur = 6.4 EDSS = N/R	Type = HC n = N/R ratio = N/R age = 39.1 (26-55) Edu = N/R	The RR-MS group performance was similar to the HC group on all cognitive tests, aside from the SDMT, where the HC group scored significantly higher. However, only 3 patients were considered impaired on the SDMT according to cut-off scores (>2 standard deviations). The RR-MS group had significantly higher scores on the measures of anxiety, depression and fatigue compared to HC. Cerebellar pathology was not correlated with any cognitive test. Imaging results found increased activity within the cerebellar cortex during the PASAT-3 in the RR-MS group compared to HC, despite no significant differences in scores.
Rocca, 2012	Case-control with MRI	To study whether cognitive failure on a neuropsychological test was associated with modifications of cerebellar-lobe connections.	Type = RR-MS n = 17 ratio = 71% age = 37.8 ± 9.9 Edu = N/R Dur = 10 (2-18) EDSS = 2.0 (1-5)	Type = HC n = 18 ratio = 55% age = 43.9 ± 16 Edu = NR	Compared to HC, the RR-MS group demonstrated a different pattern of activation between the cerebellum and prefrontal regions during the Stroop paradigm. In RR-MS, superior cognitive performance was associated with activation of the cerebellum and the frontal gyrus. Furthermore, cognitive-related cerebellar activity was negatively correlated with disease duration. None of the RR-MS group were cognitively impaired.

Study	Study Type	Objective	Case Group	Control Group	Main Findings
Romascano, 2015	Case-Control with MRI	The investigation of structural and functional integrity of cerebellar networks and relationship to clinical variables.	Type = RR-MS n = 28 ratio = 64% age = 34.32 ± 8.71 Edu = 15.98 ± 2.78 Dur = 25 (months) EDSS = 1.55 ± 0.21	Type = HC n = 16 ratio = 56% age = 33.06 ± 9.37 Edu = 16.06 ± 3.51	There were no differences in cognitive or motor performance between the two groups. There were no significant changes in the structural or functional properties of cerebellar networks in RR-MS in respect to HC. However, there were significant correlations between clinical performance, including measures of IPS, and subtle structural alterations, possibly indicative of MS pathology.
Ruet, 2014	Cohort design	To study the relationship between cerebellar function as measured by motor testing and neuropsychological performance	Type = RR-MS n = 60 ratio = 82% age = 37.3 ± 9.9 Edu = N/R Dur = 4.1 ± 3.0 EDSS = 1.5 (0-4.5)	No control group	There were significant differences in performance on the NHPT and the Computerised-Speed-Cognitive test (CSCT, a measure of IPS) between RR-MSc (n = 11) and RR-MSnc (n = 48). For the whole sample, scores on the NHPT were correlated with CSCT, EDSS and disease duration, and exclusively correlated with IPS.
Valentino, 2009	Case-Control	To explore the relationship between cerebellar symptoms in RR-MS and neuropsychological features	Type = RR-MSc n = 21 ratio = 67% age = 37 ± 7.9 Edu = 9.5 ± 3.3 Dur = 9.8 ± 8.1 EDSS = 2.5 (2-4) FSS = 4.35 (2-5.7)	Type = RR-MSnc n = 21 ratio = 67% age = 36.6 ± 7.9 Edu = 11.2 ± 3 Dur = 8.6 ± 5.2 EDSS = 2 (1.5-4.5) FSS = 4.55 (1-6.4)	In the initial sample of 111, approximately a third of RR-MS patients (31.5%) demonstrated evidence of cognitive impairment. When grouped according to cerebellar signs, patients with RR-MSc performed significantly lower on SDMT and COWAT tests when compared to individually matched RR-MSnc patients, performance was similar in other cognitive measures.
Weier, 2014	Cohort design with MRI	Investigation of the relationship between cerebellar signs in MS and cognitive performance	Type = RR-MSc* n = 50 ratio = 80% age = 41.5 ± 10.1 Edu = N/R Dur = 11.7 ± 6.2 EDSS = 1.5 (0-7.5)	Type = RR-MSnc* n = 72 ratio = N/R age = 51 ± 9.9 Edu = N/R Duration = 18.2 ± 10 EDSS = 4 (1-7.5)	Within a large cohort of patients with MS, patients with cerebellar signs performed worse on cognitive tests than those without signs. Subgroup analysis of patients with RR-MSc indicated that cerebellar pathology does not substantially contribute to development of fatigue, whereas it did partially predict performance on SDMT and PASAT-3.

Study	Study Type	Objective	Case Group	Control Group	Main Findings
Weier, 2016	Case-Control with MRI	Investigation of the relationship between cerebellar pathology and cognitive functioning in paediatric RR-MS	Type = RR-MS n = 28 ratio = 75% age = 16.3 ± 2.2 Edu = 15.7 ± 2.1** Dur = 4.6 ± 3.3 EDSS = 1.25 (0-4)	Type = HC n = 33 ratio = 79% age = 15.5 ± 2.7 Edu = 15.8 ± 1.9**	Although within acceptable norms, RR-MS patient cognitive performance was reduced relative to controls on all cognitive measures. Cerebellar volumes were not statistically different between groups, although posterior cerebellar volume and infratentorial lesion volume accounted for extra variance in vocabulary (WASI Vocabulary) and IPS (SDMT). Anterior cerebellar volume predicted performance in motor function (NHPT). Results supported involvement of cerebellum in cognitive functioning.

Notes: Groups – Type of MS phenotype; Number (n) of patients; Ratio of % female; Mean age in years; Mean education in years; Mean disease duration in years unless specified; EDSS mean.

Abbreviations: RR-MS, Relapsing-Remitting Multiple Sclerosis; RR-MSc, RR-MS with cerebellar damage; RR-MSnc, RR-MS without cerebellar damage; HC, Healthy Controls; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; N/R, Not Reported.

* Group information provided for all MS phenotypes

** Parental Education in years

2.6 Discussion

2.6.1 Summary

The present report used a systematic review to examine the contribution of the cerebellum to cognition and related factors in RR-MS using all available outcomes from studies meeting predetermined criteria. Examination of the data revealed evidence that the cerebellum predominately contributes to the cognitive domains of IPS and executive functioning as well as motor function in RR-MS. Furthermore, there was evidence to suggest cerebellar symptomatology may indicate a distinct clinical subtype of RR-MS, involving more severe and widespread cognitive impairment. There was nominal evidence that the cerebellum contributes to other cognitive domains or related variables such as mood and fatigue. However, due to the limited number of studies exploring other variables this does not preclude the cerebellar potentially having a role. A comprehensive review of study characteristics revealed substantial variability in patients included and outcome measures used despite recommended test batteries such as BICAMS (Langdon et al., 2012). Limitations of the project include the small number of eligible studies, methodological differences and a lack of follow-up data. Overall, there was substantial evidence to support that the cerebellum contributes to cognitive performance, particularly regarding IPS. Although the intricacies of the cerebellar-related cognitive impairment remain elusive, it is likely to be underpinned by integrity of cortico-cerebellar loops.

2.6.2 Validity of Findings

The findings of the systematic review support the view that the cerebellum contributes to cognitive performance in RR-MS, influencing the specific domains of IPS and executive functioning. This is in line with previous work that has considered the role of the cerebellum in MS (Sarica, Cerasa, & Quattrone, 2015; Weier et al., 2015). Furthermore, the results are also in accord with conclusions drawn from research into the impact of cerebellar lesions in other diseases such as stroke and CCAS (Koziol et al., 2014; Stoodley & Schmahmann, 2010). The review challenges the tradition dogma that the cerebellum is purely concerned with motor functions and demonstrates cerebellar function in RR-MS also plays an important role in cognition.

Although the cerebellum plays a role in cognition it was difficult to ascertain the magnitude of influence in part due to the heterogeneity in case and control groups. For instance, the review included data from adult and adolescent populations with varying disease duration. In addition, it remained difficult to isolate the precise contribution of the cerebellum from other potentially confounding demographic and clinical factors that might have accounted for differences between the two proposed RR-MS phenotypes. For example, cognitive reserve, as measured by premorbid intelligence or years of education, has been found to protect against the progression of cognitive decline over a 5 year period (Benedict, Morrow, Weinstock-Guttman, Cookfair, & Schretlen, 2010). Only half of the studies included provided information regarding years of education, therefore, it questions whether results represent two discrete phenotypes, or merely differences in patient's cognitive reserve. Arguably, there is a need to further delineate the cognitive profiles of RR-MSc and RR-MSnc before firmer conclusions can be drawn.

2.6.3 Evidence for a Typical Profile

An objective of the review was to consider the suggestion that cerebellar signs in RR-MS might be indicative of a distinct phenotype with a differential cognitive profile. Despite small numbers, there was a consistent pattern demonstrating cerebellar signs and cognitive dysfunction often occurred in parallel and cerebellar symptomatology was associated with more widespread and severe cognitive impairment. In many ways, the profile reflects the deficits observed in CCAS (Schmahmann & Sherman, 1998; Schmahmann, 2004). Regarding focal cognitive domains, the literature suggests that the RR-MSc profile is typically characterised by reduced IPS and executive dysfunction. Evidence from studies that included a neuroimaging method also suggested a lower posterior cerebellar volume and a higher lesion load in the infratentorial region were associated with worse cognitive performance. Furthermore, there is a suggestion that cerebellar pathology results in altered connectivity to compensate for damage, which in turn, is associated with inefficiencies in cognition and global decline. The collective findings imply support for a differential cognitive profile in RR-MSc patients, although disparity continues to surround the potential mechanisms.

2.6.4 Mechanisms of Cerebellar Involvement

A further aim of the review was to elucidate the potential mechanisms underlying the relationship between the cerebellum and cognition impairment. It appears there are three key mechanisms, not necessarily mutually exclusive, which might account for deficits: cerebellar atrophy and lesion; atrophy in associated cortical areas; or disrupted cortico-cerebellar connections.

Certain studies indicated that cognitive impairment is predicted by cerebellar pathology. For example, Cirillo et al (2016) found a higher cerebellar lesion load in cognitively-impaired than in cognitively-preserved RR-MS paediatric patients. In addition, Demasceno et al (2014) found a higher burden of cerebellar intracortical and leukocortical lesions were associated with worse SDMT and PASAT scores respectively. This observation was also noted in studies by Weier et al (2014, 2016) whereby both cerebellar atrophy and lesion in RR-MS contributed to cognitive impairment in IPS. In contrast, research has also indicated that cognitive deficits might be more related to grey matter pathology in supratentorial regions. For instance, Cerasa et al. (2013) found that grey matter volume loss in the frontal and temporal cortical areas were significantly correlated with performance on the SDMT and COWAT respectively. Similarly, Weier et al (2016) concluded that diffuse pathology in other parts of the brain is likely to play a role in cognitive impairment independent of the cerebellum.

Contrary to the above, there is also evidence that suggests neither cerebellar or cortical pathology significantly contributes to cognitive impairment. In the study by Valentino et al. (2009), total lesion loads in the four cortical lobes and the cerebellum

were compared with neuropsychological tests and no significant relationship was found. Additionally, Lesage et al. (2010) also found that cerebellar pathology was not correlated with any cognitive test. A recent study by Daams et al., (2016) which RR-MS patients had a minimum disease duration of ten years, also found no relationship between cerebellar lesions and cognitive impairment. Instead, the authors concluded the strongest predictor of cognitive impairment was deep grey matter atrophy and diffuse white matter damage. Therefore, an alternative mechanism for cognitive impairment might be attributed to dysfunction in salient cortico-cerebellar connections.

Neuroanatomical studies have demonstrated the existence of diverse connections between the cerebellum and the cerebral cortex that are organised into discrete 'loops' to aid communication (Kelly & Strick, 2003; Middleton & Strick, 2000). A seminal consensus paper described the cerebellum as being critical for the modulation of sensorimotor and cognitive functions by way of these multiple cortico-cerebellar loops; controlling diverse streams of information underlying a wide range of functional domains (Koziol et al., 2014). It is considered that the presence of these functionally distinct cortico-cerebellar loops disencumber cortical regions by reducing the cognitive load, so that attention can focus on higher cognitive tasks such as motor planning or reasoning (Balsters et al., 2014; Stoodley, 2012). Thus, damage to loops is likely to compromise cognitive performance.

Several of the studies included cite disrupted cortico-cerebellar connections as a further potential mechanism. For example, both Rocca et al. (2012) and Ruet et al.

(2014) suggest that cognitive impairment may be due to the employment of inefficient, compensatory loops because of MS-mediated damage to established, optimal cortico-cerebellar connections. This is demonstrated by Rocca et al. (2012) whereby superior cognitive performance on a task of executive function and information processing speed was associated with activation of the cerebellum and the frontal gyrus. Furthermore, Ceresa et al. (2012) observed poorer performance on another measure of information processing speed (PASAT) was associated with enhanced parietal lobe activation. Together, these results indicate that disruption to cortico-cerebellar loops might lead to costly inefficiencies and a saturation effect for cognitive load, resulting in cognitive deficits. Perhaps this also explains the presence of cognitive impairment even in the absence of significant correlations between neuropsychological outcomes in cerebellar pathology.

Findings from the review imply there are correlations between cerebellar pathology, neuroanatomical connections and cognitive performance; namely information processing speed and executive functions. There are several mooted mechanisms thought to underlie the relationship and although the intricacies remain elusive, there is a consensus that the cerebellum forms part of salient cortico-cerebellar loops responsible for a range of both motor and cognitive functions, and if compromised, performance is adversely affected. To further understand the interrelation of cerebellar cognitive impairment, it is proposed that higher order cognitive functions such as motor planning, which are thought to be facilitated by cortico-cerebellar loops are explored (see Empirical Paper).

2.6.5 Significance of Work

A move towards improved characterisation of MS heterogeneity has implications for increased understanding of pathophysiological mechanisms and development of tailored therapeutic interventions. The review indicates cerebellar symptomatology is indicative of a disease phenotype associated with more severe and widespread cognitive impairment. Thus, early intervention for MS individuals at increased risk of cognitive deficits provides an opportunity to optimise a differential rehabilitation approach.

Cognitive remediation is the term used for interventions designed to mediate cognitive decline and can be typically identified as one of three different approaches: cognitive stimulation (CS), cognitive rehabilitation (CR) and cognitive training (CT). It has been proposed that participation in these mentally stimulating activities offers protection from neuropathology via a cognitive reserve (Sumowski, Chiaravalloti, Wylie, & Deluca, 2009). In part, the theory states that the higher an individual's reserve which is measured by, educational attainment, leisure activity and occupation amongst other factors, the higher the threshold for any neuropathology to induce cognitive impairment (Stern, 2006).

