

**Assessment of Executive Function in Multiple Sclerosis using a Virtual,
Office-Based Task and its Relationship to Employment Performance.**

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Table of Contents

1	Executive Summary.....	8
1.1	Systematic Review	8
1.2	Empirical Study	11
1.3	Integration, Dissemination and Impact	13
2	Paper I: The Relationship Between Cognition and Employment in Multiple Sclerosis - A Systematic Review of the Literature.....	17
2.1	Abstract.....	17
2.2	Multiple Sclerosis.....	21
2.3	Subtypes of Multiple Sclerosis	23
2.4	Symptoms and Treatment	24
2.5	Employment in Multiple Sclerosis	25
2.6	Reasons for unemployment in Multiple Sclerosis.....	26
3	Methods.....	28
3.1	Search Strategy and Selection Criteria	28
3.2	Inclusion and Exclusion Criteria.....	29
3.3	Data Extraction	30
3.4	Quality Assessment.....	30
4	Results	31
4.1	Overview	31
4.2	Data extraction.	33
4.2.1	Summaries of Studies Found.....	33
4.3	Quality Assessment.....	60
4.4	Demographics	62
4.5	Measures Used.....	63
4.5.1	Neuropsychological Batteries.....	63
4.5.2	Definitions of Employment.	63
4.6	Cognition	65
4.6.1	Information Processing Speed.	66
4.6.2	Memory.	67
4.6.3	Executive Function.....	69

5	Discussion	70
5.1	Summary of Main Findings	70
5.2	Methodological Critique of Studies.....	72
5.3	Limitations and suggestions for future research.....	73
6	Conclusion	75
7	Paper II: Assessment of Executive Function in Multiple Sclerosis using a Virtual, Office-Based Task and its Relationship to Employment Performance	76
7.1	Abstract	76
7.2	Multiple Sclerosis	78
7.3	Cognitive Impairments in Multiple Sclerosis.....	80
7.4	Employment and Cognition in Multiple Sclerosis.....	82
7.5	Adaptations and Accommodations used in the Workplace	83
7.6	Testing Executive Function within MS.....	84
7.7	The Jansari Assessment of Executive Function.....	86
7.8	Aims and Hypotheses	87
8	Methods.....	89
8.1	Recruitment	89
8.2	Inclusion and Exclusion Criteria	90
8.3	Sample Size	91
8.4	Materials	92
8.4.1	The JEF©.....	92
8.4.2	Traditional Neuropsychological Battery.....	95
8.4.3	Cognitive Status Test.....	97
8.4.4	Psychological Measures	98
8.4.5	Employment Measures	100
8.5	Procedure	102
9	Results.....	103
9.1	Group Demographics	104
9.2	Disease-Related Variables	105
9.3	Neuropsychological Battery Test Scores	106
9.3.1	The JEF©.....	106

9.3.2	Executive Function and BICAMS	108
9.3.3	Employment and COPE Questionnaires	109
9.4	Relationships between Executive Function, Employment and Coping.....	110
10	Discussion	113
10.1	Summary of Relevant Findings.....	113
10.1.1	Hypothesis 1	114
10.1.2	Hypothesis 2	115
10.1.3	Hypothesis 3	116
10.2	Relationship to Existing Literature	117
10.3	Limitations	119
10.3.1	Neuropsychological Measures	119
10.3.2	The JEF©.....	120
10.3.3	Sample and Recruitment.....	121
10.4	Clinical and Research Implications	124
11	Conclusion	127
12	Paper 3: Integration, Dissemination and Impact	128
12.1	Integration.....	128
12.1.1	Challenges and Improvements.....	130
12.1.2	Personal Reflections	136
12.2	Dissemination.....	140
12.3	Impact.....	142
13	References	145
14	Appendices	165
14.1	Appendix I: Questionnaires.....	165
14.1.1	Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ)	165
14.1.2	Multiple Sclerosis Questionnaire for the Evaluation of Job Difficulties (MSQ-Job).....	168
14.1.3	COPE Inventory	171
14.1.4	Hospital Anxiety and Depression Scale (HADS)	173
14.1.5	Fatigue Severity Scale (FSS)	175
14.2	Appendix II	176

14.2.1	Graph of JEF© Results	176
14.3	Appendix III: Information Sheets and Consent Forms.....	177
14.3.1	Information Sheet for People with Multiple Sclerosis	177
14.3.2	Consent Form for People with Multiple Sclerosis.....	181
14.3.3	Information Sheet for Healthy Control Participants	182
14.3.4	Consent Form for Healthy Control Participants.....	186
14.4	Ethical Approval Documentation.....	187

Table of Tables

<i>Table 1 Acronyms of Tests and Batteries used in Systematic Review</i>	<i>19</i>
<i>Table 2 Search Terms used for Systematic Review</i>	<i>28</i>
<i>Table 3: Summary of Results</i>	<i>47</i>
<i>Table 4: Table of Results of Quality Assessment</i>	<i>61</i>
<i>Table 5: Demographic Information (means and standard deviations where appropriate)</i>	<i>104</i>
<i>Table 6: Means and Standard Deviations of MS Related Disease and Psychological Variables.....</i>	<i>105</i>
<i>Table 7: Means and Standard Deviations of JEF© Scores.....</i>	<i>106</i>
<i>Table 8: Means and Standard Deviations of Executive Function and BICAMS Tests.....</i>	<i>108</i>
<i>Table 9: Means and Standard Deviations of Employment and COPE Questionnaires</i>	<i>109</i>
<i>Table 10: Correlations between JEF© and Executive Function Index and Coping Scales</i>	<i>111</i>

Table of Figures

<i>Figure 1: PRISMA Flow Diagram.....</i>	<i>32</i>
<i>Figure 2: Screenshot of the JEF Meeting Room (taken from Denmark et al., 2017)</i>	<i>94</i>
<i>Figure 3: Screenshot of the JEF office (taken from Denmark et al., 2017)</i>	<i>94</i>
<i>Figure 4JEF Performance as a Function of Group (error bars represent one standard error).....</i>	<i>176</i>

1 Executive Summary

Multiple Sclerosis (MS) is a chronic, demyelinating disease which affects neurons in the central nervous system. Symptoms of MS include difficulties with mobility, gait, bowel and bladder dysfunction, fatigue and cognition. People with MS (PwMS) are often diagnosed in their 30s and 40s and up to 80% become unemployed within 10 years of being diagnosed. This results in a negative impact on quality of life. Levels of physical disability do not fully account for the impact of the disease on employment outcomes. In fact, approximately 45% of people with low levels of physical disability are unemployed. It is likely that the impact of “invisible” symptoms of MS, such as cognition, can explain this discrepancy. Evidence suggests that cognition is also a mediating factor between physical disabilities and unemployment. Since unemployment can have a detrimental impact to quality of life, it is important to ensure that people with MS remain employed for as long as they desire.

1.1 Systematic Review

A systematic review was conducted to investigate the link between objective reports of cognitive function and unemployment in MS. This question was developed using the PICOS tool. The search was carried out in September 2017 using three search engines: PubMed, PSYCH Info and Web of Science. Identical search terms were used for the three search engines. Inclusion criteria were peer review, availability in English, adult participants

with a specified age range of 18 to 65 with no neurological conditions prior to being diagnosed with MS. Studies needed to include objective neuropsychological reports as well as information related to employment status, adjustments or accommodations at work or any other negative work events. The search returned a total of 910 after duplicates were removed. 819 were screened by title and abstract, 91 were read in full and 13 studies were considered eligible for the qualitative synthesis.

Four studies included control groups whilst nine included only PwMS. Two studies were prospective studies. The 13 studies include a total of 1278 people with MS, the majority of whom were women (76.10%). 72.10% of participants had Relapsing Remitting MS, which is the most prevalent subtype of the disease. There was a total of 263 people in the control groups, the majority of whom were also women (71.10%). Nine studies were conducted in the North American continent, three in Europe and one in South America. Quality assessment was carried out using the Effective Public Health Practice Tool (EPHPP). Two studies were overall rated as “strong”, eight as “moderate” and two as “weak”. No studies were removed as result of their quality rating.

The eligible studies consistently found that PwMS who were unemployed or who had more negative work-related events, such as a reduction in work hours, performed worse on neuropsychological tests than both employed PwMS and healthy control groups. In addition, PwMS who were employed or had no changes in their work situation, performed worse than healthy controls on neuropsychological tests.

Significant between group differences were seen in a number of cognitive domains. These were: processing speed, delayed and immediate memory recall and memory and executive function. The most consistent difficulties were seen on tasks of processing speed, one of the cognitive domains frequently affected by MS given its demyelinating nature. Poor processing speeds were significantly associated with poorer work outcomes for PwMS. This result was seen on a number of neuropsychological tests.

Difficulties with delayed recall and short-term memory, both verbal and visual, were also associated with difficulties at work or unemployment.

The relationship between executive function difficulties and adverse work events was less consistent than those seen with processing speed, short-term memory and delayed recall, but was still present. “Executive function” is an umbrella term to describe the cognitive abilities needed to successfully carry out goal orientated behaviours which require attention and concentration. The three core executive functions are inhibition, working memory and cognitive flexibility. Other skills include planning, organisation, emotion regulation and problem solving.

One of the limitations noted by the review was the lack of consistency in what was considered employment and unemployment across the studies. As well as the difficulties of using a quality review tool largely intended for Randomised Control Trials (RCTs) rather than the methodologies required for observational, cross sectional studies.

1.2 Empirical Study

Difficulties with executive function in MS have been linked to employment and the use of maladaptive coping strategies. Maladaptive coping strategies have in turn been linked to increased rates of negative work events within the MS population.

Accurate assessment of executive function is therefore important for helping individuals to develop appropriate management strategies at home and at work. Whilst there are many well-validated tests of executive function, some of these tests lack ecological validity, do not reflect the impact of impairment in everyday life and take place in the artificial environment of the clinic room. Thus, there is a trade-off between experimental control and ecological validity in the assessment of neuropsychological difficulties. Assessment in the real world is advantageous but not always feasible due to environmental, mobility or risk issues. Immersive and non-immersive virtual reality provides a compromise between high levels of ecological validity and experimental control. There is also a generally favourable opinion of the use of virtual reality in medical settings from the public.

The Jansari Assessment of Executive Function (JEF©) is a non-immersive virtual reality test which takes place in an office environment. It has been shown to be sensitive to deficits in executive function in people with acquired brain injury, and to the effects of drugs with only anecdotal reports of executive impairment which have gone undetected by other neuropsychological tests. The JEF© has never been used in the MS

population. It was hoped that the JEF© would be able to provide results which are more reflective of every day difficulties and could be used to improve clinical management. This study aimed to compare the sensitivity of the JEF© to other executive function tests in MS, as well as determine if the results of the JEF© are more closely correlated to coping styles and employment outcomes than existing neuropsychological tests. It was hypothesised that the JEF© would be sensitive to executive function deficits in this population and would be more closely correlated to employment outcomes and coping styles than existing neuropsychological tests.

A total of 18 PwMS and 24 Healthy Controls (HC) took part in this study. The MS group was recruited through advertising on MS charity websites and social media and from MS Therapy Centres. The HC group was recruited through advertising to local community groups and by word of mouth. All participants completed the following neuropsychological battery and questionnaires: The JEF©, traditional executive function tests (Zoo Maps, Key Search and Semantic Fluency), the Brief International Cognitive Assessment for Multiple Sclerosis Assessment (BICAMS), the Test of Premorbid Function (TOPF), psychological questionnaires (Hospital Anxiety and Depression Scale, The COPE inventory and The Fatigue Severity Scale) and employment questionnaires (Multiple Sclerosis Work Difficulties Questionnaire and Multiple Sclerosis Questionnaire for Job Difficulties).

The groups were matched in terms of demographics with the exception of depression and fatigue. PwMS had significantly poorer scores on the JEF© Total Score, JEF© Creative-thinking and JEF© Action-Based Prospective

Memory subscales. There were no other significant between group differences on neuropsychological tests, with the exception of Zoo Maps. There was a significant difference between groups on the employment questionnaires, with the MS group reporting more work difficulties. The only coping scale which showed a significant between group difference was Maladaptive Coping, with the HC group using more of these strategies than the MS group. There was a significant negative correlation between the JEF© Total Score and the composite score Employment Index and a significant positive relationship between the JEF© Total Score and Adaptive Coping subscale, as well as between the composite Executive Function Index and Adaptive Coping subscale. There was no significant difference in the strengths of these correlations. The hypotheses that the JEF© would be sensitive to deficits in MS and more closely correlated to employment outcomes were supported by these results. These results provide further evidence that executive dysfunction is related to negative employment outcomes for PwMS and highlights the importance of using ecologically valid methods of neuropsychological assessment. They also provide further evidence for the use of the JEF© as a tool for the assessment of executive function.

1.3 Integration, Dissemination and Impact

This thesis has a strong focus on how cognition relates to work difficulties in MS. The systematic review demonstrated that there were consistent links between domains of cognitive impairment and employment difficulties for PwMS. Although the relationship between executive function

and employment was less consistent than those seen between other domains such as processing speed, it still provided a rationale for the need to do further research investigating this relationship. It was noted that only one study in the systematic review involved ecologically valid measures of executive function. The results of the empirical study were consistent with the themes of the systematic review. Namely, that PwMS had poorer scores on executive function tests than healthy controls as measured by the JEF© and that cognitive difficulties, particularly difficulties with executive function, are linked to adverse work events.

There were several challenges encountered whilst undertaking this work which sometimes resulted in limitations. These included changes to the neuropsychological test battery in order to prevent fatigue for PwMS, a lack of visual acuity and motor function tests, difficulties with obtaining HRA and REC ethical approval due to the JEF©'s status as a medical device and lack of CE marking, which in turn led to changes to the recruitment strategy. During testing, it was noted that the JEF© software itself posed some challenges for participants due to the interface through which the individual moves around in and interacts with the environment. Suggestions for how to overcome these obstacles include having two testing sessions to accommodate a longer test battery and the addition of validated tests of visual acuity and motor function. Suggestions of how the JEF© software could be improved were made, for example adjusting the programming so objects did not disappear as a result of human error.

Carrying out this study also stimulated much personal reflection about the importance of work, the importance of using neuropsychological assessment as part of a holistic assessment of work difficulties for PwMS, of how I have developed as a researcher and clinician through the DClinPsy course and the differences in administering neuropsychological tests within clinical and research settings.

A presentation of the empirical study has been presented to Trainee Clinical Psychologists at Royal Holloway. There are plans for the systematic review to be published in the Journal of Multiple Sclerosis and Related Disorders (MSRAD) and for the empirical report to be published in Neuropsychological Rehabilitation. Both these journals are peer reviewed and have published articles on similar topics in the past. A summary of the results from the empirical article will also be shared with the MS Charities and Therapy Centres which provided aid with recruitment, for dissemination online or in a newsletter. A longer, discursive article will be co-written with a service user, and it is hoped that this article will lead to more awareness and understanding of the impact of executive function impairment on employment outcomes.

Dissemination of this work to both service users and professionals may result in more awareness of the challenges PwMS face with regards to employment, leading to further research in this area as well as the consideration of the potential role and impact of cognitive impairment when service users report negative work events to their care team. Appropriate dissemination may also equip service users and their supporters with stronger

arguments for changes to government policy that will support PwMS to stay in employment, should they so choose. Finally, it is anticipated that the outcome of the empirical study will provide further evidence to the utility of the JEF© as an ecologically valid tool for the assessment of executive function, and the general necessity of ecologically valid neuropsychological assessments.

2 Paper I: The Relationship Between Cognition and Employment in Multiple Sclerosis - A Systematic Review of the Literature.

2.1 Abstract

Multiple Sclerosis (MS) is a chronic, demyelinating disease which affects neurons in the central nervous system. Symptoms of MS include difficulties with mobility, gait, bowel and bladder dysfunction, fatigue and cognition. Approximately 45% of people with low levels of physical disability are unemployed. It is likely that the impact of “invisible” symptoms of MS, such as cognition, can explain this discrepancy. Evidence suggests that cognition is a mediating factor between physical disabilities and unemployment.

A systematic review was conducted to investigate the link between objective reports of cognitive function and unemployment in MS. The search was carried out in September 2017 using identical search terms across three search engines: PubMed, PSYCH Info and Web of Science. Inclusion criteria were peer review, availability in English, adult participants with a specified age range of 18 to 65 with no neurological conditions prior to being diagnosed with MS, inclusion of objective neuropsychological reports and information related to employment.

The search returned a total of 910 articles after duplicates were removed and 13 studies were considered eligible for inclusion. The eligible studies consistently found that people with MS who were unemployed or who had

more negative work-related events, performed worse on neuropsychological tests than both employed people with MS and healthy control groups. People with MS who were employed or had no changes in their work situation still performed worse than healthy controls on neuropsychological tests.

Significant between group differences were seen in the following cognitive domains: processing speed, short-term memory, delayed recall and executive function.

Limitations included the lack of a consistent definition of what was considered employment and unemployment across the studies. There were also difficulties using a quality review tool largely intended for RCTs rather than the methodologies required for observational, cross sectional studies.

Table 1 Acronyms of Tests and Batteries used in Systematic Review

<u>Acronym</u>	<u>Name</u>	<u>Test(s) battery is comprised of</u>
10/36	Spatial Recall Test	
SPART		
9HPT	Nine Hole Peg Test	
AI	Ambulation Index	
BADS	Behavioural Assessment of the Dysexecutive Syndrome	DEX, Zoo Maps
BDI	Beck Depression Inventory	
BDI-FS	Beck Depression Inventory – Fast Screen	
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis	SMDT (oral), CVLT-II, BVMT-R
BNT	Boston Naming Test	
BRB-N	Brief Repeatable Battery of Neuropsychological Tests	SRT, 10/36 SPART, PASAT, WLG, SDMT
BVMT-R	Brief Visuospatial Memory Test Revised	
CES-D	Centre for Epidemiological Studies Depression Scale- German	
CMDI	Chicago Multiscale Depression Inventory	
COWAT / COWA	Controlled Oral Word Association Task	
CVLT-II	California Verbal Learning Test II	
DEX	Dysexecutive Questionnaire (self- report)	

DKEFS	Delis-Kaplan Executive Function System	
DSQ	Disease Steps Questionnaire	
EDSS	Expanded Disability Scale	
EuroQOL	European Quality of Life	
FAMS	Functional Assessment of Multiple Sclerosis	
FIS	Fatigue Impact Scale	
FSS	Fatigue Severity Scale	
HADS	Hospital Anxiety and Depression Scale	
HrQoL	Health Related Quality of Life	
JOLO	Judgement of Line Orientation Task	
KKG	Fragebogen zur Erhebung von Kontrollüberzeugungen zu Krankheit und Gesundheit (German Questionnaire of Health Locus of Control)	
LOT	Line of Orientation Test	
MACFIMS	Minimal Assessment of Cognitive Function in Multiple Sclerosis	SDMT (oral), PASAT, BVTM-R, Open Trial SRT, COWAT, JOLO
MFIS	Modified Fatigue Impact Scale	
MSFC	Multiple Sclerosis Functional Composite	9HPT, T25FW, PASAT
MSNQ	Multiple Sclerosis Neuropsychological Questionnaire	
NART	National Adult Reading Test	
NEO-FFI	NEO Five Factor Inventory	
PAM	Patient Activation Measure	
PASAT	Paced Auditory Serial Addition Test	

PDDS	Patient Derived Disease Steps
PHQ-9	Patient Health Questionnaire
RCFT	Rey Complex Figure Test (copy)
(copy)	
SET	Modified Six Elements Test
SILS	Shipley Institute of Living Scale
SRT	Selective Reminding Test
STAI	State Trait Anxiety Inventory
SDMT (oral)	Symbol Digit Modalities Test – oral version
STM	Brown Peterson Short Term Memory Test
T25FW	Timed 25 Foot Walk
TMT	Trail Making Test
TPQ	Tridimensional Personality Questionnaire
USE-MS	Unidimensional Self-Efficacy Scale for Multiple Sclerosis
WAIS-R	Wechsler Adult Intelligence Scale Revised
WASI	Wechsler Abbreviated Scale of Intelligence
WCST	Wisconsin Card Sorting Test
WLG	Word List Generation Test

2.2 Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic neurodegenerative disease of the Central Nervous System (CNS) which is characterised by inflammation, demyelination of neurons and formation of plaques at multiple sites

(Kutzelnigg & Lassmann, 2014; Milo & Miller, 2014; Nylander & Hafler, 2012; Polman et al., 2011). This demyelination and plaque formation disrupts the flow of action potentials along the neuron (Kolb & Whishaw, 2008). It is estimated that 2.3 million people worldwide are affected by MS and it is one of the leading causes of disability in young people of working age. It is also associated with a reduced life span in comparison to the general population (Bishop & Rumrill, 2015; Lunde, Assmus, Kjell-Morten, Bø, & Grytten, 2017; Wicks, Ward, Stroud, Tennant, & Ford, 2016).

The causes of MS are currently unknown, however research suggests that an interplay between genetics, epigenetics and the environment resulting in an autoimmune response within the CNS is responsible (Milo & Kahana, 2010; Nylander & Hafler, 2012; Thompson, Baranzini, Geurts, Hemmer, & Ciccarelli, 2018).

Lifestyle and environmental factors which may contribute to the development of the disease include smoking, obesity and vitamin D levels, with smoking being a chief contributor (Thompson et al., 2018). There is also evidence that there is a relationship between contracting and not contracting certain diseases and MS. For example, the hygiene hypothesis proposes that becoming infected with several infectious diseases in early childhood can decrease the likelihood of developing autoimmune diseases such as MS. On the other hand, becoming infected with diseases in early adulthood, such as the Epstein-Barr Virus, increases the risk of the individual going on to develop MS (Bishop & Rumrill, 2015; Thompson et al., 2018).

Heritability of the disease within families, which increases with the degree of relatedness, suggests a role for genetics. There is also a pattern in the geographic spread of the disease, with people living in northern areas of the world more likely to develop the disease. The disease is also more common in women than in men and in people of Caucasian ancestry rather than people of African, Asian or Hispanic descent (Bishop & Rumrill, 2015).

2.3 Subtypes of Multiple Sclerosis

Although MS has a heterogenous presentation, it can be separated into three main subtypes: Relapsing Remitting MS, Primary Progressive MS, Secondary Progressive MS.

MS often presents with the Clinically Isolated Syndrome, a demyelinating event which presages MS, frequently associated with damage to the optic nerve, brainstem or spinal cord. However, the symptoms caused by this damage often resolve and it is not until the second clinical relapse or MRI event that MS is formally diagnosed (Thompson et al., 2018).