The efficacy of cognitive remediation in RR-MS has demonstrated benefits but also suffers from methodological concerns and limitations (das Nair, Martin, & Lincoln, 2016; Goverover, Chiaravalloti, O'Brien, & DeLuca, 2018). For example, a home-based CT intervention improved performance on a measure of information processing speed (PASAT) and a memory task (CLVT-II, learning trials) but failed to include a follow-up

period to investigate whether benefits persisted (Hildebrandt et al., 2007). Another study investigating CT documented benefits across a range of cognitive domains in a group of individuals with objectively defined cognitive impairment (Pérez-Martín, González-Platas, Eguía-Del Río, Croissier-Elías, & Jiménez Sosa, 2017). However, the study pooled different phenotypes of MS, making it difficult to ascertain the magnitude of benefit for each MS group.

The field of cognitive remediation provides an exciting opportunity to potentially delay or prevent cognitive impairment in MS. However, it has been hampered by limitations and may benefit from more rigorous methodological conditions such as clearer differentiation of individuals with RR-MS included and longer follow-up periods given the progressive nature of the disease. Thus, individuals with cerebellar symptomatology therefore represent a viable population to address some of these methodological issues and would allow for a more tailored rehabilitation approach. This has clinical implications for patients, researchers and medical teams.

2.6.6 Future Directions

Gold standard neuropsychological assessment was the main focus of evaluation in the studies included. Whilst this is a strength, future research should focus on the identification of pertinent outcome measures to detect changes that may otherwise be missed in standardised neuropsychological outcomes. For example, subjective daily functioning is fundamental to a sense of wellbeing in MS, yet few studies considered the contribution of cerebellar symptomatology to non-cognitive domains. It is

recommended that additional outcomes to evaluate everyday functioning, mood and quality of life are included.

An increase in high quality randomly controlled trials, with increased sample sizes, and greater longitudinal follow-up data using an appropriate control group to control for non-specific effects is required. Rigorous participant selection using standardised diagnostic criteria should also be used to avoid pooling different MS phenotypes. Furthermore, the use of stringent criteria e.g. the use of North American Research Committee on MS Registry (NARCOMS) Tremor and Coordination Scale (TCS) (Marrie & Goldman, 2011) and neuroimaging techniques, should be used to clearly identify MS patients with cerebellar signs and provide a more accurate investigation of the influence of the cerebellum.

To elucidate the intricacies of the cerebellar cognitive relationship it is recommended that novel measures of higher cognitive function such as motor planning are employed to substantiate developing theories as to how the cerebellar affects cognition (i.e. cortical-cerebellar loops).

Finally, future studies should be equipped with a longitudinal component to provide a greater insight into the dynamics of cerebellar involvement in MS over time. Given the progressive nature of MS this would allow for longer periods of observation and address the lack of follow-up data in relation to long-term prognosis of cerebellum symptoms.

2.6.7 Limitations

A drawback of the review was the relatively small amount of studies included. A comparable literature review of the contribution of grey matter to cognition in RR-MS included data from over 28 studies (van Munster, Jonkman, Weinstein, Uitdehaag, & Geurts, 2015). A synthesis of findings from an increased number of studies would lead to greater confidence in the conclusions deduced. Furthermore, as the field develops a meta-analysis and meta-regression could also be utilised to provide a more objective estimate of the evidence.

One of the assumptions of the review was that all outcome measures within a specific domain shared homogeneity. It was beyond the scope of the review to discriminate between possible differences in outcome measures such as reliability or the underlying rationale. For example, both PASAT and SDMT are considered measures of IPS, although it has been argued that they rely on different neuroanatomical connections (Costa, Genova, DeLuca, & Chiaravalloti, 2017). In addition, performance on the PASAT is affected by mathematical ability (López-Góngora et al., 2015). To enable clearer interpretation of the results, it would have been useful to account for the variance between different outcomes, however no data on correlation between outcomes was available to allow this.

Despite employing strict inclusion criteria, the review includes a heterogenous set of patients. For example, disease duration across studies ranged from a few months to over 10 years despite using widely accepted diagnostic criteria. This makes it difficult to ascertain whether there are meaningful differences between RR-MSc and RR-MSnc, or whether findings merely reflect a different stage of MS progression. For some

studies there was a lack of clear inclusion and exclusion criteria and other factors that might have accounted for deficits were not always considered. To illustrate, visual deficits are common in MS and research has found that visual-perceptual difficulties can reduce performance on neuropsychological tests (Feaster & Bruce, 2011). Therefore, these methodological concerns make it more challenging to assess the contribution of the cerebellum as large variability between study patients may mask true effects.

2.7 Conclusion

The present systematic review has provided evidence that the cerebellum contributes to cognitive impairment in RR-MS patients. The evidence suggests the cognitive domains of IPS and executive function are the most susceptible to cerebellar damage. RR-MSc appear to be characterised by more severe and widespread damage, potentially representing a novel subtype of MS. The underlying mechanisms remain elusive; although, findings indicate the cerebellum forms part of salient cortico-cerebellar networks responsible for a range of both motor and cognitive functions, and if compromised, performance is adversely affected. The review lends support to the hypothesis that the cerebellum underpins cognitive efficiency by disencumbering cortical regions through the reduction of cognitive load, so that attention can focus on higher cognitive tasks. The field would benefit from addressing methodological criticisms such as a lack of follow-up data and patient heterogeneity. To further understand the contribution of the cerebellum to cognitive performance it is recommended that a longitudinal study to investigate motor planning deficits by comparing patients with RR-MSc, RR-MSnc and HC is conducted. This has clinical implications regarding the management, understanding, and treatment of individuals with RR-MS.

The Relation of Cognition to Cerebellar Function in Relapsing-Remitting Multiple Sclerosis: A Longitudinal Study

3.1 Abstract

Cerebellar signs and cognitive dysfunction often occur in parallel in Relapsing-Remitting Multiple Sclerosis (RR-MS). Motor planning is thought to be one area of cognition susceptible to damage but also a surrogate of cerebellar integrity. Therefore, the objective was to investigate the longitudinal relation of cognition to cerebellar function in RR-MS and how changes relate to motor planning and function.

A total of 11 RR-MS patients with cerebellar symptomatology (RR-MSc: 5 males, $\bar{x}$ age: 41), 17 RR-MS patients without cerebellar symptomatology (RR-MSnc: 2 males, $\bar{x}$ age: 40.94) and 9 matched control participants (HC: 2 males, $\bar{x}$ age: 37.78) completed the Brief International Cognitive Assessment for MS (BICAMS), the Nine-hole Peg Test (NHPT) and the Grooved Pegboard Test (GPT) at baseline and at 12 months. The GPT - NHPT difference was used to compute a Motor Planning index (MPI), the NHPT serving as a control for sensorimotor impairment.

Mixed ANOVA revealed a consistent significant group separation on all cognitive and motor tests other than visual memory that was maintained over the follow-up period. There was a significant effect of time for the visual and verbal memory suggestive of learning. There were no significant interactions between group and time. Post hoc tests showed the RR-MSc group was significantly outperformed in tests of cognition, motor function and motor planning by both RR-MSc and HC. There was a significant correlation between measures of information processing speed and MPI.

RR-MSc were characterised by greater impairment on tests of cognition, motor function and motor planning than the RR-MSc. These differences were maintained over a year. The association of the MPI and SDMT indicates information processing speed may act as a moderator of motor planning. The next step is to validate the MPI with an MRI study exploring how it relates to cerebellar lesion load and atrophy.

3.2 Introduction

A key feature of Multiple Sclerosis (MS) is the marked variation of neurological symptoms, typically associated with lesions in eloquent areas of the central nervous system. One such area is the cerebellum which plays an important role in a range of functions (Koziol et al., 2014). Cerebellar damage in MS can lead to motor disturbances such as signs of tremor and loss of coordination (Weier et al., 2015). Cerebellar dysfunction is also associated with cognitive impairment. Research has shown the cognitive profile of patients with RR-MSc is characterised by more severe and widespread deficits, especially within the domains of information processing speed (IPS) and executive functioning (see Systematic Review). In MS, the presence of cerebellar signs and cognitive impairment have both independently been linked to poor prognosis and a considerable degree of disease-related impairment (Amato et al., 2010; Langdon, 2011; Langdon & Thompson, 1999; Weier et al., 2015). As such, it is vital that research efforts focus on developing a clearer measurement of the interrelation of cerebellar cognitive impairment. This has clinical implications for the management of MS as well as the potential to inform treatment development and offer more personalised medicine.

3.2.1 Cognitive Impairment

Cognitive impairment is a common and debilitating feature of MS with limited evidence of effective treatment (Goverover et al., 2018). Various factors have been shown to influence cognition including age, sex, educational attainment and mental health status (Benedict & Zivadinov, 2011; Goretti et al., 2014; Morrow et al., 2016;

Portaccio, 2016). As such, caution must be applied when attempting to disentangle cerebellar involvement in cognition against a background of potentially confounding variables.

Research suggests there may be distinct clinical subtypes within RR-MS (Cerasa et al., 2013; Valentino et al., 2009; Weier et al., 2014). The proposition of cognitive phenotypes within sub-types of MS patients is an emerging field yet appears to be key priority for future research. For example, a recent consensus paper recommended the identification of cognitive phenotypes in MS to facilitate greater understanding of cognitive deficits through the reduction in patient variability (Sumowski et al., 2018). Furthermore, the authors endorsed the use of prospective longitudinal designs to monitor changes in cognitive ability. Therefore, the use of cognitive phenotypes represents a viable opportunity to yield an increased understanding of mechanisms underpinning cognitive deficits and could provide important prognostic and treatment planning considerations.

3.2.2 Cerebellum Function

The cerebellum is acknowledged to have a role beyond purely motor control. Pioneering neuroimaging research has demonstrated the cerebellum contributes to a multitude of functions (Buckner, 2013). To illustrate, one study used a functional magnetic resonance imaging (MRI) paradigm to document the presence of distinct connections or 'loops' between the cerebellar and cortical regions during various tasks (Stoodley, Valera, & Schmahmann, 2012). It was concluded that cognitive tasks activated specific regions of the cerebellum separate from motor tasks. Further

evidence has been demonstrated in neuronal tracing studies and cerebellum functional topography (Kelly & Strick, 2003; Middleton & Strick, 2000; Stoodley & Schmahmann, 2009). Thus, there is compelling evidence to document the relationship between the cerebellar and areas of the cerebral cortex known to be important for cognition.

Clinical studies of cerebellar damage have also demonstrated a role in cognition. In particular, the 'cerebellar cognitive affective syndrome' (CCAS) (Schmahmann & Sherman, 1998) is a condition that follows acquired lesions in the cerebellum. Sequalae include executive dysfunction, impaired working memory, visuospatial deficits as well as personality and affect changes. Additionally, damage to the integrity of cortico-cerebellar loops in MS has been linked with worse performance on several cognitive outcome measures (Cerasa et al., 2013; Valentino et al., 2009; Weier et al., 2014). However, despite research demonstrating an important role for the cerebellum in cognition, it remains unclear how the cerebellum participates in cognition.

3.2.3 Cerebellum and Motor Control

Although there is no clear consensus as to how the cerebellum contributes to motor control (Manto et al., 2012), one theory of interest is that of internal models used to emulate movement through the creation of subroutines. An internal model is a neural representation of the external world that can be generated and stored within the cerebellum (Ito, 2012). The model postulates that the cerebellum has the ability to encode an internal model through repeated performance and sensory feedback (Ito, 2008). Accordingly, during tasks such as upper arm movement the cerebellum can

develop and hold a representation of information developed in the motor cortex during motor learning as a subroutine. This subsequently acts as a template or 'shortcut' that can be used to perform precise movement without external feedback or even conscious awareness.

Support for the model is arguably demonstrated in the Nine-hole Peg Test (NHPT), a measure for assessing upper limb function, whereby superior performance, in part, is dependent on cerebellum integrity. MS patients with cerebellar damage have been found to perform worse on the NHPT compared to controls without cerebellar signs (Romascano et al., 2015; van de Pavert et al., 2016; Weier et al., 2014). It is implied that damage to the cerebellum somehow disrupts the subroutine required for precise action and consequently impairs task performance. However, one caveat is that disruption can also be attributed to more general sensorimotor deficits.

A proposed consequence of cerebellar dysfunction is the loss of efficiency. The 'Universal Cerebellum Transform' model argues that the cerebellum acts as a moderator for controlling diverse streams of information by way of multiple cortico-cerebellar loops (Koziol et al., 2014). It is assumed that the cerebellum functions by optimising task performance. Accordingly, as the cerebellum develops a subroutine, a specific task becomes more automatic and the corresponding cortical regions are freed to engage in other tasks. This results in an overall increase in task efficiency through optimal performance. In contrast, the loss of these subroutines through cerebellar damage results in greater attention being given to previously more automated, less conscious processes and a loss in efficiency. This process is named,

'Universal Cerebellar Impairment', and is thought to underpin motor and cognitive deficits (Guell, Gabrieli, & Schmahmann, 2018).

3.2.4 Cerebellum and Cognition

It has been proposed that the mechanisms underlying the role of the cerebellum in motor control can also be applied to cognitive functions (Guell et al., 2018; Koziol et al., 2014). Similar processes are considered to support the precise execution of mental acts. For example, cerebellar damage has been associated with a loss of precision and efficiency of linguistic abilities and impairment of higher-order cognitive processes typically associated with frontal regions (Guell, Hoche, & Schmahmann, 2015; Schmahmann & Sherman, 1998). Thus, cognitive impairment in MS may be associated with damage of automated subroutines, and a subsequent loss of efficiency.

Several neuroimaging studies have demonstrated cerebellar damage in MS results in the recruitment of inefficient compensatory networks (Bonnet et al., 2010; Moroso et al., 2017; M. Rocca et al., 2012, 2017). Bonnet et al (2010) concluded that the abnormal pattern of connectivity is based on 'cognitive compensation failure'. The authors state that cerebellar damage results in an inability to use automated cognitive processes (i.e. subroutines) and leads to compensatory recruitment of cortical regions usually preserved for higher-order cognitive tasks. Although this compensation might mediate the loss of cognitive ability, it is likely this also contributes to a reduction in cognitive efficiency. Therefore, it is hypothesised that the cerebellum functions as a strategic node in various networks with multiple connections; dysfunction caused by

MS pathology is likely to disrupt optimal functioning. This results in a loss of efficiency in motor and cognitive tasks as the cerebellum mediates both.

3.2.5 Motor Planning

Further research is required to substantiate the hypothesis that the cerebellum contributes to cognition in MS using subroutines. Motor planning is a cognitive ability often associated with the frontal lobe and seen as the ability to conceive, plan and execute coordinated motor responses (Kemenoff, Miller, & Kramer, 2002). Based on the internal model theory, optimal performance in motor planning is likely to be dependent on cerebellum integrity and therefore it serves as a useful indicator of cerebellar function. It is possible that there may be a relationship between motor planning deficits and a reduction in IPS due to the inefficient compensatory recruitment of cortical areas instead of being able to use subroutines to aid performance (Bonnet et al., 2010). Therefore, the recruitment of RR-MSc patients and comparing performance on motor planning and cognitive tasks with RR-MSnc and healthy controls (HC) offers an opportunity to further elucidate cerebellum involvement in cognition.