Relapsing Remitting MS (RRMS) is the most common form of MS and affects about 85-90% of the MS population. It is characterised by at least two relapses which are associated with periods of recovery where the individual may reach, or just fall short of, their previous level of functioning. This type of MS is seen more frequently in women than in men (Iwanowski & Losy, 2015; Thompson et al., 2018). Approximately 40% of people with RRMS will go on to develop SPMS within 10 years of being diagnosed. SPMS is a progressive

form of the of the disease that may or may not involve relapses.

Approximately 10% of people with MS (PwMS) will develop PPMS, which is a progressive form of the disease from its onset (Thompson et al., 2018)

.

2.4 Symptoms and Treatment

The symptoms and course of MS differ from person to person, however they involve difficulties with mobility and coordination of movement, bowel and bladder problems, visual disturbances, fatigue, neuropathic pain and cognitive dysfunction (Milo & Miller, 2014).

MS is a degenerative disease and there is currently no cure. Consequently, the aim of treatment is to speed recovery from relapses and to slow the progression of the disease so that patients can continue to engage in meaningful activities and maintain quality of life (Bishop & Rumrill, 2015). Treatment of MS may differ depending on whether the disease course is progressive or relapsing, suggesting the two subtypes have different pathogenic origins, and whether the disease activity is present or absent.

Steroids and disease modifying, anti-inflammatory drugs with immunosuppressant characteristics that target specific cells or proteins are used to treat relapsing MS (Comi, Radaelli, & Soelberg Sorensen, 2017; National Institute for Health and Care Excellence, 2014). Disease modifying drugs are aimed at the most common type of MS - RRMS - and there remains a lack of treatments for the other subtypes (Thompson et al., 2018). In addition to pharmacological interventions, PwMS may benefit from

physiotherapy, occupational therapy and psychological input to help manage symptoms and associated comorbidities (Thompson et al., 2018).

2.5 Employment in Multiple Sclerosis

Approximately half of all PwMS are unemployed which has a major negative impact on their quality of life (Kobelt, Thompson, Berg, Gannedahl, & Eriksson, 2017). Although two thirds of PwMS are working at the time of their diagnosis, up to 80% of people become unemployed within 10 years of their diagnosis (Bishop & Rumrill, 2015).

Employment in MS is related to a higher quality of life. In addition to financial benefits, employment also provides an opportunity for social interaction, support, and is often related to a sense of identity. PwMS who are employed report greater engagement in life activities, community participation, adequate social support and better life satisfaction. They also report better perceived health and that daily activities, such as walking, are less difficult. Comorbidities linked to unemployment in this population include depression, loneliness, and anxiety (Balto, Pilutti, & Motl, 2018; Dorstyn, Roberts, Murphy, & Haub, 2017).

Therefore, it is important to understand the factors related to unemployment in order to help PwMS to remain at work and maintain their quality of life and wellbeing (Bishop & Rumrill, 2015; Wicks et al., 2016).

2.6 Reasons for unemployment in Multiple Sclerosis

Unemployment in this population is related to demographic and disease related variables. For example, PwMS who are older and have few years of education are more likely to be unemployed, and the link between unemployment and physical disability in MS has been widely reported (Kavaliunas et al., 2015). In addition, unemployment is also related to increased difficulties with mobility, a progressive disease course and length of time since diagnosis.

Despite the many physical difficulties associated with the disease, 82% of PwMS are employed at a score of 0 on the Expanded Disability Status Scale (EDSS) (indicating no disability). This drops to 55% with an EDSS score of 3 or below (indicating only mild physical impairment), but barely 25% of PwMS are employed at EDSS 6.5 (moderate physical impairment) (Kobelt et al., 2017; Milo & Miller, 2014; Wicks et al., 2016). It seems unlikely that physical disability alone can explain these figures, however the “invisible” symptoms of MS, such as fatigue, mood and cognition, are possible explanations for this outcome (Cadden & Arnett, 2015).

Research has shown that cognitive impairment is a mediating factor in the relationship between disability and unemployment for PwMS (Campbell, Rashid, Cercignani, & Langdon, 2016; Deluca, Yates, Beale, & Morrow, 2015). PwMS who have cognitive impairment are more likely to be unemployed (Grech et al., 2017a). Cognitive impairment can be seen in all subtypes and stages of the disease and affects 40%-70% of PwMS (Deluca et

al., 2015). Furthermore, cognition has been shown to have an impact on income which is independent of physical disability (Kavaliunas et al., 2017). Cognitive test scores have been shown to separately and significantly benchmark groups of healthy employed people, PwMS working competently, PwMS working with difficulty and PwMS who are unemployed (Benedict et al., 2016).

Given the relationship between employment and cognition, it would be beneficial for clinicians to have a good understanding of which cognitive abilities are related to negative work place outcomes. This could be used to further inform management of the disease and improve work place adaptations to help people stay in work should they so choose.

The aim of this systematic review is to provide a comprehensive synthesis of the existing literature investigating the relationship between cognition and employment outcomes for working age PwMS. To the best of our knowledge this is the first systematic review looking at the relationship between, and impact of, cognitive impairment on employment outcomes.

3 Methods

The PRISMA recommendations for reporting systematic reviews were used for this systematic review (Liberati et al., 2009). A protocol for this review has not been published or registered in a database. The question for this review was developed using the PICOS tool (Methley, Campbell, Chew-Graham, McNally, & Cheraghi-Sohi, 2014).

3.1 Search Strategy and Selection Criteria

Electronic databases (PSYCH Info, Web of Science and PubMed) were searched in September 2017. Uniform search terms were used which can be found in Table 2. Duplicate studies were removed before screening by abstract and title. Following this, studies were read in full to determine if they met the inclusion criteria for this systematic review.

Table 2 Search Terms used for Systematic Review

Search terms
Multiple Sclerosis OR relapsing-remitting Multiple Sclerosis OR primary-progressive Multiple Sclerosis OR secondary-progressive Multiple Sclerosis OR primary-progressive MS OR secondary-progressive MS OR demyelinating disease
AND Cognition OR cognit* OR memory OR attention OR concentration OR inattention OR cognitive defici* OR cognitive impair* OR prospective memory
AND Employment OR work OR job OR occupation OR career OR workplace OR work-place OR unemployment

3.2 Inclusion and Exclusion Criteria

Studies were included in this review if they were peer reviewed, available in English, quantitative and included adults with any clinical subtype of Multiple Sclerosis aged between 18 and 65. This age range was used as it reflects the ages of the majority of people within the work force. Studies were only included if they specified the age range of their participants. This was to avoid including studies which had a mean age within employment age, but individual participants whose age fell outside of the range. Participants included in the study needed to have no other neurological conditions prior to being diagnosed with MS as this may have affected their performance on neuropsychological tests. Studies needed to include objective information about cognitive abilities obtained using standardised, neuropsychological assessments. There is evidence that subjective reports of cognition in MS can be confounded by mood as well as fatigue, and that PwMS can over- or under-estimate their cognitive abilities. (Van der Hiele, Spliethoff-Kamminga, Ruimschotel, & Middelkoop, 2012). Studies needed to provide information related to the employment status of the participant. This could include: employment status, adjustments made at work or any adverse work events which had occurred due to MS.

Participants could be recruited from both community and hospital settings and there was no restriction on publication date.

3.3 Data Extraction

Studies were initially screened by reading the title and then the abstract. Following this, studies were read in full to determine if they met the inclusion and exclusion criteria. Data from the eligible papers were extracted and put in to a table. Extracted information included: study design, study setting, participant information such as type of MS, how the researchers had defined employment and what terms they used, the battery of neuropsychological tests administered, any other questionnaires administered and outcomes.

3.4 Quality Assessment

Quality Assessment was carried out using the Effective Public Health Practice Project tool for quantitative studies (EPHPP) (Thomas, Ciliska, Dobbins, & Micucci, 2004). This was carried out by the author and verified by her supervisor (DL).

4 Results

4.1 Overview

A total of 1237 studies were found through the literature search. 327 of these were duplicates and were removed prior to screening, leaving a total of 910. After the initial screening by title and abstract, 819 studies were removed. 91 studies were read in full and 13 were deemed suitable for this review. Four studies included control groups, whilst the remaining nine recruited PwMS only. Two studies were prospective studies. See figure 1 for Prisma diagram.

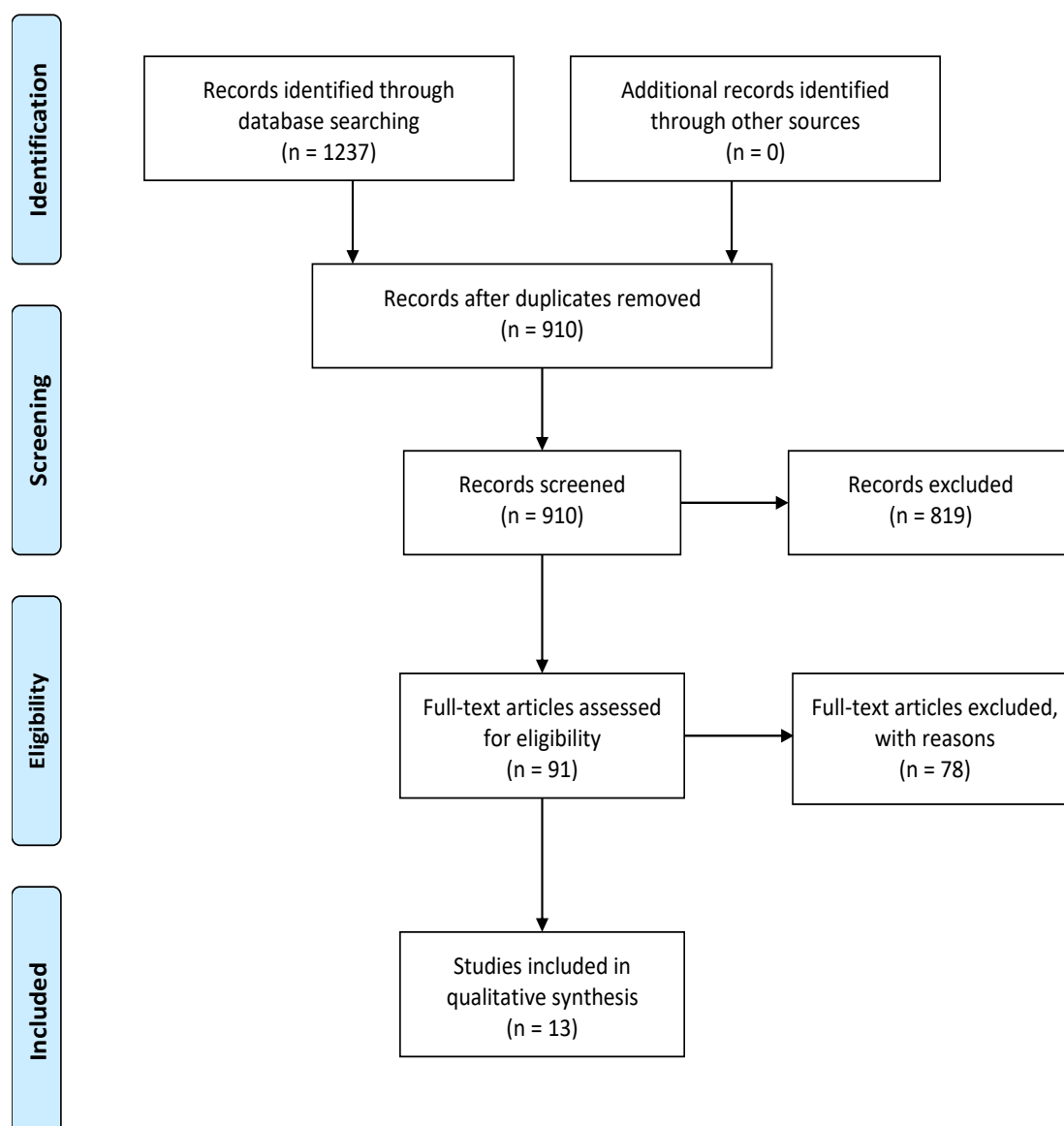


Figure 1: PRISMA Flow Diagram

4.2 Data extraction.

The search yielded 13 studies which were suitable for inclusion in this review. Relevant data from the 13 studies identified was extracted and is summarised in Table 3. Please see Table 1 for a list of abbreviations for the neuropsychological and psychological measures.

4.2.1 Summaries of Studies Found.

4.2.1.1 BICAMS in the Argentine population: relationship with clinical and sociodemographic variables.

The study by Vanotti and colleagues was carried out in Argentina. Its aim was to investigate the relationship between clinical variables of MS, such as fatigue, disease and physical disability, and the BICAMS (Vanotti et al., 2017). The study also analysed the relationship between the BICAMS and people's perception of cognitive dysfunction and other employment variables.

50 participants were recruited from MS clinics and excluded if they did not have a clinical definite presentation of MS, were not fluent in Spanish and had any psychological or motor difficulties that would affect interaction with the test materials (other than MS). In addition to the BICAMS, participants and an informant completed the MSNQ-Patient and MSNQ-Informant questionnaires about perceived cognitive function. The EDSS and the MSFC were also completed to provide information about neurological disability. Self-report questionnaires were used to provide information on mood and fatigue.

Participants also provided information about their employment status and work hours. Employment was dichotomised into “employed” and “unemployed specifically due to disability”.

Analysis showed that the variables with the strongest association to BICAMS scores were the EDSS and MSFC, which measure neurological disability and function respectively, and employment status. There were also significant associations between BICAMS performance and mood, work hours and fatigue. In terms of individual subtests, employment status was a significant predictor of CVLT-I performance and had moderate associations with SDMT performance.

4.2.1.2 Benchmarks of meaningful impairment on the MSFC and BICAMS.

Research conducted by Benedict’s group in America aimed to identify meaningful benchmarks of impairment on the components of the MSFC and the BICAMS, recognising that clinical interpretation associated with the scale scores did not always reflect the individual functional ability (Benedict et al., 2016). Degrees of workplace failure were used as measures of functional impairment. A retrospective analysis of data was carried out for 275 PwMS and 114 Healthy Controls, who were recruited through advertising.

Participants were required to complete the BICAMS, the PASAT (which forms part of the MSFC), the T25FW and the NHPT. Information was gathered regarding a range of negative work events following mistakes at

work in the preceding 30 months, including verbal criticism from superiors and formal disciplinary action. Any patient reporting two or more negative work events was considered to be at risk of losing their job. PwMS were assigned to three groups based on their work experience. Work-stable: full time employment, no disability benefits and no negative work events. Work-challenged: full time employment with two or more negative work events. Work-disabled: unemployed and receiving disability benefits.

All the motor and cognitive tests were able to discriminate between the vocational benchmarks created, with the SDMT and the T25FW being the most discriminating.

4.2.1.3 Cognitive impairment among patients with multiple sclerosis: associations with employment and quality of life.

A study carried out in the UK by Campbell and colleagues also investigated the utility of the BICAMS in outpatient clinics and considered how cognitive impairment in MS is related to physical disability, employment and quality of life (Campbell et al., 2016).

49 PwMS were recruited from an NHS outpatient clinic, all of whom completed the BICAMS, two questionnaires related to quality of life – EuroQOL and a generic quality of life questionnaire, a questionnaire measuring fatigue, a generic measure for chronic illness management, the unidimensional self-efficacy scale for Multiple Sclerosis (a measure of patient

empowerment in MS), the HADS, the MSNQ (patient-report) and the FSS. Cognitive impairment was defined as performance below the fifth percentile after accounting for age, sex and level of education.

Results found that PwMS who were unemployed were significantly more likely to show cognitive impairment on at least one test. The SDMT was the most significant predictor of unemployment, with poorer performance being linked to unemployment. Higher levels of quality of life were associated with higher scores on the SDMT and the MSNQ. The study concluded that the BICAMS is an easy to administer battery suitable for use in British outpatient settings.

4.2.1.4 Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS): Canadian contribution to the international validation project.

The Canadian validation study of the BICAMS was also considered eligible for this study (Walker et al., 2016). The aims of this study were to establish whether the BICAMS could be used as a tool in a Canadian clinic, to contribute to the international validation of the BICAMS and to investigate whether the BICAMS is related to employment status and subjective measurements of cognition.

The study involved 57 PWMS as well as 51 healthy controls (HC) matched for age, sex and education. Participants completed the BICAMS, the MSNQ (informant and self-report versions), the PHQ-9 (to assess depression)

and the MFIS (to assess fatigue). Participants were asked to return for a follow up one to three weeks later to assess the reliability of the battery. Participants completed alternate versions of the BICAMS subtests to prevent practice effects.

The study found that the BICAMS was able to identify impairment in 57.9% of their sample, with impairment being defined as “one or more abnormal tests”. This is similar to the statistics reported in the literature. The SDMT had the most robust findings out of the BICAMS subtests with regards to test-retest reliability. Only the SDMT and BVMT-R were able to discriminate between healthy controls and PwMS after taking depression and fatigue into account. Logistic regression was used to determine if the BICAMS was a predictor of employment status and found that the only predictor was the BVMT-R which is in contrast to other studies which have found that SDMT is a stronger predictor of vocational status. The study concluded that the BICAMS would be a suitable measure to use in clinics and showed good ecological validity through its relationship to employment status and ability to identify impairment.

4.2.1.5 Disclosure of disease status among employed multiple sclerosis patients: association with negative work events and accommodations.

An American study by Frndak’s group investigated the relationship between measures of clinical outcome, (in particular psychiatric and cognitive

symptoms), and disclosure of MS to employers (Frndak et al., 2015). It also aimed to investigate whether disclosure was related to negative work experiences as seen in other populations.

This study used both a longitudinal and cross-sectional design: 143 PwMS in the cross-sectional sample and 103 PwMS in the longitudinal sample, with 47 participants being in both groups. The cross-sectional group were subject to a clinical exam which included a battery of neuropsychological tests. They also completed the DSQ and provided information about general demographic details, their experience of using accommodations at work and any negative work events. The neuropsychological tests were: the BVMT-R, CVLT-II, SDMT, and the PASAT. Participants also completed the T25FW, NHPT and the BDI-FS. EDSS scores were calculated by a neurologist for 103 participants. The longitudinal group completed this clinical assessment four times. Six people in the longitudinal group disclosed the MS status during the study and were used as case examples of disclosure.

There was no difference in disease course or neuropsychological tests scores between the group who had disclosed their status to their employers and group who had not. However, there was a difference between groups on their T25FW scores, EDSS scores and the DSQ, with the disclosure group having significantly poorer outcomes on these measures. People who chose to disclose also experienced more negative work events, had more accommodations at work and worked longer hours.

4.2.1.6 Factors that moderate activity limitation and participation restriction in people with multiple sclerosis.

Goverover and colleagues' study (Goverover, Strober, Chiaravalloti, & DeLuca, 2015) looked into the relationship between cognitive ability, activity and participation for PwMS in America. Employment and breakfast preparation were used as proxies for activity and participation respectively.

72 employed and unemployed PwMS took part and were asked to complete the MACIFIMS, depression, anxiety and fatigue measures as well as rate their cooking abilities. Participants were separated into four functional groups: people who were employed and cooked, people who were unemployed and cooked people who were employed but did not cook and people who were unemployed and also did not cook.

Unemployment was correlated to increased levels of fatigue and poorer performance on the SDMT and BVMT-R from the MACIFIMS. On the other hand, cooking ability was positively correlated with processing speed, verbal and working memory.

4.2.1.7 Identifying employed multiple sclerosis patients at-risk for job loss: when do negative work events pose a threat?

Kordovski's group aimed to compare the frequency of work difficulties and accommodations between PwMS and healthy controls who were otherwise matched on demographic variables (Kordovski et al., 2015). Since

they predicted that there would be differences in disease variables and employment status between the groups, a second aim was to develop normative expectations for these variables to guide clinical management.

The study was set in New York, America with 138 PwMS and 61 HCs taking part. All participants reported being employed and working at least 30 hours a week. Participants completed an online survey which took information regarding disease characteristics, demographics details, MSNQ (informant), employment information, including negative work events and job accommodations, and the PDDS. Objective cognitive tests included the SDMT, PASAT, CVLT-II and BVMT-R. The T25FW and NHPT were completed to assess motor function. The BDI-FS was administered to assess depression.

HCs out performed PwMS on the following measures: T25FW, BVMT-R, CVLT-II total learning and SDMT. 33% of PwMS would have been considered cognitively impaired. PwMS were more likely to report job difficulties and need accommodations at work. Work-challenged PwMS (reporting at least one negative event) performed poorer than their work-stable counterparts on the T25FW, NHPT, PASAT and BVMT-R. Whilst work-challenged PwMS needed significantly more cognitive accommodations than work-stable PwMS, there was no difference in the number of cognitive accommodations used by controls and PwMS in general.

4.2.1.8 Work participation and executive abilities in patients with relapsing-remitting multiple sclerosis.

Van der Hiele and colleagues (Van der Hiele et al., 2015) specifically investigated the relationship between executive function and employment for people with RRMS in the Netherlands. Appropriate data was taken from a previous study on cognition and MS in the Netherlands. Data from 55 PwMS were considered suitable for inclusion for this research. Two groups were created based on employment status: employed and unemployed. Both groups completed the DEX, a subjective assessment of executive dysfunction from the BADS, as well as the NART, TMT, SCWT, WCST, RCFT (copy) and the BADS.

Participants also provided self-reported information on anxiety, depression and fatigue using the HADS and FSS. 60% of unemployed PwMS reported difficulties with planning and organisation, however this was not seen on the overall DEX score. There was a significant difference between self-reported sustained attention, with the unemployed group reporting more difficulties than the employed group. The only executive function test that was significantly different between the groups was on WCST category completion. Overall, there were below average scores in a cognitive domain in 2-55% of participants. The highest percentage of below average scores was seen on the RCFT copy and the PASAT.

4.2.1.9 Employment status in multiple sclerosis: impact of disease-specific and non-disease-specific factors.

Krause and colleagues (Krause, Kern, Horntrich, & Ziemssen, 2013) conducted a study in Germany to investigate the disease and non-disease related factors which impacted employment status for PwMS in comparison to healthy controls. This included looking at the role of health locus of control for people with MS.

87 PwMS were recruited from a health centre and 37 age and sex matched healthy controls were recruited through local advertising. The MS group was further subdivided into PwMS who had taken early retirement and PwMS who had remained in employment. PwMS were asked to complete the MSFC and a neurologist rated their disability on the EDSS. All participants completed the BRB-N, which tests long term memory, attention and information processing speed and executive function. Participants also completed measures of depression, fatigue, health related quality of life and health locus of control. A measure of fatigue was completed by the MS group only.