To calibrate cerebellar function, a novel measure of motor planning is required. Upper limb function is considered an important driver of disability in MS (Lamers & Feys, 2014). In addition, grassroots campaigns (e.g. #ThinkHand on social media) have made calls for greater emphasis on the contribution of upper limb impairment. Taking this into consideration and given MS involves physical symptoms and restrictions on sensorimotor function, which might confound motor planning requirements in

standardised upper limb outcome measures, a Motor Planning Index (MPI) will be utilised (see Method 3.4.6).

3.2.6 Summary

Cognitive impairment affects a significant proportion of people with MS. It has been proposed that the cerebellum forms part of salient cortico-cerebellar loops responsible for intact cognitive functioning. The cerebellum is thought to optimise task performance through automated templates called subroutines. Damage to the cerebellum leads to inefficiencies in motor and cognitive function through the disruptions of subroutines and the forced employment of compensatory networks. Motor planning is a higher-order cognitive ability and considered to be a measure of cerebellar integrity. Thus, it is likely that inefficiencies of motor planning will be associated with cognitive decline, particularly IPS, as the cerebellum mediates both. There is an opportunity to further elucidate cerebellum involvement in cognitive impairment by investigating how cerebellar damage in MS underpins motor planning, and whether this relates to cognitive function.

3.3 Outline of the Research: Objectives and Rationale

The study builds on earlier cross-sectional study investigating cognition and motor planning in MS by adding a longitudinal component to offer greater insight into disease-related cognitive change. Data from the previous study by Hinchcliffe (2017) will be combined with the present study to address the research questions (see 3.3.1).

The proposed study aims to explore the longitudinal relation of cognition to cerebellar function in RR-MS. The study focuses on three areas of inquiry: (i) whether cognitive deficits at baseline remain stable over the course of a year; (ii) calibrating motor planning and upper limb function changes over the year; and, (iii) whether differences in motor planning between MS subtypes and healthy controls are related to IPS given the hypothesised role of the cerebellum increasing task efficiency. The study has several clinical implications such as modified rehabilitation pathways, as well as a potentially providing a precise measure of cerebellar function via a novel measure of motor planning.

Given the progressive nature of MS it is important to have longer periods of observation. There are currently no longitudinal studies examining the aforementioned relationship over time. Therefore, the research is justified given the lack of longitudinal studies in the area and the ability to detect cognitive changes in MS over relatively short follow-up periods (López-Góngora et al., 2015; Weier et al., 2015). The research also aligns with wider NHS research policy recommending increased focus on understanding cognitive impairment in MS (NICE, 2014), and the use of cognitive phenotypes to offer a more precise estimate of impairment (Sumowski et al., 2018). Finally, grassroots campaigns involving social media (e.g. Burke, 2018) and a comprehensive review of assessment tools for upper extremity function have emphasised the need for research to consider the contribution of upper limb functional impairment (Kraft et al., 2014). Therefore, the battery has been amended to include a patient reported outcome measure of upper limb function

which will enable a synthesis of objective and subjective motor function and thus enhance understanding of upper extremity function in MS.

Therefore, the study will re-assess participants from the three groups: RR-MSc, RR-MSnc and healthy controls (HC) after 1-year and compare results to baseline.

3.3.1 Hypotheses

(i) The baseline finding that patients with RR-MSc have a differential cognitive profile to RR-MSnc and HC, demonstrated by worse performances on tests of IPS, memory and verbal fluency will be replicated at 1-year follow-up.

(ii) The performance of patients with RR-MSc on cognitive and motor planning tasks will decline over a 1-year period compared to patients with RR-MSnc and HC, who in turn, will remain stable.

(iii) Differences in motor planning will be related to differences in information processing speed at 1-year follow-up.

3.4 Method

3.4.1 Research Approval

The study protocol was approved following a favourable ethical review from the NHS Health Research Authority (See Appendix 1). Subsequently, the Research and Development (R&D) department in a Surrey NHS Foundation Trust gave permission for the recruitment of MS participants (See Appendix 2). Ethical approval was then obtained from the research ethics committee at Royal Holloway, University of London.

3.4.2 Participants

Between December 2017 and April 2018, a total of 28 RR-MS patients and 9 control participants were recruited for the follow-up study. The number and reason for drop-outs are described in Results section 3.5.2. MS patients were previously allocated into RR-MSnc or RR-MSc based on the North American Research Committee on MS Registry (NARCOMS) Tremor and Coordination Scale (TCS) (Marrie & Goldman, 2011). The total number of participants who completed the study were as follows: RR-MSnc 17/21 (two males, a mean age of 41 and a mean premorbid IQ of 106.7); RR-MSc 11/14 (five males, a mean age of 41 and a mean premorbid IQ of 100.9); HC 9/28 (2 males, a mean age of 37.8 and a mean premorbid IQ of 107.0).

3.4.3 Recruitment

MS participants were restricted to those previously recruited from NHS Foundation Trusts in Surrey and Wandsworth. Permission to be contacted by the researcher was sought via a letter sent by the clinical team. Upon contact, a participant information

sheet (see Appendix 3) was sent via email and a home visit arranged to gain written informed consent (See Appendix 4) and for data collection. Participants with MS were previously known to the research team; thus, home visits were deemed safe and appropriate. An invitation letter was sent to individuals whom requested it (see Appendix 5). Participants were told that they were able to decline participation in the follow-up study and free to withdraw at any time, without giving a reason, and that this would not affect their clinical care or legal rights.

As mentioned, participants were previously allocated to RR-MSnc or RR-MSc based on the NARCOMS-TACS, a validated self-report measure of cerebellar involvement. Participants 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'. The scale was again administered at follow-up to ascertain whether any changes had occurred during the follow-up period.

For controls, an invitation letter (See Appendix 6) was sent along with a participant information sheet (See Appendix 7). All participants contacted the researcher if they wished to be involved, and an appointment was arranged to gain written informed consent (see Appendix 8). All HC were assessed in the researcher's home and informed participation was voluntary and they were entitled to withdraw at any time without giving a reason.

3.4.4 Inclusion and Exclusion Criteria

All participants were fluent English speakers, whose first language was English and aged between 18-60 at baseline. Specific inclusion criteria for MS groups at baseline assessment were twofold: a clinically definite RR-MS based on Polman et al., (2011) or equivalent; and an Expanded Disability Status Scale, telephone version (EDSS) score from 0 – 5 (Lechner-Scott et al., 2003). If a RR-MS participant no longer met inclusion criteria due to disease progression (e.g. EDSS >5), data were still collected and analysed.

Exclusion criteria for all participants included: a diagnosis of psychiatric illness, substance misuse disorders, epilepsy or head injury; significant visual, motor, or hearing impairments which would deny full engagement in cognitive tests; or, a lack of capacity to consent.

3.4.5 Power Analysis

A mixed analysis of variance (ANOVA) was selected due to the combination of between- and within-subject factors. The number of participants required to be retained was calculated using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007).

The Symbol Digit Modalities Test (SDMT) is considered one of the most reliable and sensitive neuropsychological tests for MS (Benedict et al., 2017). The mean effect size using Cohen's *d* (Cohen, 1992) for MS and HC comparisons has been established as *d* = 1.11 (Benedict et al., 2017). Therefore, a large effect size of *d* = 1.1 was utilised for the power analysis.

The power calculation for a mixed design ANOVA using the following: α = .05, power = .8, effect size (*d*) = 1.1, group number = 3, measures = 8 and correlation between repeated variables conservatively estimated at 0.5 indicated that 11 participants per group were required, a total of 33 participants for an actual power = .96.

3.4.6 Materials

The test battery consisted of questionnaires, neuropsychological tests and peg tests designed to provide a comprehensive measure of cognitive, motor and cerebellum functioning. The battery was selected based on best available evidence, whilst considering the effects of fatigue on performance. Standardised test instructions were adhered to so to allow comparisons to baseline performance and to published norms. Testing was completed over the course of a single session with breaks if required and efforts to reduce potential distractions within the immediate vicinity made. Competency in the delivering of the test battery was assessed by a Professor in Neuropsychology. The test battery was amended from baseline to include a measure of visual acuity and a patient reported outcome measure of upper limb function.

(a) Questionnaires

Expanded Disability Status Scale (EDSS) Telephone Version - Lechner-Scott et al., (2003): A telephone adapted version of the EDSS to provide a quantitative overall measure of disability in MS (see Appendix 9). Scores on the EDSS range from 0 (no disability) to 10 (death due to MS) using 0.5 increments. The telephone version has been demonstrated to have a robust correlation with the physician-led physical

examination (r = .95) (ibid). Psychometric properties for the EDSS have demonstrated concurrent validity in RR-MS with neuroimaging markers (Kalkers et al., 2001), good internal consistency ($\alpha \leq .96$) and test-retest reliability (r = .87) (Schäffler et al., 2013). The EDSS remains the most widely used outcome measure for disability progression in MS.

In the present study, MS participants were attributed a score either based on impairment to walking (EDSS 5.0 – 9.0) or via functional system (FS) scores including: vision, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, and cerebral functional systems (EDSS 4.5 – 1.0). The single worse score in each FS subsection determined the FS score which was then used in conjunction with FS frequency tables to determine an EDSS score. Permission was granted from Professor Ludwig Kappos (senior author of Lechner-Scott et al., 2003) to utilise the English version.

Tremor and Coordination Scale (TCS), NARCOMS - Marrie & Goldman (2011): A single response questionnaire-based measure comparing both frequency and impact of tremor and/or co-ordination to experience before developing MS (see Appendix 10). Scores on the TCS range from 0 (minimal tremor or loss of coordination) to 5 (total disabling tremor or loss of coordination). Psychometric properties for the NARCOMS-TCS has shown adequate construct validity and criterion validity for those with an EDSS of 0 - 6.5 with moderate Spearman's rank correlations with the cerebellar functional system score (r = .51) and the Nine-hole Peg Test (r = -0.51) (Marrie & Goldman, 2011).

The Fatigue Severity Scale (FSS) - Krupp, LaRocca, Muir-Nash, & Steinberg (1989): A subjective measure of fatigue with the ability to discriminate between depression and fatigue (see Appendix 11). It has 9 statements and respondents rate how much they endorse these from 1 (strongly disagree) – 7 (strongly agree), and a mean response is calculated. Psychometric properties of the FSS have reported strong internal consistency for MS populations (α = .81) and test-retest reliability (Krupp et al., 1989). Construct validity (r = 0.74) was demonstrated when compared to the Modified Fatigue Impact Scale (MFIS) (Amtmann et al., 2012).

The Hospital Anxiety and Depression scale (HADS) - Zigmond & Snaith (1983): A 14-item scale with seven statements measuring anxiety (HADS-A) and seven statements measuring depression (HADS-D) (see Appendix 12). 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 with cut-off scores 0 – 7 (normal range), 8 – 10 (mild range), 11 – 14 (moderate range) and 15 – 21 (severe range). The psychometric properties for the HADS have recently been studied in relation to several other mood screening tools in MS (Marrie et al., 2018). For HADS-D and HADS-A, specificity (95% and 86%) was generally higher than sensitivity (31% and 64%) but provided superior estimates of depression and anxiety over other tools. Both the HADS-D (α = 0.82) and HADS-A (α = 0.86) demonstrated acceptable internal consistency reliability.

ABILHAND - **A self-report measure of manual ability** – Penta, Thonnard, & Tesio (1998). A 26-item measure of manual ability for adults with upper limb impairments (see Appendix 13). The scale measures patient-perceived difficulties in performing

activities of daily living. The measure has been validated in MS and reliability found to be high (Barrett, Cano, Zajicek, & Hobart, 2013).

(b) Cognitive Tests

The cognitive battery includes the three tests (SDMT, BVMT-R learning trials and CVLT-II learning trials – see below) from the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS; Langdon et al., 2012) as well as a two tests (WLG and PASAT-3) which form part of the Brief Repeatable Battery of Neuropsychological Tests (BRB-N; Boringa et al., 2001). Each test has been demonstrated to be sensitive to measuring cognitive impairment in MS, with BICAMS considered the gold standard for cognitive screening in MS. The battery also included a test of predicted intelligence (PFSIQ) to ensure the groups are matched for premorbid IQ function and a visual acuity measure to ensure visuo-perceptual difficulties cannot account for test performance.

Test of Premorbid Functioning (TOPF) – Wechsler (2011): The TOPF is a brief test to predict premorbid intelligence (IQ) (see Appendix 14). It consists of 70 words with abnormal grapheme/phoneme translations. Participants read the list aloud, and the number of phonetically correct words spoken provides a score. The raw score is combined with demographic information including age, sex and years of education to compute a predicted full-scale IQ (PFSIQ). The test was used to ensure groups were matched for premorbid function that might otherwise influence performance. Psychometric properties for the TOPF are well established, there is good test re-test reliability (r = .89 to .95) and high split-half reliability (r = .92 to r = .99) (Wechsler,

2011). It also demonstrates concurrent validity with the WAIS-IV verbal comprehension index (r = .75), processing speed index (r = .37) (Wechsler, 2011).

Symbol Digit Modalities Test (SDMT) – Smith, 1982: A test of IPS whereby symbols are paired with numbers (see Appendix 15). Following a practice phase, individuals are required to orally state the numbers that correspond to figures presented. The total score is the number of correct responses within a 90-second limit. The SDMT is the most commonly used test in standard MS batteries due to the ease of administration, accessibility and excellent psychometric properties (Benedict et al., 2017). The SDMT demonstrates good test–retest reliability (r = 0.97) in MS (Benedict, 2005), demonstrated the largest effect size (*d* = 1.1) amongst a number neuropsychological tests in discriminating between MS and control groups (Benedict et al., 2006) and has good construct validity in MS as it is strongly associated with neuroimaging disease markers (Christodoulou et al., 2003).

Word List Generation (WLG) Version A: The WLG is a 90-second test of semantic fluency naming as many words within a given category (see Appendix 16). The category was 'fruits and vegetables'. The total score is the number of words stated fitting the category. Psychometric properties include a sensitivity of 82% and specificity 66% in discriminating cognitive impairment in syndromes suggestive of MS when using a cut-off of <28 (Viterbo, Iaffaldano, & Trojano, 2013). Good construct validity has been demonstrated with neuroimaging markers of atrophy (Morrow, Menon, Rosehart, & Sharma, 2017).