The early retirement MS group were significantly older and had fewer years of education in comparison to the employed MS group. Rates of the progressive subtypes of MS (SPMS and PRMS) were also higher in the early retirement group. The early retirement group also had higher levels of disability on the EDSS and poor scores on the MSFC. Further analysis showed that the employed MS group performed better than the early

retirement group on the PASAT and SDMT. However, no cognitive test was found to be an independent predictor of early retirement in MS.

4.2.1.10 Multitasking in multiple sclerosis: can it inform vocational functioning?

The study by Morse and colleagues investigated the relationship between multitasking ability and whether a person managed to retain their work hours or had to reduce them (Morse, Schultheis, McKeever, & Leist, 2013).

30 PwMS were recruited from an outpatient clinic in America and were separated into two groups according to vocational status: cutback-employment (including unemployed people) and same-employment. Multitasking ability was assessed using the SET and participants completed the following neuropsychological battery: COWAT, PASAT, SDMT, TMT, Zoo Maps and WASI. Mood and fatigue were assessed using the BDI-II and the FSS respectively. Information on changes to working hours was self-reported.

The cutback-employment group had significantly slower CompletionSET scores compared with the same-employment group and it was concluded that decreased multitasking ability had a negative effect on employment outcome. Fatigue was also found to have a significant effect on employment outcome and accounted for over half the variance in employment outcome. It was also noted that using a total profile score of SET resulted in the loss of qualitative information about the individual's performance. This information is particularly

useful in a clinical population which has a heterogeneous presentation of cognitive difficulties, such as MS.

4.2.1.11 *Unemployment in multiple sclerosis: the contribution of personality and disease.*

Strober's group researched the impact of personality type on employment status for PwMS in comparison to the following disease related variables: neurological and cognitive impairment, fatigue, mood and demographics (Strober et al., 2012).

Data were taken from the baseline of a clinical trial on cognition in America. Employment status was used to form two groups: "unemployed", which consisted of disabled PwMS, and "employed", which consisted of paid workers, students, homemakers and volunteers. Participants were required to complete measures of mood, fatigue and personality. EDSS scores were calculated and a neuropsychological battery comprised of the COWAT, JOLO, PASAT, SDMT, SRT, 10/36 SPART and the sorting task from the DKEFS was administered.

The employed group performed significantly better on the SDMT and SRT compared with the unemployed group. Regression analysis found that EDSS score, SDMT performance and the personality trait "persistence" accounted for 24% of the variance in employment status. SDMT performance was found to be a critical predictor of employment status, having a large effect size of $d = 0.8$.

4.2.1.12 *Predicting employment status in multiple sclerosis patients: the utility of the MS Functional Composite.*

Honarmand's group investigated how much demographic, personality and psychological variables impacted employment outcomes in MS in addition to cognitive and physical abilities (Honarmand, Akbar, Kou, & Feinstein, 2011).

62 PwMS were recruited from a Canadian clinic and were asked to complete a battery of tests. Neurological status was assessed using the MSFC and EDSS scores. The BRB-N was used to assess cognitive ability, mood was assessed using the HADS and personality was assessed using the NEO-FFI.

The study found that unemployed PwMS were more likely to be female, have progressive subtypes of MS and longer disease duration. They had poorer EDSS and MSFC scores, greater levels of depression and scored lower on the personality scales of extraversion and agreeableness. There were significant group differences on the SDMT, PASAT-3.0, PASAT-2.0 and WLW with employed PwMS scoring higher on these tests. There was no difference in the overall levels of cognitive impairment between the two groups. The MSFC was found to be the most robust predictor of employment status as it incorporates measures of physical and cognitive ability.

**4.2.1.13 *Demographic, clinical, and cognitive characteristics
of multiple sclerosis patients who continue to work***

The study by Beatty and colleagues aimed to identify the factors which resulted in unemployment in MS (Beatty, Blanco, Wilbanks, Paul, & Hames, 1995).

102 PwMS were recruited from neurology practices and local support groups in America. Participants were separated into two groups: employed and retired and completed a large battery of neuropsychological tests to assess verbal ability, attention and concentration, information processing speed, naming, visuospatial perception, memory and problem solving. Participants also completed the BDI, a visual acuity test, the AI and a handedness inventory.

PwMS who were employed performed better on cognitive measures than their unemployed counterparts. There was a significant difference in performance on digit span, LOT and the percentage of perseverative responses on the WCST.

Table 3: Summary of Results

<u>Author</u> (First name and year)	<u>Quality</u> Assessment	<u>Study</u> design	<u>Recruitment</u> Location	<u>Sample size</u> and type of MS	<u>Employment</u> Definitions	<u>Measures</u>	<u>Outcomes</u>
Beatty (1995)	Weak	Cross Sectional	Neurology practices, Support groups	102, Clinically definite MS	Employed (full time, part time, attending college at least part time) vs retired “housewife” or “househusband” not considered employed.	BDI, visual acuity, AI, handedness. SILS, WAIS-R Digit Span, letter fluency and category fluency. SDMT, BNT, Benton Line Orientation, SMT, New Map Test, SRT, WCST, SILS abstraction test.	Employed patients better cognitive performance. STM-Correct, SRT recall, FAS significant predictors of employment.
Benedict (2016)	Moderate	Case Control Study	Retrospective analysis of data from PwMS. HC recruited	275 clinically definite MS, 114 HCs	“Gainfully” employed (not including people who have left	MSFC, BICAMS. General employment information, work related problems or	MS Work Disabled group consistently performed

through advertising	the workforce voluntarily i.e. students and homemakers)	accommodations, specific negative work events	worse in comparison to the other groups. Followed by MS Work Challenged and MS Work Stable. HC Work Stable group had the best performance consistently across tests. All motor and cognitive tests significantly differentiated the three MS
	MS Work Stable (full time employment, no disability benefits, no negative work events), MS Work Challenged (employed but having significant difficulties at work), MS Work		

					Disabled (unemployed <i>and</i> receiving well defined monetary benefit e.g.: private disability benefits) HC Work Stable (employed, no negative work events)		groups. T25FW was the only test with scores that were significant different between the MS Work Stable and HC Work Stable groups. SDMT the most discriminating cognitive test.
Campbell (2016)	Moderate	Cross sectional	MS Clinics	62, clinically definite MS	Employed vs unemployed	EDSS, BICAMS, EuroQOL, FAMS, PAM, USE-MS, HADS, MSNQ, FSS	Patients with cognitive impairment on more than one test more likely to be

							unemployed. SDMT most significant predictor of unemployment, after adjusting for education.
Frndak (2015)	Weak	Mixed design: Cross sectional and prospective.	Unknown	Cross sectional sample: 143, clinically definite MS. Longitudinal sample: 107 (47 overlapped with cross	Employed: more than 10 hours a week (not self- employed) (Employed PwMS only)	Online survey work status (Demographics, disease characteristics, self-reported symptoms, DSQ General employment information, work-related problems/accommodations), T25FW, 9-HPT, CVLT-II, BVMTR, PASAT, BDI-FS, EDSS obtained for 103 people.	No significant impact of neuropsychological performance on the decision to disclosure MS status.

				sectional group.)			
Goverover (2015)	Moderate	Cross sectional	Advertisements, support groups, participant database at Kessler Foundation.	72, clinically definite MS	Employed full time or part time vs Unemployed or Disabled. Retirees (due to age) not included.	MACFIMS, Sorting Task (from DKEFS), CMDI, STAI,	Employment status significantly correlated with worse performance on measures of processing speed and visual memory (SDMT & BMVT-R)
Honarmand (2011)	Moderate	Cross Sectional	MS clinics	106, confirmed MS.	Employed vs unemployed	EDSS, MSFC, BRB-N, HADS, NEO-FFI	Unemployed people significantly worse on SMDT, PASAT 3.0, PASAT 2.0

							and WLG. MSFC accounted for 30.9% of the variance.
Kordovski (2015)	Strong	Case control study	Tertiary MS Centre. Controls recruited through advertisements.	138, clinically definite MS	Employed: 30 hours+ per week. (PwMS Employed only)	MSNQ, general employment information, negative work events, PDDS, T25FW, 9-HPT, SDMT (oral), PASAT, CVLT-II, BVMTR, BDI-FS.	MS group cognitively impaired compared with controls. Work challenged participants performed significantly worse on T25TW, NHPT, PASAT, BVTR Delay, CVLT-II total learning.

							MS participants experiencing challenges at work reported using cognitive accommodations more frequently.
Krause (2013)	Strong	Case Control Study	MS Clinic Control group recruited through local postings.	87, clinically definite MS 37 Healthy controls	Employed vs Early retirement due to MS	EDSS, MSFC, BRB-N, SRT, 10/36 SPART, PASAT, WLG, CES-D, MFIS, HrQoL, FAMS, KKG, (German questionnaire Health Locus of Control).	Differences in cognitive scores between groups. Early Retirement MS group were the worst performing group. Significant differences between Early

							Retirement MS and Employed MS groups on: SMDT and PASAT. Early Retirement group differed from controls on SRT-CLTR, SPART-DR, SDMT, PASAT 3.0 and 2.0. No individual cognitive measure found to be a predictor of ER.
Morse (2013)	Moderate	Cross sectional	MS Clinic	30, clinically definite MS	Cutback Employment (including	SET, COWAT, PASAT, MSFC, SDMT, Trail making test, Zoo maps, Vocabulary	Significant correlations between

unemployed) (hours cut back due to MS, included unemployed) vs Maintained Employment. (Employment: Services provided for compensation over the last 30 days. Unemployment = no hours of work)	(WASI for premorbid IQ). BDI-II, FSS	completion of SET and SMDT. SET profile also correlated with COWAT z test score. Cutback employment group had significantly lower SET scores compared with same employed group. SET a significant predictor of vocational status. Overall
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							executive function not retained as significant predictor.
Strober (2012)	Moderate	Cross sectional	Baseline data taken from drugs trial.	101, clinically definite MS.	Employed (paid worker, volunteer worker, student, homemaker) vs Unemployed (disabled). Retired people excluded.	Occupational Functioning Questionnaire, CMDI, FSS, TPQ, EDSS, COWAT, JOLO, PASAT, SDMT, SRT, 10/36 SPART, Sorting task (DKEFS).	Unemployed group performed worse on cognitive measures. Lower mean scores on all cognitive tests. Only significant for SDMT, and SRT. SDMT a significant predictor of employment

							status through regression analysis with effect size of 0.8.
Van der Hiele (2015)	Strong	cross sectional	Dutch MS and employment inventory.	55, RRMS only.	Employed (full time, part-time) vs Unemployed (without a paid job including homemakers, volunteers, patients receiving disability allowance or unemployment benefits, on prolonged medical leave	BADS DEX (self-report) NART, Trail Making Test, Stroop, PASAT, WCST, Rey Complex Figure (copy only), BADS, HADS, FIS.	Patients with paid employment completed more categories on WCST. No group differences in premorbid intelligence or other types of executive functioning.

					or early retirement)		
Vanotti (2017)	Moderate	Cross Sectional	MS Clinics	50, clinically defined MS	Unemployed specifically because of disability vs Unemployed for reasons unrelated to disability.	BICAMS (Spanish version of CLVT-I used, not CLVT-II), MSNQ-Informant and -Patient (Argentinian adaptation), EDSS, MSFC, BDI-FS, FSS	Strong association between the BICAMS and work hours. Employment status a predictor of CLVT-I performance.
Walker (2016)	Moderate	Prospective study, case control	MS Clinics. Controls recruited by word of mouth.	57 PwMS, clinically defined MS. 51 healthy controls	Self-reported vocational status.	BICAMS (alternate forms used for follow-up), MSNQ (informant and self-report), PHQ-9, MFIS, EDSS	Case control group: BVMT-R and EDSS score used in regression. Full model significantly predicted

employment.
Model
accounted for
23.6-32.8% of
the variance in
employment
status.