Paced Auditory Serial Addition Test (PASAT) - Gronwall and Sampson, 1974: This is a test of IPS and sustained and divided attention as well as working memory and calculating speed (see Appendix 17). The examiner presents numbers every three seconds (recorded for standardisation), and the participant must add this number to the previous number presented. The total score is the correct number of responses. The PASAT-3 was preferred to the PASAT-2, whereby numbers are presented every two seconds, for participant tolerability and to enable direct comparisons to baseline performance. Psychometric properties have shown the PASAT-3 to have good inter-rater reliability (r = .90 to .97) and test-retest reliability good test-retest reliability (r = .92) (Solari, Radice, Manneschi, Motti, & Montanari, 2005) and reported a sensitivity of 73% and specificity of 59% for cognitive impairment (López-Góngora et al., 2015).

California Verbal Learning Task (CVLT-II) – Woods, Delis, Scott, Kramer, & Holdnack (2006): A measure of verbal learning and memory (see Appendix 18). The CVLT-II learning trial involves a list of 16 words split into four categories. The experimenter reads all words (<1 word/second), and the participant recalls as many words as possible. The score is the total number of words recalled over five trials. The CVLT-II involves several trials yet only the learning trial was included to reduce the number of cognitive processes involved (Langdon et al., 2012). Psychometric properties were therefore inferential. The test has demonstrated good internal consistency (α = .83 to .96) and test-retest reliability in MS populations (Woods et al., 2006). Construct validity within the MS population to employment status has also been demonstrated (Stegen et al., 2010).

Brief Visual Memory Test – Revised (BVMT-R) – Benedict, Schretlen, Groninger, Dobraski, & Shpritz (1996): A test of visual learning and memory (see Appendix 19). 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 in the same position as the stimulus sheet. A point is awarded for accurate drawing and correct location with a maximum score of 36 over three trials. The BVMT-R incorporates other trials, yet only the learning trials were included for similar reasons to the CVLT-II. Thus, inferred psychometric properties demonstrate good inter-rater reliability ($r > .90$), and good test-retest reliability ($r = .80$) (Benedict, 1996). It has been demonstrated to be sensitive to impairment with MS populations (Benedict et al., 2001; Langdon et al., 2012) and construct validity shown through associations with neuroimaging disease markers (Benedict et al., 2001; Langdon et al., 2012).

Snellen Pocket Visual Acuity Test – Snellen, 1862. This standardised test examines the ability to discriminate high contrast fine detail at a distance; the acuity of vision (see Appendix 20). The pocket version has been adapted for testing at 12 – 14 inches. A score was recorded for the smallest line of letters which were all correctly read. A cut-off score based the logMAR scale of >0.5 (defined as 'moderate' visual impairment; Colenbrander, 2002) was inferred as a marker of impaired visual acuity and thus likely to impair neuropsychological performance (Colenbrander, 2002).

(c) Peg Tests

Nine-hole peg test (NHPT) – Mathiowetz, Weber, Kashman & Volland, 1985: This provides a quantification of upper limb motor function and physical disability (see Appendix 21). Participants are required to pick up pegs, one at a time, and fill the holes in any order on a board before returning them, one at a time, to the container. The test is repeated twice with both hands and a mean time across trials is used to provide a score. Important psychometric properties have illustrated high inter-rater (r = .84 - .96) (Feys et al., 2017; Solari et al., 2005), internal consistency (α = .93) (Rasova, Martinkova, Vyskotova, & Sedova, 2012), and reduced performance is indicative of cerebellar atrophy (Ruet et al., 2014; van de Pavert et al., 2016).

Grooved Pegboard Test (GPT) – Trites (1989): The test consists of a pegboard with 25 holes (see Appendix 22). Boat-shaped pegs must be inserted into randomly positioned holes in the correct orientation sequentially from the opposite side of the board to the hand that they are using. The first row is demonstrated before the participant completes the remaining holes. Each hand is tested before a mean time is used to provide a score. In comparison to the NHPT, the GPT requires more motor planning and co-ordination. Psychometric properties for the GPT indicate variable test-retest reliability within healthy controls (r = .67 to .86) (Levine, Miller, Becker, Selnes, & Cohen, 2004; Ruff & Parker, 1993) and a weak/modest association with activities of daily living and GPT scores in MS (Kessler, Cohen, Lauer, & Kausch, 1991).

Motor Planning Index (MPI): To calibrate a measure of motor planning, a MPI score was calculated by subtracting the NPHT from the GPT. The rationale underlying the MPI is based on subtraction logic to isolate a critical component and often used in MS

research (Roth, Denney, & Lynch, 2015; Shoben, Cech, & Schwanenflugel, 1983). It is assumed that the GPT has a greater motor planning component than the NHPT, but both have a sensorimotor component. By subtracting the time taken on the NHPT from the GPT, we have an indication of motor planning whilst controlling for sensorimotor function.

3.4.7 Design and Procedure

The design was based on an earlier study by a previous DClinPsy trainee investigating how the cognitive profile of RR-MSc related to motor planning and motor function, and how this differed from RR-MSnc and HC (Hinchliffe, 2017). A total of 56 participants completed the test battery and statistical analysis revealed the RR-MSc group showed greater impairment than RR-MSnc on cognitive tests and motor tasks.

Therefore, the present design involved a repeat test battery of questionnaires, neuropsychological tests and two peg board tests to all participants at 1-year follow-up. Each participant had previously been allocated an anonymised participant identification number which was used to amalgamate baseline and follow-up data. Name and identification number pairings were kept in separate encrypted and password-protected spreadsheets.

The battery was identical to the baseline assessment with the additional of two tests (ABILHAND and Snellen Pocket Eye Test) and was administered in same order except for the additional tests which were added into the schedule before the start of the cognitive tests to minimise interference. Home visits were completed in accordance

to the Camden and Islington NHS Foundation Trust Lone Working Policy (September 2015).

Upon arrival at the testing location, each participant was provided with an oral agenda of the assessment and informed that the test battery would take an estimated time of 60 minutes. Participants were provided the opportunity to ask specific questions before written informed consent was gained and they were advised of their ethical and legal rights.

During a short clinical interview, demographic information (gender, age, and educational level) and time since diagnosis was cross-referenced with information collected at baseline. Participants were then asked about changes in medication and whether they had experienced a relapse within the last two months. All data were recorded on paper before transferred to an electronic spreadsheet which was encrypted and password-protected. Next, all questionnaires were administered before participants completed the test battery in the order demonstrated in Table 6 and in accordance with their baseline randomisation number to dictate the order of the peg board tests.

Table 6 *Questionnaire, cognitive test and pegboard administration order*

Procedure	Tests administered (in order)
Questionnaires	1. EDSS Telephone Version

	2.	NARCOMS-TACS
	3.	FSS
	4.	HADS
	5.	ABILHAND
	6.	Snellen Pocket Eye Test
Pegboard Test 1	7.	NHPT/GPT*
Cognitive Tests	8.	TOPF
	9.	SDMT
	10.	CVLT-II Learning Trials
	11.	BVMT-R Learning Trials
Pegboard Test 2	12.	NHPT/GPT*
Cognitive Tests	13.	WLG
	14.	PASAT-3

*Order established by counterbalancing

3.4.8 Analysis

The Statistical Package for the Social Sciences 21.0 (SPSS) was utilised to analyse data (IBM Corp., 2013). All variables were subject to exploratory data analysis to assess whether assumptions for parametric analysis were met. Variables were subject to transformations if data at either baseline or follow-up was found to have a non-normal distribution.

Only participants with a full dataset were included in the main analysis. No participants were excluded. Successful matching of participants between groups with regards to pre-morbid intelligence, depression, anxiety, fatigue, EDSS and age was checked using a one-way between-subjects ANOVA. A mixed design ANOVA was utilised to make comparisons of RR-MSnc, RR-MSnc and HC (Group factor) on neuropsychological and pegboard test means between baseline and follow-up (Time factor). To investigate the relationship between objective motor function (NHPT and GPT) and subjective motor function (ABILHAND), a Pearson's correlation (*r*) analysis

and correlation coefficients were calculated. Finally, to examine the strength of the relationship between MPI and measures of IPS, data was subjected to Pearson's correlation (*r*) analysis and correlation coefficients calculated when significant correlations were present.

Post hoc adjustments were considered to protect the family-wise error rate. However, due to the number of multiple comparisons within the battery and to prevent utilising a too stringent corrected p-value (e.g. Bonferroni), and thus greater likelihood of rejecting a meaningful difference (Field, 2009) (type II error), Least Significant Difference (LSD) values (equivalent to no adjustments) were utilised to clarify significant findings. If group variances were found to be non-equivalent, Games-Howell comparisons were used instead.

3.5 Results

3.5.1 Exploratory Data Analysis

A prerequisite for parametric tests is the assumption of a normal distribution; therefore, a cut-off of ±2.58 ($p < .01$) for skewness and kurtosis was utilised to check the distribution of scores (Field, 2011). For baseline data, converted z-scores revealed MPI for the RR-MSnc group was positively skewed. In addition, for follow-up data ABILHAND data was negatively skewed for the RR-MSnc group and NHPT was positively skewed for the RR-MSc group. For all other data, skewness and kurtosis fell below ±2.58, thereby meeting normality assumptions for parametric tests ($p < .01$) (See Appendix 23 & 24)

Field (2011) recommends using a reverse score, square-root transformation for negatively skewed data. The ABILHAND was significantly negatively skewed for the RR-MSnc group ($z = -2.75$, $p<.01$). After subtracting the highest score + 1, a square root transformation was carried out, which resulted in the data being normally distributed ($z = -1.49$, $p<0.1$). Furthermore, Tabachnick and Fidell (2013) recommend a logarithmic transformation (Log10) for substantially positively skewed data. As the MPI for the RR-MSnc group ($z = 2.90$, $p<0.1$) at baseline and the NHPT for the RR-MSc group ($z= 3.13$, $p <0.1$) at follow-up were both highly positively skewed, a Log10 transformation was applied to achieve a normal distribution (MPI: $z = 1.83$, $p <0.1$; NHPT: $z = 2.13$, $p<0.1$) (See Appendix 25)

According to Field (2011), to compare differences between variables (e.g. change in a variable over time), the same transformation must be applied. Therefore, variables

that were transformed at either baseline or follow-up had corresponding data transformed to facilitate comparisons.

3.5.2 Baseline demographics

An overview of the descriptive statistics for demographic information at baseline for participants who completed and dropped out are presented in Table 7. There were no significant differences for age ($F(2,34) = .41$, $p = .665$), years of education ($F(2,34) = 2.44$, $p = .103$) or predicted full-scale IQ ($F(2,34) = 1.44$, $p = .251$) between the groups. For disease duration, separate variance estimates were used as homogeneity of variance was not met ($F = 5.96$, $p = .022$). Although non-significant, RR-MSc had trending significance for a higher length of disease duration compared to RR-MSnc ($t(16) = 2.08$, $p = .055$). A Fisher's exact test revealed no significant differences in gender ($p = .153$), although there was a significant difference in employment status ($p = .002$). None of the above variables were considered in subsequent analysis. Employment status was not included in further analysis as MS patients are much less likely to be employed than those without MS, even at low levels of disability (Kobelt et al., 2017). There was a significant difference for the length of follow-up period between groups ($F(2,34) = 18.44$, $p < .001$). Subsequent t-tests using separate variance estimates revealed a significant difference between the HC group with both the RR-MSc group ($t(8) = 3.33$, $p = .010$) and RR-MSnc group ($t(8) = 3.85$, $p = .004$). There was no significant difference between the MS subgroups ($t(26) = 2.34$, $p = .08$). This reveals that the follow-up period was significantly shorter for the HC group compared to the

RR-MS subgroups. Nevertheless, the result implies that practice effects were accounted for.

Statistical analysis was restricted to those who completed the study. Due to small sample size, statistical analysis examining participants who dropped out was not considered appropriate. However, qualitatively the reasons for drop out for the RR-MSc group included: declined for personal reasons (1); unable to complete during recruitment window (1); unable to contact (1); the RR-MSnc group: declined for personal reasons (1); unable to complete during recruitment window (3); the HC group: declined for personal reasons (8); moved out of area (8); unable to contact (2).

All participants were rated as having at least near-normal vision (logMAR ≥ 0.5) according to the Snellen Pocket Eye Test. It was therefore assumed that reading ability would not influence test performance. Therefore, no participants were excluded due to visual acuity concerns.

Table 7 *Baseline demographic characteristics of all participants including those who dropped out*

Characteristic	RR-MSc				RR-MSnc				HC				Significance
	Complete (n = 11)		Dropout (n = 3)		Complete (n = 17)		Dropout (n = 4)		Complete (n = 9)		Dropout (n = 18)		*p* value*
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age (Years)	41	8.64	42	11.53	40.94	8.86	38.75	3.95	37.78	10.29	38.44	12.89	.665
Education (Years)	13.55	1.57	15	3.61	16.06	3.21	18.75	0.96	15.67	3.91	17	2.47	.103
PFSIQ	100.03	8.03	99.1	8.96	107.34	12.8	117.23	5.83	107.08	13.67	114.93	7.88	.251
Disease Duration (Years)	10.4	7.58	1.86	2.72	5.02	5.08	4.33	4.67	-		-		.055
Follow-up period (Days)	370	16.74	-		387	28.57	-		268	91.14	-		**<.001**
Employment: F/P/U	4/1/6		1/0/2		8/7/2		4/0/0		9/0/0		17/1/0		**.002**[A]
Gender (F/M)	6/5		2/1		15/2		0/4		7/2		10/8		.153

SD: Standard Deviation; PFSIQ: Predicted Full-scale IQ; Employment: Full-time (F), Part-time (P), Unemployed or Sick Leave (U). *One-way ANOVA for participants with complete dataset only. **BOLD** – statistically significant. P value = .05. [A]Fisher's Exact test for participants with complete dataset.

3.5.3 Clinical Variables

An overview of descriptive statistics for clinical variables at baseline and follow-up is presented in Table 8.

Data for the ABILHAND questionnaire was only available at follow-up. A one-way independent ANOVA to compare ABILHAND scores revealed significant group differences ($F(2,34) = 4.80$, $p = .015$). As homogeneity of variance assumptions were not met ($F(2,34) = 5.66$, $p = .008$), post hoc Games-Howell tests showed the both the RR-MSc group ($p = .001$) and the RR-MSnc group ($p = .017$) scored significantly lower on ABILHAND compared to HC. There were no significant differences between the two MS subgroups ($p = .617$). This suggests both RR-MS groups had greater perceived difficulty with upper limb movement compared to HC.

For subjective levels of fatigue, a mixed ANOVA showed a significant interaction of group and time ($F(2,34) = 4.8$, $p = .015$). There was a non-significant effect of time ($F(1,34) = .016$, $p = .899$) and a significant effect of group ($F(2,34) = .016$, $p = .001$). Further analysis showed that each group was significantly different from one another: RR-MSc vs RR-MSnc groups ($p = .029$), RR-MSc vs HC groups ($p < .001$), and RR-MSnc vs HC groups ($p = .014$). Furthermore, fatigue scores were only significantly different over time for the RR-MSnc group ($p = .009$). In combination with the mean scores, the results indicate that despite the magnitude of difference between groups remaining stable, the RR-MSnc group reported fewer symptoms of fatigue at follow-up. In contrast, RR-MSc and HC groups reported similar symptoms of fatigue at baseline and follow-up.

For HADS-A, there were no significant effects of time ($F(1,34) = .261$, $p = .115$), group ($F(2,34) = .943$, $p = .399$) or interaction ($F(2,34) = .520$, $p = .599$). In contrast, HADS-D had a significant main effect of group ($F(2,34) = 4.07$, $p = .026$), indicating symptoms of depression were different across groups. Post hoc tests demonstrated the effect was accounted for by a significant difference between HC and RR-MSc ($p = .007$). There were no other significant differences in terms of self-reported symptoms of depression between groups. No other comparisons were found to be significant (time: ($F(1,34) = .029$, $p = .886$; interaction: ($F(2,34) = .007$, $p = .993$). This implies that the HC group had significantly lower depression symptoms compared to RR-MSc. This result will be discussed in more detail later (Section 3.6.2).

A mixed 2x2 ANOVA for EDSS scores revealed significant effects of group ($F(2,34) = 20.5$, $p < .001$) and interaction ($F(2,34) = 6.49$, $p = .017$) and a non-significant effect of time ($F(1,34) = .298$, $p = .590$). Examination of the means suggests EDSS scores for the RR-MSc increased whereas RR-MSnc decreased. Post hoc t-tests compared EDSS scores at baseline and follow-up between both MS groups. As expected, both baseline ($t(26) = 4.08$, $p > .001$) and follow-up ($t(26) = 4.76$, $p > .001$) scores were significantly different from one another. This indicates that although there were statistically significant differences between the MS groups at baseline and follow-up, the rate of disability grew progressively worse for RR-MSc compared to RR-MSnc, which in turn, remained stable. There were no significant changes over time for the NARCOMS score ($F(1,34) = 1.81$, $p = .19$).

Table 8 *Clinical variable scores of participants at baseline and follow-up*

Variable	RR-MSc (n = 11)				RR-MSnc (n = 17)				HC (n = 9)				*p* value		
	Baseline		Follow-up		Baseline		Follow-up		Baseline		Follow-up		Time x Group	Time	Group
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
ABILHAND √	-	-	3.22	0.96	-	-	2.61	1.35	-	-	1.27	0.55	-	-	**.015**[A]
FSS	5.30	1.32	5.32	1.28	4.40	1.51	3.90	1.60	2.53	0.85	2.96	1.14	**.015**	.899	**.001**[B]
HADS-A	6.82	3.28	8.36	5.46	5.71	3.31	6.00	2.81	5.89	3.48	6.67	3.71	.599	.115	.399[B]
HADS-D	6.36	3.23	6.46	2.94	4.94	3.61	5.06	2.95	2.89	1.62	2.89	2.57	.993	.866	**.026**[B]
EDSS	4.55	0.57	4.73	0.79	3.03	1.14	2.91	1.09	-	-	-	-	**.017**	.590	**<.001**[C]

SD: standard deviation; √: Square Root; FSS: Fatigue Severity Scale; HADS: Hospital Anxiety and Depression Score, A - Anxiety score, D - Depression score; EDSS: Expanded Disability Status Scale; NARCOMS: North American Research Committee on MS. **BOLD** = statistically significant *p* value = .05. [A] One-way ANOVA; [B] 2x3 Mixed ANOVA; [C] 2x2 Mixed ANOVA.

3.5.4 Cognitive and Motor tests

A mixed model ANOVA was used to explore the main effect of group, time and interaction of the factors for each of the cognitive and motor measures. The descriptive statistics and significance values (p = .05) for each dependent variable are presented in Table 9.

(a) Cognitive Tests

There was no significant interaction effect for the BVMT-R ($F(2,34) = .387$, $p = .682$), CLVT-II ($F(2,34) = .991$, $p = .382$), PASAT-3 ($F(2,34) = .387$, $p = .682$), SDMT ($F(2,34) = .056$, $p = .946$) or WLG ($F(2,34) = .565$, $p = .574$). The lack of significance suggests that the magnitude of differences across all groups remained broadly similar over the study period. This would imply that the cognitive profile of the RR-MSc did not significantly deteriorate over the course of a year in comparison to RR-MSnc and HC groups.

There was a significant effect of time for the BVMT-R ($F(1,34) = 4.74$, $p = .037$) and the CVLT-II ($F(1,34) = 18.83$, $p < .001$), indicating that scores of visual and verbal memory improved over time. To consider this effect further, examination of means and post hoc tests were conducted. For the BVMT-R, there was a significant difference between scores at baseline and follow-up, suggesting an improvement in performance ($p = .04$). Neither the RR-MSnc or HC group had any significant differences in performance. This would imply that the significant effect of time for the BVMT-R was accounted for by an improvement in score by the RR-MSc group. In addition, further analysis of the CVLT-II scores revealed both the RR-MSc ($p = .006$) and RR-MSnc ($p < .001$) scored

significantly higher on the CVLT-II at follow-up, whereas there was no significant improvement for the HC group. There were no significant effects of time for IPS (PASAT-3: ($F(1,34) = 2.32$, $p = .137$); SDMT: ($F(1,34) = 3.69$, $p = .063$)) or verbal fluency (WLG: ($F(1,34) = .913$, $p = .346$)).

Finally, there was a significant effect of group for the CVLT-II ($F(2,34) = 8.52$, $p = .001$), PASAT-3 ($F(2,34) = 4.48$, $p = .019$), SDMT ($F(2,34) = 6.12$, $p = .005$) and WLG ($F(2,34) = 4.94$, $p = .013$). Interestingly, there was no significant group effect for the BVMT-R ($F(2,34) = 2.18$, $p = .129$). For the CVLT-II, post hoc comparisons revealed there was a significant difference between the RR-MSc and RR-MSnc group ($p = .002$) and the HC group ($p = .005$) but no significant difference between the RR-MSnc and HC groups ($p = .999$). This pattern was also repeated for the PASAT-3 (RR-MSc vs RR-MSnc, $p = .008$; RR-MSc vs HC, $p = .024$; RR-MSnc vs HC, $p = .963$), SDMT (RR-MSc vs RR-MSnc, $p = .007$; RR-MSc vs HC, $p = .003$; RR-MSnc vs HC, $p = .457$) and the WLG (RR-MSc vs RR-MSnc, $p = .013$; RR-MSc vs HC, $p = .007$; RR-MSnc vs HC, $p = .052$). Taken together, the results suggest that the group effect was largely accounted for by the superior performance on a range of cognitive abilities by the RR-MSnc and HC groups compared to RR-MSc. There were no significant differences between RR-MSnc and HC groups.

(b) Motor Tests

A similar strategy was utilised to examine the performance of motor tasks. There was no significant interaction effect for the NPHT ($F(2,34) = .047$, $p = .954$), GPT ($F(2,34) = .885$, $p = .422$) or MPI ($F(2,34) = .138$, $p = .872$. There was also no significant effect of time for the NHPT ($F(1,34) = .373$, $p = .545$), GPT ($F(1,34) = .904$, $p = .348$) or MPI

(F(1,34) = 1.51, p = .226). The results indicate motor function and motor planning remained stable across all groups and again implies the RR-MSc group did not significantly deteriorate compared the other groups as was previously predicted.

As expected, there was a significant effect of group for NHPT (F(2,34) = 29.11, p <.001), GPT (F(2,34) = 11.74, p <.001) and MPI (F(2,34) = 14.19, p <.001). Inspection of the means and post hoc analysis revealed that for the NHPT there was a significant difference between the RR-MSc and RR-MSnc groups (p = .001) and HC groups (p <.001). Furthermore, there was a significant difference between the RR-MSnc and the HC group (p = .004). This pattern was also demonstrated for the GPT (RR-MSc vs RR-MSnc, p = .041; RR-MSc vs HC, p = .006; RR-MSnc vs HC, p = .003) and the MPI (RR-MSc vs RR-MSnc, p = .023; RR-MSc vs HC, p = .001; RR-MSnc vs HC, p = .003). The results show that there was significant magnitude of difference between each group: the HC group outperformed the RR-MSnc group, who in turn, outperformed the RR-MSc group on measures of motor functioning and motor planning.

Table 9 *Baseline and Follow-up scores for cognitive and motor tasks and results of mixed ANOVA significance levels*

	RR-MSc (n= 11)				RR-MSnc (n= 17)				HC (n= 9)				Significance (p-value)		
Test	Baseline		Follow-up		Baseline		Follow-up		Baseline		Follow-up		TxG	Time	Group
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
BVMT-R	19.00	9.77	20.82	10.22	24.65	8.15	26.82	6.37	24.89	5.53	25.56	5.25	.682	**.037**	.129[A]
CVLT-II	38.82	9.01	45.73	11.09	52.18	11.27	59.53	9.76	55.22	8.23	58.22	10.34	.382	**.001**	**<.001**
PASAT-3	34.09	12.77	36.00	12.97	45.29	9.41	46.65	10.64	45.22	7.45	46.33	7.65	.946	.137	**.019**
SDMT	39.73	10.57	42.09	9.88	52.06	11.86	54.88	14.78	56.67	8.92	57.22	8.91	.639	.063	**.005**
WLG	23.18	5.38	22.18	7.43	28.24	4.8	28.53	7.44	30.56	3.57	29.22	5.61	.574	.346	**.013**
NHPT	28.61	5.51	28.56	7.59	21.22	2.26	20.83	3.12	18.32	1.29	18.15	1.43	-	-	-
NHPT Log10	1.45	0.08	1.44	0.1	1.33	0.05	1.31	0.06	1.26	0.03	1.26	0.04	.954	.545	**<.001[A]**
GPT	96.97	37.12	102.4	43.53	65.62	16.33	65.02	11.81	51.78	2.54	52.69	2.62	.422	.348	**<.001[A]**
MPI	68.35	33.42	73.93	36.95	43.81	13.87	44.19	9.67	33.35	2.21	34.49	2.14	-	-	**-**
MPI Log10	1.8	0.18	1.82	0.2	1.62	0.12	1.64	0.1	1.52	0.03	1.54	0.03	.872	.226	**<.001[A]**

SD - standard deviation; **BOLD** – significant result using P value = .05. All analysis conducted with a 2x3 ANOVA with Least Significant Difference or [A] Games-Howell.

3.5.5 Correlations of Motor Function, Planning and Information Processing Speed

Correlations between measures of IPS and motor tasks from data collected at 1-year follow-up are presented in Table 10. The results indicate that the SDMT was more strongly correlated with the motor tests compared to the PASAT-3. This implies that there was a moderate negative correlation for the SDMT and all motor tests, indicating that there was a tendency for low SDMT scores to go with slower performance on both tasks of motor functioning (NHPT) and motor planning (MPI), thus highlighting inefficiencies.

Table 10 *Correlations of IPS and self-reported motor difficulties with motor function and planning*

	SDMT		PASAT-3		ABILHAND	
	r	*p*	*r*	*p*	*r*	*p*
NHPT	-.67	**<.001**	-.52	**.001**	.39	**.017**
GPT	-.61	**<.001**	-.52	**.001**	.35	**.033**
MPI	-.61	**<.001**	-.5	**.002**	.37	**.026**

BOLD: Significant at the 0.05 level. r = Pearson's

Fisher transformations were computed to ascertain whether there was a statistically significant difference between correlation coefficients. The SDMT revealed no significant difference between correlations coefficients for NHPT v GPT (z = -.44, p = .66), GPT v MPI (z = 0, p = 1) or NHPT v MPI (z = -.44, p = .66). For the PASAT-3, there was no significant difference between correlation coefficients for NHPT v GPT (z = 0, p = 1), GPT v MPI (z = -.12, p = .91), or NHPT v MPI (z = -.12, p = .91). This suggests that IPS is not contributing more to motor planning than motor function.

An exploratory approach evaluating the relationship between subjective motor performance (ABILHAND) and objective motor functioning (NHPT and GPT) was also undertaken and results are presented in Table 10. The results indicate that there was a weak positive correlation between subjective and objective motor performance suggesting a linear relationship between perceived difficulties and slower motor performance. ABILHAND was not significantly correlated with any other self-report measure (e.g. FSS, HADS).

3.5.6 Summary

The results indicate all groups were successfully matched on all demographic variables aside from employment status. As expected, there were significant differences between RR-MS subgroups on the EDSS and NARCOMS score. There was a significant difference in symptoms of depression between groups, with HC reporting significantly lower symptoms of depression compared to RR-MSc. There were no differences in symptoms of anxiety. The cognitive profile of each group remained broadly similar between baseline and follow-up. HC did not outperform the RR-MSnc on any measure. However, HC did significantly outperform RR-MSc on the SDMT and CLVT-II. RR-MSnc significantly outperformed RR-MSc on the SDMT, PASAT-3 and CLVT-II. On tests of motor function and motor planning, HC significantly outperformed RR-MSnc (aside from the NHPT) and RR-MSc, and RR-MSnc outperformed RR-MSc. There was a significant negative moderate-strong correlation between the MPI and measures of IPS. However, there were no significant differences between the strengths of the correlations for the MPI, GPT and 9HPT with either measure of IPS.

3.6 Discussion

3.6.1 Summary

There is a consistent pattern demonstrating cerebellar signs and cognitive dysfunction often occur in parallel and RR-MSc is associated with more widespread and severe cognitive impairment. To develop a clearer measure of cerebellar involvement, the present study investigated the longitudinal relation of cognition to cerebellar function in RR-MS and how changes relate to motor planning and function.

3.6.2 Hypothesis (i): The baseline finding that patients with RR-MSc have a differential cognitive profile to RR-MSnc and HC, demonstrated by worse performances on tests of IPS, memory and verbal fluency will be replicated at 1-year follow-up.

The RR-MSc group were significantly outperformed by RR-MSnc and HC groups on all cognitive measures aside from the BVMT-R. There were no significant differences between RR-MSnc and HC groups. The results suggest that the cognitive profile of RR-MSc appears to be consistently weaker when compared to RR-MSnc and HC, involving more severe and widespread cognitive impairment. This replicates the baseline finding that a differential cognitive profile exists for RR-MSc compared to RR-MSnc and HC (Hinchcliffe, 2017). These findings are possibly associated with the 'universal cerebellar transform', suggesting that cerebellar damage would result in impairment across several domains (Koziol et al., 2014; Schmahmann, 2004).