4.3 Quality Assessment.

The results of the quality assessment are presented in Table 4 below. The majority of studies found were rated as “moderate” or “strong”. Two studies were rated as “weak” (Beatty et al., 1995; Frndak et al., 2015). Both studies had weak participant selection methods and study design. The study by Frndak (2015) did not mention if there was any attrition from their longitudinal group or reasons for people deciding drop-out. No studies were removed from this review as a result of their quality assessment.

Table 4: Table of Results of Quality Assessment

<u>Study (first author, year)</u>	<u>Selection Bias</u>	<u>Study Design</u>	<u>Confounders</u>	<u>Blinding</u>	<u>Data collection Method</u>	<u>Withdrawals and Dropouts</u>	<u>Overall Quality Rating</u>
Beatty (1995)	Weak	Weak	Strong	Moderate	Strong	N/A	Weak
Benedict (2016)	Moderate	Moderate	Strong	Moderate	Strong	N/A	Moderate
Campbell (2016)	Moderate	Weak	Strong	Moderate	Strong	N/A	Moderate
Frndak (2015)	Weak	Weak	Strong	Moderate	Strong	Weak	Weak
Goverover (2015)	Strong	Weak	Strong	Moderate	Moderate	N/A	Moderate
Honarmand (2011)	Moderate	Weak	Strong	Moderate	Strong	N/A	Moderate
Kordovski (2015)	Moderate	Moderate	Strong	Moderate	Strong	N/A	Strong
Krause (2013)	Moderate	Moderate	Moderate	Moderate	Strong	N/A	Strong
Morse (2013)	Moderate	Weak	Strong	Moderate	Strong	N/A	Moderate
Strober (2012)	Moderate	Weak	Moderate	Moderate	Strong	N/A	Moderate
Van der Hiele (2015)	Moderate	Moderate	Strong	Moderate	Strong	N/A	Strong
Vanotti (2017)	Moderate	Weak	Strong	Moderate	Strong	N/A	Moderate
Walker (2016)	Moderate	Moderate	Strong	Moderate	Strong	Weak	Moderate

4.4 Demographics

The majority of the studies were conducted in the North American continent (n=9), followed by Europe (n=3) and South America (n=1).

The 13 studies included a total of 1278 participants with MS. PwMS were frequently recruited from outpatient or community settings. One study used a database and support groups for recruitment, two studies analysed retrospective data and one study did not specify their source of participants. 972 PwMS were female (76.1%) and the remaining 306 were male (23.9%).

Most PwMS were diagnosed with Relapsing Remitting MS (n=921, 72.1%). This was followed by Secondary Progressive MS (n=177, 13.8%), Primary Progressive MS (n=45, 3.5%), Clinically Isolated MS (n=7, 0.5%) and Progressive Relapsing MS (n=4, 0.3%). This reflects the breakdown of the subtypes of MS within the population (Bishop & Rumrill, 2015). 21 people did not know what type of MS they had been diagnosed with (1.6%) and 103 were unspecified (8.1%). Studies which had participants with unspecified diagnoses recruited through databases (Goverover et al., 2015), conducted a retrospective analysis on data (Benedict et al., 2016) and were reliant on a self-reported diagnosis (Frndak et al., 2015). Despite recruiting from MS clinics, two studies were unable to obtain a confirmed diagnosis of MS from a neurologist and did not specify reasons why this was the case (Honarmand et al., 2011; Kordovski et al., 2015)

There was a total of 263 healthy control participants over the four studies which included control groups. 187 of these participants were female (71.1%),

whilst the remaining 76 were male (28.9%). Control participants were recruited by word of mouth or through advertisements in the local community.

4.5 Measures Used

4.5.1 Neuropsychological Batteries.

A variety of different neuropsychological tests were used in the final 13 studies. The most commonly used test was the PASAT, which was used in five studies, followed by the BICAMS battery, which was used in four studies. It is worth noting that the PASAT also forms part of the MACFIMS battery, which was used by one study, and the BRB-N, which was used by two studies. The PASAT is also the cognitive component of the MSFC, which was used in five studies. Although the MSFC contains a cognitive test, the PASAT, it also contains two motor tests. Therefore, the MSFC will only be discussed where appropriate.

The most commonly assessed cognitive domain was processing speed, which was tested 19 times across the 13 studies, and working memory which was tested 14 times.

4.5.2 Definitions of Employment.

Employment information was self-reported in each study. Many studies dichotomised employment status into “employed” and “unemployed”. However, the precise definitions of these terms, and therefore people excluded or assigned to these groups, varied. Three studies grouped participants using the terms “employed” and “unemployed” without further

explanation of what was considered “employed” or taking into account reasons for unemployment.

One study defined employment as “working 30 hours a week or more”. Another study excluded self-employed people and people working less than 10 hours per week. Four studies created groups which were “employed” and “unemployed or retired due to MS”, thus excluding people who were retired due to age from their unemployed group. One of these studies also included people who self-identified as disabled in their unemployed group.

One paper included people who were not engaged in paid employment in their unemployed group, i.e. volunteers, homemakers, participants receiving disability benefits, people on long-term medical leave and people who had taken early retirement.

Another paper also grouped participants into employed and retired, however included part-time students in the employed group. In that particular study homemakers were not considered employed. Another study specified that employment had to be “gainful”. It also used a questionnaire to form three functional anchor groups for PwMS. These groups were defined not only by employment status, but also by the number of negative work events and accommodations that had to be made.

One study looked at the relationship between MS and employment hours rather than employment status.

4.6 Cognition

12 of the studies in this systematic review found that there was a relationship between employment status and cognition in MS. Namely, poorer scores on cognitive tests and impairment on a greater number of tests were significantly related to unemployment or reduced hours of work. Although this relationship between cognition and employment status or hours worked was found in the majority of papers, there was not a significant difference between groups on all cognitive tests administered.

For example, Beatty and colleagues (1995), assessed a broad range of cognitive abilities: verbal ability, attention-concentration, information processing speed, naming, visuospatial perception, memory and problem solving abstraction. Non-significant differences were found for attention-concentration (digit span), visuospatial perception and preservative responses on the WCST.

The remaining study was investigating the factors related to the disclosure of MS in the workplace (Frndak et al., 2015). Thus, there were no inferential statistics relating to the impact of cognition on work performance. This study did find that there was no significant relationship between cognition and the decision to disclose MS status to employers. This is in contrast to the results for the relationship between physical disability and the decision to disclose and of course, physical disabilities are more apparent to work colleagues or employers.

4.6.1 Information Processing Speed.

Many of the studies found that information processing speed was significantly related to employment status. In these studies, employed PwMS had better scores on tests of information processing speed in comparison to their unemployed peers.

Beatty and colleagues (1995) found that performance on a timed phonemic fluency task was a significant predictor of employment status. Whilst phonemic fluency tasks are typically considered to be tests of executive function, the timed element means that general information processing speed may impact performance (Henry & Beatty, 2006).

The SDMT is a test that is frequently used to assess processing speed in this population. A significant difference in performance in groups of unemployed and employed participants with MS was observed on this test in several studies (Benedict et al., 2016; Campbell et al., 2016; Goverover et al., 2015; Honarmand et al., 2011; Strober et al., 2012). Performance on the SDMT was also seen to be a significant predictor of work hours amongst PwMS (Vanotti et al., 2017) and employment status (Benedict et al., 2016; Campbell et al., 2016; Strober et al., 2012; Vanotti et al., 2017). Furthermore, Krause and colleagues found that there was a significant difference between PwMS who had retired early and employed PwMS (2013). In addition, the study by Benedict and colleagues (2016) found that performance on the SDMT was significantly different between their three MS anchor groups and was the most discriminating cognitive task in their study. It was also the only

test with significantly different results for the MS Work Stable group and the Healthy Control group.

The PASAT, which was the most commonly used test, was also able to distinguish between groups of unemployed and employed PwMS. Honarmand and colleagues (2011) found that two speeds of delivery of the PASAT (PASAT 3.0 and the PASAT 2.0) were both able to significantly differentiate between groups of employed and unemployed PwMS. In addition, a binary logistic regression found that the MSFC, which includes the PASAT, accounted for 30.9% of the variance in scores for employed and unemployed PwMS. Krause and colleagues (2013) also found that PwMS with reduced working hours also performed worse on the PASAT-3.0 in comparison to PwMS who continued to work as before. Moreover, healthy controls significantly outperformed both these groups on the same task. Benedict and colleagues (2016) found that their MS anchor groups had significantly different results on the PASAT, however there was no significant difference between the employed MS Work Stable group and the Healthy Control group. Moreover, a ROC curve analysis found that the PASAT was not a test that could be used to accurately discriminate between their anchor groups.

4.6.2 Memory.

There were significant differences between groups on tasks of memory recall. The BVMT-R is an immediate visual memory recall task that was able to differentiate between groups of employed and unemployed PwMS in some

of the studies in this review. Poor performance on the BVMT-R was significantly associated with unemployment (Goverover et al., 2015) and was a significant predictor of employment status (Walker et al., 2016). The study by Beatty's group also found that the number of correct responses on the STM was a significant predictor of employment status (1995). Similarly, Vanotti and colleagues (2017) found that the CVLT-I, a measure of verbal immediate recall, was significantly related to employment status and work hours, as well as being a significant predictor of unemployment with a large effect size. In addition, Kordovski's group found that total learning on the CVLT-II was significantly worse for employed PwMS who were reporting challenges at work (Kordovski et al., 2015). Benedict's group found that there was a significant difference in performance on the CVLT-II overall between the MS group and the healthy control group, as well as between the different MS anchor groups. However, the CVLT-II was not a significant discriminator for the different MS anchor groups (Benedict et al., 2016).

There were also significant differences seen on tasks of long term memory. Performance on the delayed trial of the SRT was also shown to be significantly different amongst unemployed and employed PwMS by Strober and colleagues (2012). Beatty and colleagues found that the delayed trial of the SRT was a significant predictor of unemployment in MS (1995).

4.6.3 Executive Function.

There were many different tests of executive function used in the 12 studies found, however there were few significant differences in performance between groups of employed and unemployed PwMS. Van der Hiele's group found that people with RRMS who were in paid employment completed significantly more categories on the WCST in comparison to their peers who were not in paid employment (2015). This suggests that people with RRMS in paid employment were better at idea generation and set shifting. This study found no significant difference on other measures of executive function.

A study by Morse and colleagues (2013) found that PwMS who were able to maintain their work hours performed significantly better on the SET, a multitasking task. Honarmand's group found that unemployed PwMS performed significantly worse than employed PwMS on the WLG, a task of verbal fluency (Honarmand et al., 2011). A similar outcome was found by Beatty and colleagues on a tests of semantic and phonemic fluency (1995). However, this result on the WLG was not replicated by Krause's group (2013).