As all groups were successfully matched for age, gender and premorbid IQ, these variables cannot account for the differences observed. There were however statistically significant differences between the MS and HC groups in self-reported depression and fatigue. As the prevalence of depression and fatigue is higher in MS populations than the general population (Boeschoten et al., 2017; Weiland et al., 2015), the finding might represent an inherent difference between groups rather than noise or error variance. Attempting to control pre-existing, meaningful group differences is not recommended as it may lead to the removal of telling variation (Miller and Chapman, 2001). Therefore, a decision was taken not to statistically control for these variables.

The follow-up period was also significantly shorter for the HC. Due to a large amount of attrition, more controls were recruited to negate the loss. Consequently, the time between baseline and follow-up was inevitably shorter. A study of practice effects using a similar neuropsychological battery in healthy adults found test intervals of 6 months or more were largely resistant to practice effects (Bartels, Wegrzyn, Wiedl, Ackermann, & Ehrenreich, 2010). Moreover, the inclusion of controls with a shorter follow-up would have clearly accounted for any practice effects in the MS groups. Therefore, as the mean follow-up period for HC was more than six months, no efforts were made to control for the difference.

The RR-MSnc and HC group performed significantly better on both measures of IPS compared to the RR-MSc. This replicates findings from baseline data and previous studies (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) and provides theoretical support that cerebellar integrity is crucial for cognitive efficiency as measured by IPS. The SDMT is a superior measure of IPS (Benedict et al., 2017), and therefore it is of relevance that the SDMT had larger significant group differences compared to the PASAT-3, which contains addition components (i.e. arithmetic and working memory; Costa, Genova, DeLuca, & Chiaravalloti, 2016). This provides strong evidence of IPS vulnerability in relation to cerebellar damage.

There were significant verbal memory deficits for the RR-MSc group, as indicated by CVLT-II performance, that were replicated over the testing period. In contrast, no such replication was found for visual memory, represented by BVMT-R performance. The absence of a significant group difference for BVMT-R could be related to the high standard deviation indicating scores were widely spread and thus making it more difficult to detect an effect. From clinical observations, it is important to state that the drawing component of the BVMT-R was unaffected by cerebellar signs.

However, examination of CVLT-II and BVMT-R means reveals a consistent pattern whereby RR-MSc performed worse than the other groups. This pattern of results might reflect that both measures were revised from the original format (e.g. delayed recall performance was removed), which may have affected the psychometric properties. In addition, although both verbal and visual memory deficits have been found to be associated with cerebellar signs (van der Pavert et al., 2016), this finding has not always been replicated (Ceresa et al., 2013; Valentino et al., 2009). Another reason for the discrepancies might be related to the study being underpowered which

will be discussed in later sections. Nevertheless, despite evidence of variability, the findings to some extent demonstrate memory deficits for the RR-MSc group were replicated at baseline and follow-up.

Finally, there were consistent deficits in verbal fluency as measured by WLG. This replicates previous findings for verbal fluency tests in MS (e.g. Bodini et al., 2013; Hynčicová et al., 2017; Morrow, Menon, Rosehart, & Sharma, 2017) as well as significant differences found between RR-MSc and RR-MSnc (Ceresa et al., 2012; Valentino et al., 2009). It is possible that a lack of efficient integration between the frontal lobes and the cerebellum are responsible for executive dysfunction and therefore optimal performance is reliant on intact cerebellar function. This finding might be related to 'cognitive compensation failure' whereby the forced recruitment of alternative regions to aid task performance led to a decrease in efficiency as indicated by the reduction in words generated by the RR-MSc group.

3.6.3 Hypothesis (ii): The performance of patients with RR-MSc on cognitive and motor planning tasks will decline over a 1-year period compared to patients with RR-MSnc and HC, who in turn, will remain stable.

In contrast to the prediction that the RR-MSc group would decline on cognitive and motor planning tasks compared to other groups, the results indicated that the magnitude of differences remained stable. Previous research demonstrated sensitivity of the SDMT and PASAT to cognitive decline in individuals with RR-MS within a similar time frame (López-Góngora, Querol, & Escartín, 2015). One explanation for the discrepancy might be related to the small sample size of the RR-MSc group and again

whether there was sufficient power to detect changes. For instance, the aforementioned study had longitudinal data for 196 MS patients. Furthermore, the follow-up was relatively short compared to other studies investigating cognitive decline. To illustrate, two studies investigating disease-related cognitive decline used a follow-up period of 10 years (Amato et al., 2001; Schwid et al., 2007). It is likely that having longer periods of observation with increased sample size might have yielded a more robust sensitivity to change.

Upper limb function is of particular importance in MS (Burke, 2018; Lamers & Feys, 2014). Yet further research is needed to establish the validation of cut-off scores for normal versus abnormal function and meaningful change in test scores (Feys et al., 2017). Longitudinal data of over 2 years have suggested a change of 15%–20% of the NHPT baseline value appears robust in differentiating between progression or stability in MS patients (Kragt, van der Linden, Nielsen, Uitdehaag, & Polman, 2006; van Winsen, Kragt, Hoogervorst, Polman, & Uitdehaag, 2010). Thus, using a more stringent cut-off of a 15% change as a sign of progression, the data revealed relative stability for the NHPT as only 2/11 RR-MSc showed signs of progression compared to 1/17 of RR-MSnc and 0/9 HC.

Interestingly, application of similar principles to the MPI reveals the RR-MSc group were not as stable as initially thought. Again, using a 15% cut-off it appears that 7/11 RR-MSc compared to 2/17 RR-MS and 1/9 HC group showed a deterioration in MPI performance. This potentially provides support for the MPI as a useful tool in aiding

early identification of MS patients at risk of decline. However, without further psychometric and MRI validation, any interpretation remains highly inferential.

It is worth considering that although both RR-MSnc and HC outperformed the RR-MSc group, RR-MSnc and HC did not differ significantly aside from on the GPT and MPI. Previous research has suggested that significant differences might also have been expected (Langdon, 2011). Given the cognitive deficits of the RR-MSc group, perhaps the pooling of RR-MSc and RR-MSnc groups in the generation of normative data is one factor to explain this discrepancy, and thus stresses the importance of trying to reduce variation in a heterogenous condition. On the other hand, it might also suggest that the GPT and MPI are more sensitive to detecting subtle differences which are not captured with cognitive measures in short follow-up periods. Theoretically, the GPT and MPI involve more motor planning components and therefore are particularly susceptible to cerebellar damage. Thus, the highly significant differences between RR-MSnc and HC on motor planning ability might represent the presence of increased cerebellar involvement.

Related to the above point, there was evidence of progression in the EDSS score for the RR-MSc group that was not replicated in any cognitive measure. This might be explained by weight attributed to certain functions (e.g. limb function) or questionable psychometric properties of the EDSS (Hobart, Freeman, & Thompson, 2000), but it also highlights the complex relation between cognition, motor function and disability and the need to develop better tools to understand this interaction.

3.6.4 Hypothesis (iii): Differences in motor planning will be related to differences in information processing speed at 1-year follow-up.

The MPI served as a measure of motor planning, which in turn, was used as a putative surrogate of cerebellar integrity. Data collected at 1-year follow-up demonstrated a moderate strength in the relationship between reduced IPS (SDMT/PASAT-3) and slower performance on tests of motor function (NHPT) and motor planning (GPT/MPI). As predicted, the purer measure of IPS, the SDMT, was more strongly correlated with the MPI than the PASAT-3. As there were no significant differences in the strengths of the correlations between motor function and motor planning, it can be deduced there is no unique contribution of IPS to motor planning.

Nevertheless, the correlations indicate support for previous findings by Bonnet et al. (2010) and Ruet et al. (2014) suggesting 'cognitive compensatory' strategies. The results also replicate findings from baseline data (Hinchcliffe, 2017). One explanation might be that MS-induced damage to cortico-cerebellar loops triggers functional changes and possibly compensatory recruitment of cortical regions usually preserved for higher-order tasks. As a by-product, this may lead to a saturation effect on cognitive load and a reduction in cognitive efficiency which is reflected in IPS measures. Several task-related fMRI studies have demonstrated evidence of altered connectively in the cerebellum (Rocca et al., 2017; Rocca et al., 2012; Saini et al., 2004). This theory might explain the highly significant differences between all group levels for motor planning tasks: HC significantly outperformed RR-MSc, who significantly outperformed RR-MSnc. It appears compensatory strategies mediated

the loss of cognitive ability through task completion, yet the increasing burden led to an overreliance on cortical regions for higher order thinking and thus progressively worse MPI scores.

The inclusion of the ABILHAND questionnaire was to enable comparisons between a novel synthesis of objective and subjective motor function and motor planning. As there were only weak correlations, findings suggest that the measure might be not adequately capturing upper limb functional difficulties in MS. This is also supported by the non-significant difference in mean scores between RR-MSc and RR-MSnc, who undoubtedly have differences in motor function. This reflects a wider issue, whereby there is a lack of subjective outcome measures to capture upper limb dysfunction and more research is clearly required. Moreover, the finding exemplifies the difficulties with self-report questionnaires which are known to be affected by psychosocial factors (Nauta et al., 2018).

3.6.5 Limitations

Despite employing strict inclusion criteria, there was evidence of heterogeneity in the RR-MS groups. This makes it more challenging to assess the contribution of the cerebellum to cognition as patient variability may mask true effects. For example, results showed that RR-MSc group had significantly higher EDSS scores and a longer disease duration than the RR-MSnc group. This is potentially problematic as one study of MS patients with a minimum disease duration of ten years found there was no relationship between cerebellar function and cognitive impairment (Daams et al., 2017). As the present study did not include imaging methods to corroborate lesions in

the cerebellum, perhaps findings are more closely associated with global pathology rather than cerebellar pathology. Alternatively, findings could merely represent different stages in the progression of MS. On the other hand, the influence of disease variables is not always consistent in research (Langdon, 2011).

Concerns with the neuropsychological battery were also noted which may have precluded further conclusions. There was only a single measure of executive function, a domain associated with frontal regions and encompassing several higher-order cognitive abilities. Inclusion of another test such as the Delis-Kaplan Executive Function System (D-KEFS) colour-word interference (Delis, Kaplan, & Kramer, 2001) might have allowed for further exploration of the central hypothesis that the cerebellum disencumbers the cognitive load of frontal regions. Furthermore, IPS has been considered as the unitary underlying deficit in MS (Denney, Lynch, Parmenter, & Horne, 2004). Therefore, the battery may have benefited from the inclusion of tests without a timed component to negate any unwanted influence of IPS. For example, inclusion of the Figure Copy and Short Story subtest from the Adult Memory and Information Processing Battery (Coughlan & Hollows, 1985) for visual and verbal memory. Similarly, to extricate IPS from attentional processes, specific attention tasks might have been beneficial. Despite these limitations, the selected battery utilised internationally recognised tests of MS, including the BICAMS, and has been found to demonstrate sensitivity and specificity to cognitive impairment in MS. As such, the battery was considered suitable to effectively test the proposed hypotheses.

To infer motor planning ability using subtraction logic, there must be an assumption of shared homogeneity in task components. However, there are several variations between the NHPT and GPT which were not taken into consideration when used to compute the MPI. Although both peg board tests require coordination of perceptive, visuospatial and motor functions, the GPT has a larger field of operations than the NHPT (20 pegs to position as opposed to 9 pegs); requiring additional dexterity and precise motor control. Furthermore, there are differences in task complexity. Participants are provided with additional instructions for the GPT (i.e. placing pegs sequentially), whereas the NHPT relies on intuition to complete the task. These additional executive demands may also have influenced performance. Therefore, a key limitation of the MPI is the unequal sensorimotor components of the NHPT and GPT, thereby reducing confidence in any presumed assumptions.

It is also important to acknowledge the circularity of using motor function tasks in a group defined by difficulties with tremor and coordination. This questions whether results merely reflect pre-existing sensorimotor effects rather than differences in motor planning ability. To address the issue of circularity, it would be useful to corroborate findings through the employment of neuroimaging techniques to confirm the presence of lesions in the cerebellum.

There were also methodological concerns within the study that might have hampered the strength of conclusions drawn. Firstly, the high rate of attrition (20% for MS groups and 70% for HC) raises the possibility of bias and questions the validity of the results. Attempts to alleviate concerns about potential differences between those completed

and dropped-out were made by providing a baseline table with demographic information. Given the small sample, further statistical analysis was not warranted, and visual inspection of data deems it was unlikely results would have been significantly influenced. However, a possibility of bias remains.

Related to attrition was the issue of small sample size and thus the study being underpowered to detect effects. The observed effect sizes for the SDMT were as follows: main effect of group, d = 1.2; main effect of time d = 0.7; and, main effect of interaction d = 0.3. This implies that the study was sufficiently powered for detecting main effects of group and time, but underpowered for detecting any interactions and therefore at risk of type II error. Increasing sample sizes may have yielded improved confidence in results drawn, although this was hard to achieve in the context of a longitudinal design.

Multiple tests on the same experimental data increases the familywise error rate and likelihood of type I error. Post-hoc adjustments of the p-value are often implemented to reduce the chance of making type I error. However, if a test is too conservative then it is likely to result in a lack of statistical power and increase likelihood of type II error (Field, 2009). Within the study, multiple statistical analyses were carried out due to the number of tests included in the battery. Attempts to correct the p-value would result in a very stringent p-value and the risk of rejecting meaningful group differences. Therefore, following recommendations by Perneger (1998), a decision was made not to make corrections to the p-value. Accordingly, results should be

interpreted with caution due to lack of control over the familywise error rate and increased propensity of type I error.

3.6.6 Implications

Despite the wide prevalence, the pattern of cognitive impairment is not uniform; moreover, there is evidence of distinct patterns of cognitive impairment (i.e. cognitive phenotypes) (Leavitt, Tosto, & Riley, 2018). The study provides evidence that cerebellar symptomatology may be associated with a distinct cognitive phenotype characterised by more severe and widespread damage. The use of phenotypes in future research may help reduce patient variability and more personalised medicine. This aligns with research in other neurological conditions such as dementia, whereby more tailored interventions have used cognitive phenotypes considered at greater risk of progression (Belleville, Gauthier, Lepage, Kergoat, & Gilbert, 2014). Thus, the findings highlight the benefit of adopting phenotypes to address issues with patient heterogeneity. As a result, future research studies would also be better equipped to evaluate the discrete features of the disease.

Considering RR-MSc is indicative of poor prognosis (Amato et al., 2010), the group serve as a viable target for differential treatment approaches. For example, there is growing interest in the use of cognitive rehabilitation interventions as a result of evidence associating cognitive training (CT) and cognitive benefit in populations with mild cognitive impairment (Campbell, Langdon, Cercignani, & Rashid, 2016; Reijnders, van Heugten, & van Boxtel, 2013; Sumowski et al., 2018). Preliminary evidence for CT in MS have demonstrated benefits in several domains including IPS, memory and

executive functions (Amato et al., 2014; De Giglio et al., 2015; Messinis et al., 2017; Pérez-Martín, González-Platas, Eguía-Del Río, Croissier-Elías, & Jiménez Sosa, 2017). Therefore, the findings of the study could support the proposal of new clinical treatment pathways tailored for RR-MSc, with more emphasis on neuropsychological assessment and cognitive rehabilitation. This might provide benefits for those with RR-MSc through early identification and intervention as well as cost-efficiencies for services through appropriate allocation of resources.

There are several theoretical ramifications of the study. Chiefly, the study provides support that cerebellar integrity is vital for optimal cognitive and motor performance and damage is associated with reduced inefficiencies through the loss of automated subroutines and forced recruitment of cortical regions. This is the first study to demonstrate the link using motor planning, a higher-order cognitive ability, within a longitudinal design. The MPI appears to be a useful tool with seemingly good test-retest reliability, although it would benefit from further research to establish psychometric properties. In addition, combining data with neuroimaging techniques to corroborate cerebellum pathology and the use of functional MRI to provide evidence of compensatory cortical recruitment would also increase the theoretical confidence in the conclusions drawn.

3.6.7 Future research

A further study with increased sample sizes, longer periods of observation and continuing to use an active control group to control for non-specific effects is required. Rigorous participant selection using neuroimaging techniques for more accurate

diagnosis of those with cerebellar symptomatology should also be used. The inclusion of a more expansive executive function battery might also aid understanding of important theoretical underpinnings and further substantiate the cognitive profile of RR-MSc.

The MPI is a promising new measure for the field. The next step would be to conduct a MRI study to validate that the MPI is linked to cerebellar lesion load and atrophy. From a theoretical perspective, this would substantiate that motor planning is a key factor in the disability that cerebellar involvement imposes and ensure that results do not merely reflect the influence of disease severity.

Furthermore, to enable clearer interpretation of the MPI, it would be useful to address some of the methodological concerns by the manufacture of a new pegboard with equal sensorimotor components to the GPT but without the motor planning component. Cardboard versions with equitable psychometric properties to the plastic versions are entering research which would suggest this is a feasible and cost-effective option (Dubuisson et al., 2017). The development and refinement of an MPI measure also aligns with research priorities around upper limb dysfunction (NICE, 2014) and therefore potentially provides an informative tool for future clinical and research purposes. The clinical usefulness of the MPI would also benefit from the generation of age-matched norms and development of meaningful change scores.

3.7 Conclusion

The present longitudinal study aimed to explore the relation of cognition to cerebellar function using a novel motor planning measure. Results consistently demonstrated a differential cognitive profile for RR-MSc characterised by greater impairment in tests of cognition, motor function and motor planning. The poor performance of the RR-MSc group on the GPT and MPI implies the likelihood of a cerebellar effect on motor planning, which could not be explained by increased sensorimotor deficits. Theoretically, the reduced performance is thought to related to a reduction in cerebellar function through the loss of subroutines which are considered important for driving wider network efficiency. Evidence supporting this theory was shown by moderate to large negative correlations between the MPI, a putative surrogate of cerebellar integrity, and measures of IPS, the domain most susceptible to MS pathology.

Integration, Impact and Dissemination Summary

4.1 Integration

The aim of the thesis was to investigate the longitudinal relation of cognition to cerebellar function in Relapsing-Remitting Multiple Sclerosis (RR-MS), and how changes relate to motor planning and function. The intention was to use the systematic review as an opening to the topic of cognitive impairment in MS and the relationship to cerebellar function. This provided a comprehensive background so that the empirical study could address specific questions about how motor planning relates to cognition over a year. The integration process provided several challenges such as how to focus on a specific area of cognition, extending the work from an earlier DClinPsy project and encountering issues with attrition. Therefore, this section covers how issues were address and to what extent the aim was accomplished.

Given the vast literature on cognition in MS, it was important that a more precise aspect of topic was established. Discussions with my supervisor revealed it was becoming increasingly recognised that individuals with MS who show physical symptoms of cerebellar involvement such as tremor and poor coordination, have a differential cognitive profile. Therefore, it was agreed that the thesis should focus on the cognitive difficulties experienced by individuals with MS and cerebellar symptoms. This would enable a novel exploration of recent phenomena and align with research objectives recommended by a NHS report expressing a need to develop a better understanding of cognition in MS.

Consequently, the systematic review provided an opportunity to summarise the impact of the cerebellum to cognition and related-variables in MS. This was useful in

aiding my own understanding of the field but also to provide the reader with a comprehensive background of the aetiology and symptomatology of MS. This was a significant component to the integration as it meant the empirical study could subsequently use the review as a foundation for more detailed explanation of complicated topics. Furthermore, the review provided clarity as to what areas required more research and, more specifically, what was the general problem that needed to be addressed by the empirical study. As such, the identification of a specific topic and the refinement of a problem through an objective review of the literature, certainly aided the integration of the thesis.

Researching the systematic review also coincided with a placement at a neuropsychological department. The placement predominately involved conducting comprehensive neuropsychological assessments for a range of conditions including MS. Working in a department related to the thesis topic was beneficial for several reasons. For the systematic review, increasing my knowledge of brain function and understanding of psychometrics meant I was better equipped to comprehend terminology in papers and to critique research methodology and findings. In addition, with the experience of conducting multiple assessments I became more confident with the administration and interpretation of the various neuropsychological tools. This was helpful during data collection for the empirical study whereby my experience meant I was more efficient in the delivery of the test battery. Moreover, the placement offered an opportunity to learn more about the differential neurorehabilitation treatments for MS, which had direct links with recommendations

outlined by the thesis. The concurrent clinical experience complemented the research and had a positive influence on the integration of thesis components.

The thesis was a longitudinal study based on previous baseline work completed by another trainee. There were several challenges linked to the integration of the two studies. For example, the original study was initially conceived using a cross-sectional design. As such, adding a longitudinal component meant further considerations required attention if the follow-up study was to be a success. To overcome issues required periodic communication between the researchers and the clinical team to ensure everyone was aware of the shared vision for the research. Practical steps were also taken such as obtaining permission from relevant ethical boards for myself to aid with recruitment to counter potential issues of attrition. This additional input to the formative stages of present thesis was essential in safeguarding the success of the empirical study when later difficulties occurred.

In contrast, building on a previous study also provided benefits which strengthened the integration. For example, a concern raised with the initial findings was that visual acuity may have accounted for performance in certain neuropsychological tests. Liaising with the research team meant that the study protocol could be amended to include a test of vision to account for the potential influence. From a theoretical perspective, adding a longitudinal component to a pre-existing study also meant that additional aspects of research could be explored such as the dynamic of time. This was relevant as the systematic review identified the lack of follow-up data as a criticism of the field.

An initial draft of the empirical paper was presented to service users affected by MS and they were invited to share comments on the acceptability of the study methodology. Although no subsequent changes were made, opening conversations was useful in reflecting how to use real-life examples to explain the nature of the investigation and 'humanising' the research (Youngson & Blennerhassett, 2016). Furthermore, this experience had repercussions in terms of how to maximise the impact of research findings and an example of how various factors have influenced the thesis.

One of the difficulties encountered was the amount of attrition. Although attempts were made to minimise the impact of attrition (e.g. additional participant recruitment), it was hard to predict how many participants would be lost to follow-up. In total, retention was approximately 80% for the MS groups, whereas it was much lower for controls at around 20%. The first indication that attrition might be a concern was when 16 controls dropped out over the course of two days. The loss had several implications. Since the sample size estimates were the minimal to allow sufficient power to detect large effect size differences, one implication was that falling short of required sample size might preclude certain statistical analysis. Certain measures were taken to try to address these issues. For instance, a decision was taken to pool data from all groups to estimate the correlation between measures of interest rather than analyse separate groups. However, a wider implication for the study was whether there was sufficient power to test hypotheses. If the study was underpowered to detect effects, then conclusions must be taken with caution.

Overall, I am pleased with the integration of the multiple components of the thesis. I wanted the thesis to have a clear narrative, beginning with the wider issues faced by those living with MS before focusing on a pertinent issue and conducting clinically-relevant research to address the problem. The context of the thesis was influenced by personal experiences, supervision, clinical experience on placement and valued input from other members of the research team.

4.2 Impact

The wide heterogeneity observed in the MS population is one factor that has hampered efforts to develop effective treatments. Therefore, a clearer understanding of the heterogeneity is needed to advance understanding and enable tailored therapeutic strategies. The thesis findings suggest that patients with RR-MS can be categorised further as having cerebellar signs (RR-MSc) or no cerebellar signs (RR-MSnc). In RR-MSc, the cognitive profile is characterised by greater impairment and associated with a worse prognosis compared to RR-MSnc. Although the development of specific MRI and neuropsychological criteria would further validate the RR-MS subtypes, these preliminary findings are significant as they represent a feasible means to reduce patient heterogeneity.

There are several benefits associated with the use of distinct subtypes. From a research perspective, targeted enrolment of RR-MSc has the potential aid study designs. For example, it might provide greater clarity in MRI studies investigating structural and functional changes in cortico-cerebellar loops by the reduction of variation. This would help understand consequences of MS damage and hence inform theoretical models such as the role of subroutines. Furthermore, it might provide a reasonable answer to discrepancies found in pre-existing research investigating cognition in MS whereby RR-MS subtypes are pooled together (e.g. Damasceno, Damasceno, Cendes, Tinelli, & Benner, 2014; Romascano et al., 2015).

For clinicians, the findings provide prognostic information about cognition and motor planning for patients with RR-MSc. This could be useful in providing members of the

clinical team a greater insight into the likelihood of expected difficulties (e.g. mental health, employment) and facilitate more personalised information sharing and education for the person and the family. Enabling honest and open conversations is also a precursor for effective preparation for the future. For example, proactive referrals to vocational support services to ensure reasonable adjustments are in place to aid job retention. This appears to be particularly important given the significantly lower rates of employment found in the study for the RR-MSc group.

As the RR-MSc group were considered at risk of greater cognitive impairment then identification might lead to an earlier intervention of cognitive rehabilitation. One area that continues to grow in popularity is computerised cognitive training (CCT). CCT refers to interventions that aim to improve cognitive domains through repeated practice on theoretically motivated skills and strategies. It has been proposed that participation in mentally stimulating activities offers protection from neuropathology via a cognitive reserve. The theory states that persons with a higher reserve can withstand more severe neuropathology before suffering cognitive impairment (Stern, 2006). Consequently, CCT provides an opportunity to continue engaging in mentally stimulating activities, which in turn may offer further protection. CCT can be used without significant cognitive or functional difficulties and is therefore well suited for individuals with RR-MSc. The therapeutic potential of CCT of RR-MSc is unknown, yet CCT represents an example of new opportunities for targeted interventions which may be beneficial for a group with traditionally poor rehabilitation outcomes.

Upper limb functional impairment remains a key priority for future research. The #ThinkHand campaign was launched in 2016 to raise awareness of hand and arm function within the MS community. The movement has found many people with MS rate upper limb function as more important than lower limb function for independence and quality of life. Objectives of the campaign include advocating for the use of the Nine-hole Peg Test (NHPT) as a primary outcome measure and the development of a new outcome measures for assessing hand function. The thesis has several implications for the campaign and may offer a beneficial impact through alignment with certain objectives. For example, the study used the NHPT as a primary outcome measure, considered the properties of a new self-report upper limb measure (i.e. ABILHAND) and proposed the use of a novel outcome measure based on motor planning function. It is hoped that the findings will help the campaign to gain further momentum and influence regulatory authorities to shift focus onto upper limb function.

The Motor Planning Index (MPI) represents a potential new outcome measure for clinicians in the field of MS. To maximise the benefit of the tool, correlations with MRI data and psychometrics would need to be researched and published. If realised, the tool could be publicised as a quick and easy to administer test to obtain rapid information about the integrity of the cerebellum. This would be beneficial for clinicians in providing a measure of sensorimotor function, upper limb dysfunction and motor planning ability. This information would provide an estimate of potential life restrictions and disability and furthermore aid consultations with patients and family. Furthermore, it could be incorporated as a key outcome measure for the use of

pharmacological interventions given the breath of information it provides or as part of safety planning (e.g. assessment of driving proficiency).

One of the research objectives was the synthesis of objective and subjective motor function. This was part of a wider effort to enhance understanding of upper extremity function in MS. The findings indicated that ABILHAND, a newly developed self-report measure, had only weak correlations with the established tests of upper limb function, the NHPT and GPT. The publication of this finding would be useful for several stakeholders including original developers and the broader community interested in outcome measures for upper limb function. Providing feedback for developers might lead to amendments or lead to recommendations that the outcome measure is not suitable for the MS population. Alternatively, the result forms part of evidence-based practice for upper limb function assessment in MS, which benefits other researchers in the field in the selection of appropriate outcome measures.

Numerous organisations such as MS Trust have recommended the study of cognition in MS as a priority as often it is a 'hidden' problem that contributes to the clinical situation. Moreover, NICE (2014) guidelines explicitly recommend research focusing on cognition. The present study offers insight into cognitive difficulties experienced by individuals with MS and therefore aligns with policy goals. Moreover, by 'revealing' cognitive difficulties associated with MS, there is the hope that it has a beneficial impact for all those affected by the disease. This might take form at an individual level by increasing awareness of cognitive symptoms or at an organisation level such as an employer making reasonable adjustments in the workplace to accommodate cognitive

changes. By the virtue of conducting research within the area, the research has the potential to have a beneficial impact in many spheres, therefore it is important to consider how to achieve this impact (see Dissemination).

Finally, meeting people with MS over the thesis has also had a personal impact. It was a privilege to conduct research with such a welcoming group and I thoroughly enjoyed all the offers of tea, coffee and cake. I was struck at how many people were willing to make the time to participate in research and to hear the reasons for doing so. My impression is that there was a sense of cohesion in the shared experience of MS and people felt strongly about 'doing their bit' for future generations. The experience has taught me about the real-world challenges of living with MS but also how it is possible to live a rich and meaningful life. I saw the value of having a supportive network around a person in terms of family, friends and accessible services. As a result, I am in a stronger position going forward in terms of my insight into the challenges facing those living with a chronic condition and knowledge of resources which should aid in my future career aspirations in neuropsychology.

4.3 Dissemination

For the research to reach a diverse audience, the dissemination strategy focuses on a communication campaign across several channels, including social media and more traditional routes such as relevant journals to communicate the research. The main aim is to make the research widely available to encourage engagement and promote participation in research of cognition in MS.

The initial dissemination strategy includes a plain English summary of the research to the participants who indicated they would like to receive a summary of findings on the consent form. This process involves consultation with the other research collaborators to produce an agreed version before sharing with participants. Many participants expressed an interest in the outcome of the research, given their involvement in the study over the last 12 months, so this is an important part of the strategy.