5 Discussion

5.1 Summary of Main Findings

This systematic review was conducted to investigate the relationship between cognitive ability in MS and employment outcomes for working age people of this population.

One study which investigated the relationship between cognition and disclosure of MS status to employers found that there was no significant relationship between cognition and disclosure. The remaining 12 studies which looked explicitly at the relationship between cognition, employment and unemployment, found that PwMS who were unemployed or who had reduced their working hours performed worse on cognitive tests in comparison to PwMS who had no change to their employment status or hours. It is worth noting that these group differences did not always reach statistical significance. Studies that included a control group found the control group performed better than both unemployed and employed PwMS.

One of the most consistent findings was the difference in information processing speed between groups. This effect was seen in half of the studies in this systematic review and irrespective of the type of information processing task administered as part of the battery. In some studies, scores on tasks of information processing were able to significantly predict employment status using regression modelling. Given the prevalence of information processing speed deficits in MS and the hypothesis that it is the cause of other cognitive

impairments in this population, it is not surprising that it was one of the most consistent deficits identified in this review (Costa, Genova, DeLuca, & Chiaravalloti, 2017; M. A. Drew, Starkey, & Isler, 2009; Forn, Belenguer, Parcet-Ibars, & Avila, 2008). Not only can slowed processing affect performance on other cognitive tests, but it can also impede performance in the workplace. For example, on the completion of time sensitive tasks or generally needing more time to problem solve difficulties.

Differences in immediate and delayed recall were also observed to be significant between groups. Short term memory was impaired across both verbal and visual modalities and tasks of short term memory were able to significantly predict employment status. Two studies found that the performance of people who were unemployed was significantly worse on the SRT delay trial in comparison to employed PwMS.

There was also a relationship between certain executive functions and employment, specifically on tasks requiring idea generation, and set shifting. Once again, PwMS who were employed or who were able to maintain their premorbid working hours performed better than people who had to make changes to their employment because of their MS. It is worth noting that the majority of the studies were cross sectional, and therefore it is possible that unemployment resulted in cognitive difficulties in this group rather than being the result of them.

5.2 Methodological Critique of Studies

Using the EPHPP as a measure for a quality assessment of the studies in this review found that eight studies were rated as “moderate”, three were rated as “strong” and two were rated as “weak”.

One of the difficulties encountered was that the majority of the studies, seven in total, were cross-sectional observational studies. These studies often created groups of unemployed or employed people using demographic data collected after recruitment, rather than deliberately recruiting a particular group.

The EPHPP was created to evaluate research investigating new interventions (Armijo-Olivo, Stiles, Hagen, Biondo, & Cummings, 2012; Thomas et al., 2004). It is a well-used quality evaluation tool and its accompanying dictionary of terms makes it easy to use. Furthermore, its use was recommended in a systematic review evaluating quality assessment tools (Deeks et al., 2003).

Since the EPHPP evaluates intervention studies, randomised control trials (RCTs), often considered the “gold standard” approach for such research, are rated as a strong methodological approach. Conversely, studies which are observational, investigating relationships between variables involving other methodologies, are rated as “moderate” or “weak” despite being the best approach for answering their research question or aims.

An improvement on this systematic review might be to use a quality assessment tool specifically created for observational, cross-sectional studies.

5.3 Limitations and suggestions for future research

The different definitions of “employment”, “unemployment” and “retired” used across the 13 papers means that there is some degree of heterogeneity and that people considered employed in one study may not be considered employed in another. Despite the relative consistency of the findings in these studies, it is possible that this difference may impact results. It may be that the development of standardised definitions of “employment” and “unemployment” would be useful in further research. This could include ensuring that unemployment or a reduction of working hours being described is a direct result of the symptoms of MS since people may choose to leave work or reduce their hours for many reasons.

None of the papers described in this review took into account the type of job or sector that people were currently or had been employed in as part of their analyses. It is possible that different types of employment (skilled, unskilled, manual, etc) may be affected by particular cognitive difficulties due to the nature of the work involved. As highlighted by Vanotti and colleagues (2017), countries or regions which have industries dependent on manual labour may see a greater impact of physical impairments rather than cognitive impairments.

Of note, there are no studies from the Asian, Australasian or African continents. This may reflect the global geographical spread of MS and the lower prevalence rates in these areas, however given the mix of industries across the continents, it would be interesting to compare data from these

regions to studies from North America and Europe (Leray, Moreau, Fromont, & Edan, 2016; Wade, 2014).

There is also variation in the employment rates due to MS across Europe. These rates range from 28% in Russia to 64% in Denmark and it may be that there are socioeconomic or political reasons behind these differences (Kobelt et al., 2017). For example, a country which provides disability or sickness benefits may find that there is a higher rate of unemployment in MS as it is a more financially viable option in comparison to a country with little or no financial aid for people with disabilities or chronic health conditions. These socioeconomic factors were not considered by the studies in this review. Neither were gender differences. MS is more prevalent in women than in men and it may be that attitudes about gender roles also affect the decision to withdraw from the workforce (Thompson et al., 2018).

It should be a priority to manage employment challenges for PwMS and help them to maintain or regain their employed status should they so wish. Australia has demonstrated impressive, real gains in employment rates for PwMS by facilitating work adjustments and guidance is available for health professionals to address this issue (Cardone, 2017; Van Dijk, Kirk-Brown, Taylor, & van der Mei, 2017). However, for some people, retiring due to MS is the right thing for them to do and they may not consider it to be a loss or detrimental to their quality of life. It is important that these decisions are respected by clinicians.

6 Conclusion

The aim of this review was to provide a synthesis of the literature about the impact of cognition on employment outcomes for PwMS. The findings were that PwMS who were unemployed or had reduced working hours had a greater level of cognitive impairment than PwMS who remained employed or maintained their working hours. Employed PwMS still had greater levels of cognitive impairment than healthy controls. Information Processing Speed, short-term memory delayed recall and executive functions were the domains that were frequently significantly different between the two groups. Further research might focus on identifying meaningful benchmarks of impairment in these areas which are related to employment for PwMS, building on the work that has already started in this area (Benedict et al., 2016).

The need to have a more consistent definition of “employment” was highlighted by this review as was the need to clarify reasons for unemployment within this group.

7 Paper II: Assessment of Executive Function in Multiple Sclerosis using a Virtual, Office-Based Task and its Relationship to Employment Performance

7.1 Abstract

Multiple Sclerosis (MS) is a chronic and progressive disease which is characterised by inflammation, demyelination of neurons and formation of plaques at several sites in the Central Nervous System. Unemployment can be a major challenge for people with MS (PwMS). Impairments in executive function in MS have been linked to employment difficulties and the use of maladaptive coping strategies. Accurate assessment of executive function is therefore important for helping individuals develop management strategies at home and at work.

The Jansari Assessment of Executive Function (JEF©) is a non-immersive virtual reality test which takes place in an office environment. It has been shown to be sensitive to deficits in executive function in other clinical and non-clinical populations. This study aimed to compare the sensitivity of the JEF© to other traditional executive function tests in MS, as well as determine if the results of the JEF© were more closely correlated to coping styles and employment outcomes than these existing tests.

A total of 18 PwMS and 24 Healthy Controls (HC) took part in this study. All participants completed the JEF©, a battery of traditional executive function neuropsychological tests, the BICAMS and questionnaires about employment difficulties, mood, anxiety, fatigue and coping styles.

PwMS had significantly poorer scores on the JEF© Total Score, JEF© creative-thinking and JEF© Action-Based Prospective Memory subscales.

There was a significant difference between groups on the employment questionnaires and a significant negative correlation between JEF© Total Score and employment questionnaires. The only coping scale which showed a significant between group difference was Maladaptive Coping, with the HC group using more of these strategies.

There were significant positive relationships between the JEF© Total Score and Adaptive Coping subscale, and the composite Executive Function Index and Adaptive Coping subscale, but no significant difference in the strengths of these correlations.

Unemployment can be a major challenge for people with Multiple Sclerosis (MS). Although one might expect difficulties with employment to eventually accompany a degenerative disease, such as MS, in its later stages, studies have shown that even people with minimal physical disabilities can have difficulties maintaining employment (Kobelt et al., 2017).

Research has shown that cognition is a mediating factor between disability and unemployment in this population and that executive function is one of the cognitive domains which has specifically been linked to unemployment (Cadden & Arnett, 2015; M. Drew, Tippet, Starkey, & Isler, 2008; Van der Hiele et al., 2015).

Assessment of cognitive ability is essential for successful management of the disease. The Jansari Assessment of Executive Function (JEF©) is a new assessment utilising non-immersive virtual reality which could be used to evaluate executive dysfunction in this group.

7.2 Multiple Sclerosis

MS is a chronic and progressive disease which is characterised by inflammation, demyelination of neurons and formation of plaques at several sites in the Central Nervous System (CNS) (Kutzelnigg & Lassmann, 2014; Milo & Miller, 2014; Nylander & Hafler, 2012; Polman et al., 2011). The myelin sheath surrounding neurons supports the propagation of action potentials along the neuron through the process of saltatory conduction at the nodes of

Ranvier. Damage to the myelin sheath therefore disrupts the transmission of action potentials in the CNS (Kolb & Whishaw, 2008).

MS is a heterogenous disease, however it can be divided into three main subtypes: Relapsing Remitting, Secondary Progressive and Primary Progressive. Approximately 80-90% of patients will be diagnosed with Relapsing Remitting MS (RRMS) following an initial Clinically Isolated Syndrome - a single demyelinating event. RRMS is characterised by periods of relapse followed by periods of clinical stability where the individual can return to their pre-relapse level of function. 40% of people with RRMS will then go on to develop Secondary Progressive MS (SPMS) within 10 years of their initial diagnosis. SPMS is characterised by an irreversible progression of the disease. 10-15% of people will be diagnosed with Primary Progressive MS (PPMS) which is distinguished by a progressive course from the outset (Iwanowski & Losy, 2015; Milo & Miller, 2014; Nylander & Hafler, 2012).

It is estimated that 2.3 million people in the world have MS, with 30 being the average age of diagnosis (Milo & Miller, 2014). MS has a significant impact on quality of life and is one of the major causes of disability for young people in the world, with 50-80% of people becoming unemployed within 10 years of diagnosis and a reduced life expectancy in comparison to the general public. (Lunde et al., 2017; Wicks et al., 2016).

Symptoms of MS vary greatly and include a range of physical difficulties such as numbness, visual disturbances, dizziness, ataxia, fatigue, poor coordination, problems with gait, bladder and bowel dysfunction to name but a few (Milo & Miller, 2014; Wicks et al., 2016). There is also a higher rate of

psychological difficulties such as depression or anxiety in this population in comparison to the general public (Murphy et al., 2017).

7.3 Cognitive Impairments in Multiple Sclerosis

Cognitive impairment affects 40-70% of people with MS (DeLuca et al., 2015). It can be seen in all subtypes and stages of the disease and is associated with lesions and atrophy of grey and white matter in the CNS. People with MS (PwMS) who have cognitive impairment are more likely to be unemployed, have mental health difficulties and have more problems with activities of daily living (Grech et al., 2017b). Cognitive impairments, therefore, negatively impact quality of life for people in this population. Cognitive symptoms of MS typically include difficulties with processing speed and memory (Chiaravalloti & DeLuca, 2008; Grech et al., 2017b; Langdon, 2011; Rao et al., 1991; Roman & Arnett, 2016).