Following a conversation with a study participant, it was agreed that a short oral presentation at a local MS peer-led group attached to a neurology clinic may be another opportunity to share the findings of this research. This would enable us to reach an audience beyond those involved in the study and an interactive session to ask specific questions and open conversations about the implications of the results. This could encourage wider participation in research and lead to further opportunities to communicate the research further afield.

A separate version of the research summary will be produced for the clinical teams at both participant identification sites. The process will be similar to the above, all

collaborators will be invited to share thoughts on an initial draft before an agreed version is shared. This summary is tailored to clinicians rather than participants, so there may be some subtle differences.

A key part of the dissemination strategy is the submission of an abstract for the ECTRIMS 2018 conference in Berlin. The European Committee for treatment and research in Multiple Sclerosis (ECTRIMS) is the world's largest scientific meeting dedicated to the understanding and treatment of MS. It offers an opportunity to disseminate research through an annual international conference. If the abstract is accepted, it would provide an excellent means of maximising the findings of the research to a targeted global audience. In addition, the research would be stored on an online library so that others can access the research abstract after the conference and published in the Multiple Sclerosis Journal Online. Furthermore, there is an opportunity for an oral poster presentation if deemed 'outstanding' by the committee.

Beyond the immediate participants and recruitment sites, dissemination to a wider audience involves communication with larger relevant organisations and popular online MS or medical blogs, as well as more traditional publication routes. Some key priorities include:

- **The MS Trust** offers numerous channels to market and publicise recent research, such as Open Door, a free quarterly newsletter for people with MS and applying to present a poster at the next MS Trust Conference in September 2018.

- **The Barts and The London Neuroimmunology Group's BartsMS Blog** - http://multiple-sclerosis-research.blogspot.com, has also been identified as a useful blog to contact as they have behind several successful social media campaigns (e.g. #ThinkHand) and remain a consistent source of information for MS research. This blog has a special interest in the use of upper limb function in MS and given the relevance of our outcome measures, it is anticipated that the blog would be interested in learning more about the study. An element of flexibility in the method of disseminate the findings would be needed for larger organisations (e.g. short, snappy headline with links to a fuller description).
- **Multiple Sclerosis and Related Disorders (MSARD) journal** has been identified as suitable for approaching for publication of the systematic review and this would enable a reach to a more traditional audience in academia. The journal has a special interest in MS neuropsychology and measurement scales with options for open access.
- **Multiple Sclerosis Journal (MSJ)** has been considered suitable for publication of the empirical study. A shorter version of the thesis would be prepared with other collaborators and a manuscript sent for review. If unsuccessful, alternative journals will be considered.

Social media is a valuable marketing communication tool to help promote the research to a much wider audience to encourage engagement and interest. Throughout the duration of this thesis, I have used my social media account on a periodic basis to raise the profile of the research, identifying key findings and points of discussion and using

hashtags contributing to other relevant conversations to gain further visibility and followers. Post-thesis submission, part of the dissemination strategy includes producing a YouTube video with a short 2-minute video with a summary of the research and then posting this on Twitter/ YouTube and various blogs to generate further engagement. In addition, the strategy includes weekly tweets on Twitter for 6 - 8 weeks post-thesis around key themes in the research and timed around major events to provoke further conversations related to the research, share future developments (e.g. ECTRIMS abstract acceptance) and provide links to some of the materials mentioned above.

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Appendices

Appendix 1: HRA Letter of Ethical Approval (dated 05/10/17)

NHS
Health Research Authority

Mr Jack Cahill
Department of Clinical Psychology
Royal Holloway
Egham, Surrey
TW20 0EX

Email: hra.approval@nhs.net

05 October 2017

Dear Mr Cahill

Letter of HRA Approval

Study title:	**The relation of cognition to cerebellar function in Multiple Sclerosis.**
IRAS project ID:	**224861**
REC reference:	**17/YH/0321**
Sponsor	**Royal Holloway, University of London**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details

and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

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

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received 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/.

IRAS project ID	224861

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **224861**. Please quote this on all correspondence.

Yours sincerely

Simon Connolly
Senior Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Annette Lock, Royal Holloway University of London*
Ms Freda Gomes, Research & Development Department, Ashford & St. Peter's Hospitals NHS Foundation Trust

Appendix 2: Ashford & St. Peter's R&D Letter of Access (Dated 13/10/17)

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

Research & Development Department

R&D Ref: 2017JKC01SP

Jack Cahill
(Trainee Clinical Psychologist)
Department of Clinical Psychology
Royal Holloway
Egham, Surrey
TW20 0EX

St Peter's Hospital
Guildford Road
Chertsey
Surrey
KT16 0PZ
Tel: 0193-272-3534
Fax: 0193-272-3395

Date: 13th October 2017

Dear Jack

Letter of Confirmation of Capacity and Capability at ASPH

Study title:	**The relation of cognition to cerebellar function in Multiple Sclerosis.**
IRAS project ID:	**224861**
REC reference:	**17/YH/0321**
Sponsor	**Royal Holloway, University of London**

Thank you very much for submitting your study for an R&D review. I am writing to confirm that **Ashford & St Peter's Hospitals (ASPH) NHS Foundation Trust** has the capacity and capability to deliver the above referenced study.

Please consider the enclosed Statement of Activities as an agreement between the sponsor and the ASPH site. Model agreement- not required.

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.

We agree to start this study on **13th October 2017** or as soon as the sponsor activates this site.

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

Yours sincerely,

Gomes

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

Cc: Dr Isaac John, Deputy Director of R&D, ASPH

Appendix 3: MS Patient Information Sheet

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

Study Title: Cognition in Multiple Sclerosis: a longitudinal study

Ethics Committee Reference Number: 17/YH/0321
IRAS Number: 224861

We would like to re-invite you to take part again in our follow-up 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: Jack Cahill
Department of Clinical Psychology, Royal Holloway University of London, Egham, Surrey, TW20 0EX
Tel: 01784 414012
Email: Cerecog@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).

Information Sheet: 12.09.17 V1.1MS

Complaints procedure

If you have any concerns or questions about any aspects of the study, please contact the principal investigator (Jack Cahill) 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….

- understand how the cognitive profile (strengths and weaknesses in thinking skills) of individuals with MS changes over a year compared 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.
- Follow-up individuals who participated in the earlier study by inviting them again to repeat the same tests to compare how the cognitive profile (strengths and weaknesses in thinking skills) may have changed over time. 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 have previously participated in the previous research study carried out by Jonathan Hinchcliffe.

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, Jack Cahill 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 be asked to complete the same questionnaires and tests that you previously completed so that we may compare the results. 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 Jack Cahill 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 (Jack Cahill), 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. A consultant neurologist (Dr. Khaled Abdel-Aziz) is a collaborator 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 4: MS Consent Form

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

Consent Form

Study Title: Cognition in multiple sclerosis: a longitudinal study
Name of principal investigator: Jack Cahill
IRAS Number: 224861
Participant reference number:
Ethics Committee Reference Number: 17/YH/0321

	Please initial to confirm
1. I confirm that I have read and understand the information sheet for the above study dated Information Sheet: 12.09.17 V1.1MS	
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. I give permission for these individuals to have access to my records.	
5. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
6. 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.	
7. 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 2018. I give permission for my address to be held by the above named researcher until the end of the research to facilitate this.	
8. I agree to take part in the above research study.	

_____ Date: _____
Name of participant

_____ Date: _____
Name of person taking consent

Consent form: 12.09.17 V1.1MS

Appendix 5: MS Letter of Invitation

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

Jack Cahill (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: a longitudinal study*'. This a follow-up project to an earlier study of cognition in multiple sclerosis carried out by Jonathan Hinchliffe, this project aims to invite original participants to now repeat the study. We want to look at how the thinking abilities of individuals with multiple sclerosis change over the course of a year, 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: The purpose of the study is to understand how the cognitive profile (strengths and weaknesses in thinking skills) of individuals with MS changes over a year compared 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? Jack Cahill (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 Jack Cahill, either at your own home or at St. Peter's Hospital. You will then be asked to repeat the questionnaires and tests that you previously completed in the previous project. 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 Jack Cahill 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 Jack. 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,

Jack Cahill
Trainee Clinical Psychologist / Principal Investigator
Tel: 01784 414012
Email: Cerecog@rhul.ac.uk

Appendix 7: Invitation Letter for HC

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

Jack Cahill (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: a longitudinal study'*. This a follow-up project to an earlier study of cognition in multiple sclerosis carried out by Jonathan Hinchliffe, this project aims to invite original participants to now repeat the study. We want to look at how the thinking abilities of individuals with multiple sclerosis change over the course of a year, 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: The purpose of the study is to understand how the cognitive profile (strengths and weaknesses in thinking skills) of individuals with MS changes over a year compared 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? Jack Cahill (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.

What is involved? Involvement in the study will take less than two hours. You will be invited to meet with Jack Cahill, either at Royal Holloway University of London or other appropriate venues. You will then be asked to repeat the questionnaires and tests that you previously completed in the previous project. Again, 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 Jack Cahill 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 Jack. 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,

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

Appendix 7: HC Information Sheet

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

Study Title: Cognition in Multiple Sclerosis: a longitudinal study

Ethics Committee Reference Number:
IRAS Number: 224861

We would like to re-invite you to take part again 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: Jack Cahill
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 (Jack Cahill) 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

Information Sheet: 12.09.17 V1.1HC

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 understand how the cognitive profile (strengths and weaknesses in thinking skills) of individuals with MS changes over a year compared 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 have previously participated in the previous research study carried out by Jonathan Hinchcliffe. However, 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 since previously participating. 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, Jack Cahill 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 be asked to complete the same questionnaires and tests that you previously completed so that we may compare the results. The tests will measure various areas of cognition including verbal fluency, processing speed, attention, working memory, verbal learning, memory, premorbid IQ, dexterity and extremity function. Again, 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 see 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 Jack Cahill 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 (Jack Cahill), 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. A consultant neurologist (Dr. Khaled Abdel-Aziz) is a collaborator 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 8: HC Consent Form

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

Consent Form

Study Title: Cognition in multiple sclerosis: a longitudinal study
Name of principal investigator: Jack Cahill
IRAS Number: 224861
Participant reference number:
Ethics Committee Reference Number:

	Please initial to confirm
1. I confirm that I have read and understand the information sheet for the above study dated Information Sheet: 12.09.17 V1.1HC.	
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 understand that relevant sections of my data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
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 2018. 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: 12.09.17 V1.1HC

Appendix 9: EDSS Telephone Version – Reproduced with Permission from Prof. Kappos

[Removed from online version]

Appendix 10: NARCOMS Tremor and Coordination Scale

[Removed from online version]

Appendix 11: Fatigue Severity Scale

[Removed from online version]

Appendix 12: Hospital Anxiety and Depression Scale

[Removed from online version]

Appendix 13: ABILHAND

[Removed from online version]

Appendix 14: Test of Premorbid Functioning (TOPF)

[Removed from online version]

Appendix 15: Symbol Digit Modalities Test (SDMT)

[Removed from online version]

Appendix 16: Word List Generation (WLG)

[Removed from online version]

Appendix 17: Paced Auditory Serial Addition Test (PASAT)

[Removed from online version]

Appendix 18: California Verbal Learning Test – Version II (CVLT-II)

[Removed from online version]

Appendix 19: Brief Visual Memory Test – Revised (BVMT-R)

[Removed from online version]

Appendix 20: Snellen Pocket Visual Acuity Test

[Removed from online version]

Appendix 21: Nine-hole Peg Test (NHPT) Instructions

[Removed from online version]

Appendix 22: Grooved Peg Test (GPT) Instructions

[Removed from online version]

Appendix 23: Skewness and Kurtosis Calculations Baseline Data

	RR-MSc		RR-MSnc		HC	
	Skew	Kurtosis	Skew	Kurtosis	Skew	Kurtosis
BVMT-R	-0.28	-1.21	-1.86	-0.31	0.92	-0.83
CVLT-II	-0.65	-0.70	0.22	-0.76	0.16	-0.98
FSS	-1.28	-0.49	-1.20	-0.76	0.12	-0.22
GPT	2.54	1.42	2.33	0.95	0.40	0.90
HADS A	0.74	-0.29	0.75	-0.83	2.56	1.62
HADS D	-0.05	-1.03	0.80	-0.82	0.32	1.18
MPI	2.52	1.43	**2.90***	1.54	0.46	-0.66
NHPT	0.86	-0.96	0.22	-0.88	-0.88	-0.73
PASAT-3	0.62	-0.94	-1.47	-0.25	0.11	-0.98
SDMT	-0.63	-0.81	-0.93	1.19	2.03	1.20
TOPF	1.24	1.40	-0.24	0.38	0.22	-0.83
WLG	-0.56	-0.93	-0.22	-0.77	-1.26	1.28

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

Appendix 24: Skewness and Kurtosis Calculations Follow-up Data

	RR-MSc		**RR-MSnc**		**HC**	
	Skew	Kurtosis	Skew	Kurtosis	Skew	Kurtosis
ABILHAND	-0.41	-1.13	**-2.75***	1.18	-2.26	0.72
BVMT-R	-0.70	-1.07	-2.47	1.09	-0.24	-0.75
CVLT-II	-0.45	0.41	-1.10	-0.85	0.04	0.32
FSS	-0.76	-0.93	0.09	-0.82	-0.29	-1.06
GPT	2.08	1.11	0.66	-0.69	0.49	-0.58
HADS A	1.08	-0.65	0.73	-0.45	0.76	0.96
HADS D	0.00	-0.94	-0.60	-0.65	1.17	0.70
MPI	1.96	0.89	0.74	-0.22	0.06	-1.07
NHPT	**3.13***	2.05	2.53	1.37	-0.02	-1.16
PASAT-3	-0.67	-0.88	-1.99	0.76	0.43	-0.88
SDMT	-0.90	-0.44	-0.88	0.79	0.96	-0.95
TOPF	0.09	-0.62	0.31	-1.04	0.27	-0.63
WLG	0.26	-0.92	0.23	-0.62	0.18	-0.91

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

Appendix 25: Skewness and Kurtosis Transformations

Variable		RR-MSc		RR-MSnc		HC	
Transformation		Skew	Kurtosis	Skew	Kurtosis	Skew	Kurtosis
ABILHAND	Square Root	0.06	-1.16	1.49	-0.21	2.26	0.72
MPI Baseline	Log 10	1.49	0.48	1.83	0.80	0.30	-0.65
MPI FU	Log 10	0.50	0.50	-0.28	0.21	-0.02	-1.06
NHPT Baseline	Log 10	0.58	-0.99	-0.05	-0.96	-1.01	-0.64
NHPT FU	Log 10	2.13	1.51	1.74	0.95	-0.04	-1.14

Scores < ±2.58 meet criteria for normal distribution ($p < .01$).