PwMS may also have impaired executive function (Van der Hiele et al., 2015). There are many theories regarding how executive function is organised and exactly what abilities fall under the label. However, it is generally agreed that “executive function” is an umbrella term describing the cognitive functions needed to successfully carry out goal-directed behaviours which require attention and concentration. There are three core executive functions from which the other, higher order executive functions stem: inhibition, working memory and cognitive flexibility. Other abilities include planning, organisation,

emotion regulation and problem solving (Diamond, 2013; Langdon, 2011; Miyake et al., 2000).

Impairments in executive function are observed less frequently in this population in comparison to other cognitive domains such as processing speed (Ferreira, 2010). Nevertheless, studies have shown that PwMS perform significantly worse on traditional executive function tasks such as verbal fluency tests, the Wisconsin Card Sorting Test, as well as the Delis-Kaplan Executive Function System (DKEFS) (M. Drew et al., 2008; Henry & Beatty, 2006; Parmenter et al., 2007). A relationship has also been seen between performance of tasks of executive function, functional status and the ability to carry out activities of daily living (Kalmar, Halper, Gaudino, Moore, & DeLuca, 2008). Executive dysfunction can therefore have an impact on quality of life for people with MS.

Poor executive function has been linked to the use of maladaptive coping strategies, such as avoidance, in the MS population. This in turn has been linked to increased psychological difficulties (Grech et al., 2017b). “Coping” refers to the collection of behaviours and thoughts which an individual uses to manage their emotions during times of stress. These stressors may be internal and/or external. Coping behaviours are used in order to regain a state of emotional equilibrium when an individual feels that their efforts to reach important goals are being thwarted (Folkman & Moskowitz, 2004).

Although there are many factors which influence which coping strategy an individual chooses, it has been suggested that the executive functions of

cognitive flexibility, working memory and inhibition play key roles in the selection of the most appropriate strategy (Hofmann, Schmeichel, & Baddeley, 2012). The use of maladaptive coping styles has also been linked to higher rates of negative work events and unemployment within the MS population. This may be related to the increased focus on emotion and mental disengagement which the individual uses to cope with stress (Grytten et al., 2016; Van der Hiele et al., 2016).

7.4 Employment and Cognition in Multiple Sclerosis

Up to 45% of PwMS with minimal disabilities, as measured by the Expanded Disability Status Scale (EDSS), are unemployed (Kobelt et al., 2017). Research has shown that cognitive impairment is a mediating factor in the relationship between physical disability and unemployment for PwMS (Campbell et al., 2016; Deluca et al., 2015).

The systematic review conducted as part of this thesis found that unemployment or reduced work hours are associated with poor performance on cognitive tasks. This was primarily seen in the areas of information processing speed, immediate recall, delayed recall and executive function. Please see section 4.6 (p. 65) of this thesis for further discussion of the relationship between employment and cognition in MS.

7.5 Adaptations and Accommodations used in the Workplace

Accommodations are frequently used by PwMS to try and prevent their symptoms from interfering with their work responsibilities. Since the disease is heterogenous in its effect, people will need to have accommodations tailored to suit their needs and reviewed in the event of a relapse or deterioration.

Adaptions to manage fatigue include rearranging the work day to economise energy, building in regular rest periods into the work day or being able to work from home. Ergonomic work stations and computer screens with options for text enlargement or changes in contrast can be used to help manage motor difficulties and visual disturbances respectively. Adaptations to help manage cognitive dysfunction include memory aids and calendars which can send reminders as texts or emails to prompt the individual. Structuring the day to maximise the use of routines and reducing cognitive load can also be beneficial, as can reducing the need for multitasking where possible (Benedict, Rodgers, Emmert, Kininger, & Weinstock-Guttman, 2014; Johnson & Bruyere, 2001).

It is worth noting that for accommodations to be implemented, the individual needs to disclose that they have MS to their employers. Unfortunately, not all employees feel able to do this for fear of discrimination, being treated differently or having their managers doubt their capacity (Rumrill, Fraser, & Johnson, 2013).

7.6 Testing Executive Function within MS

Accurate assessment of executive dysfunction is essential for developing management strategies (Frndak et al., 2016). However, there are some obstacles to this.

There are many well-validated tests of executive function which are available to clinicians, such as the Wisconsin Card Sorting Test. Despite this, some of these tests lack ecological validity and do not reflect the impact of cognitive impairment in everyday life (Chaytor & Schmitter-Edgecombe, 2003). For example, some of these tasks are highly structured by the examiner, thus taking away the burden of planning which is in itself an executive function. Nevertheless, the structure of traditional pen and paper neuropsychological tests means that there is a high degree of experimental control. There is therefore a trade-off between the need for ecological validity and experimental control (Bohil, Alicea, & Biocca, 2011; Parsons, 2015).

Clinicians could ask patients to report on areas of difficulty, however self-report can be biased by factors such as depression or other mental health problems common in MS, and the accuracy of self-report in the literature is inconclusive (Bruce, Bruce, Hancock, & Lynch, 2010; Hanssen, Beiske, Landrø, & Hessen, 2014; Smith & Arnett, 2010; Van der Hiele et al., 2012). Family members or carers of people with MS could be asked to provide collateral information, however this is still a subjective report, though closer to objective findings (Benedict et al., 2004).

There are currently some neuropsychological batteries and tests which have been designed with ecological validity in mind. The Behavioural Assessment of Dysexecutive Syndrome (BADS) is an example of an ecological valid test (Wilson, Alderman, Burgess, Emslie, & Evans, 1996). However, it still takes place within the artificial environment of the clinic room.

The Multiple Errands Test (MET) is another example of an ecologically valid test (Shallice & Burgess, 1991). The MET is particularly note-worthy as it takes place in a shopping centre or hospital, rather than the clinic room. The participant is given a list of tasks, with associated rules by the administrator but are left to decide the best way to complete the tasks. This is contrary to other neuropsychological batteries made up of short, discrete subtests where order and task initiation is largely decided by the test administrator (Shallice & Burgess, 1991). Assessment in a real-world environment, such as a shopping centre, is advantageous as it gives a more accurate representation of ability than assessment in a clinic, however this is not always practical as service users may not be physically capable. In addition, it requires the consent and cooperation of local business which they may not be willing to provide.

Virtual reality, both immersive and non-immersive, can be a way of achieving a compromise between ecological validity and experimental control for neuropsychological tests. Virtual reality tests have also been shown to be sensitive to executive dysfunction (Besnard et al., 2016; Davison, Deepröse, & Terbeck, 2017; Rand, Basha-Abu Rukan, Weiss, & Katz, 2009). They are also likely to be more engaging and portable than traditional pen and pencil neuropsychological tests. Furthermore, public responses to the use of virtual

reality in medical settings is generally positive (Dascal et al., 2017; Keller et al., 2017).

7.7 The Jansari Assessment of Executive Function

The Jansari assessment of Executive Function (JEF©) is a new, non-immersive virtual reality test based on the MET but set in an office environment. It has been shown to be sensitive to dysexecutive symptoms in people with acquired brain injury, as well as to the effect of drugs which have only anecdotal reports of executive dysfunction undetected by other neuropsychological batteries, for example: nicotine, caffeine and ecstasy (Jansari et al., 2014; Jansari, Froggatt, Edginton, & Dawkins, 2013; Montgomery, Hatton, Fisk, Ogden, & Jansari, 2010; Soar, Chapman, Lavan, Jansari, & Turner, 2016). To date the JEF© has not been used in the MS population. Having results which accurately reflect real world experiences is necessary for improved disease management as well as being able to support PwMS in maintaining activities that are important to them, including employment.

Since the JEF© has been shown to be more sensitive than other tests of executive function in other clinical and non-clinical populations, it is possible that it will provide results which are more accurate and more reflective of the experiences of PwMS with executive impairment than traditional pen and paper neuropsychological tests.

7.8 Aims and Hypotheses

The aims of this study are as follows: to compare the sensitivity of the JEF© to existing traditional neuropsychological tests of executive function within the MS population and how they correlate with measures of employment performance and coping styles.

As the JEF© has not been used in the MS population before, it will also be necessary to confirm that the JEF© is sensitive to deficits within this population. It is hypothesised that the JEF© will be sensitive to deficits in executive function in the MS population. In addition, the JEF© will be more closely correlated to employment outcomes and coping styles in comparison to the pen-and-paper neuropsychological tests.

People with RRMS and healthy control participants will therefore be asked to complete the JEF© as well as the following traditional, pen-and-paper neuropsychological tests of executive function: Zoo Maps and Key Search subtests from the BADS (Wilson et al., 1996) and a verbal fluency test (Henry & Beatty, 2006). Participants will be matched according to age and IQ using the Test of Premorbid Function, UK Version (TOPF-UK) (Wechsler, 2011). Participants will also be required to complete the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (Langdon et al., 2012).

All participants will complete questionnaires covering a range of workplace experiences which may affect employment for people with MS. These are: the Multiple Sclerosis Questionnaire for Job Difficulties (MSQ-Job)

(Schiavolin et al., 2016) and the Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ) (Honan et al., 2012).

Participants will also complete the COPE Inventory (Carver, Scheier, & Weintraub, 1989), which asks participants about their coping strategies. The Fatigue Severity Survey (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) and the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) will also be administered to take into account confounding variables of mood and fatigue. Please see Appendix I for copies of the questionnaires used in this study.

The scores on the JEF© and traditional neuropsychological tests will be compared to see if there is a significant difference between the MS group and the control group. Correlations will also be carried out to assess the relationship between results on the employment questionnaires, the JEF© and the pen-and-paper neuropsychological tests. Tests will also be carried out to ascertain if there is a significant difference between the strength of these correlations.

8 Methods

8.1 Recruitment

A total of 18 participants with MS were recruited through advertising on websites and social media accounts specifically for people with MS: www.MS-UK.org and <https://Shift.MS>. MS Therapy Centres in and around London were also contacted for support with recruitment. MS Therapy Centres are third sector charity organisations which provide non-pharmacological therapies, such as physiotherapy and oxygen therapy, to members. Some MS Therapy Centres were also able to provide a room for testing to take place on their premises.

MS Therapy Centre staff were asked to either directly approach members who they thought might be eligible or to put up a poster in a suitable location if they felt uncomfortable or unable to directly approach service users. Advertising also went out in Therapy Centres newsletters or through their social media platforms as appropriate.

A summary of the inclusion and exclusion criteria were given to centres to help them identify suitable participants, as well as adverts which could be displayed on a noticeboard.

If service users were approached by a member of staff at the charity, their contact details were given to the researcher with their consent. They

were then emailed a copy of the consent form and a time was scheduled for an eligibility check over the telephone

24 participants were recruited to the healthy control group (HC). HC participants were recruited through word of mouth. Several community groups and places of work were approached for support with advertising the study, however all participants in the healthy control group were personally known to the researchers or were referred by friends.

Testing took place in a suitable room at an MS Centre, on Royal Holloway premises (both the Egham campus and Bedford Square) or in the Royal Holloway rooms at Senate House in Central London.

8.2 Inclusion and Exclusion Criteria

Inclusion criteria for the both groups were as follows: age between 18 and 65, no historic or current significant mental health difficulties, no sensorimotor difficulties that could impact the interface with the JEF©. For the MS group participants also needed a diagnosis of RRMS, no relapse in the last 6 weeks and no significant changes in medication. The RRMS subtype was chosen as it is the most common subtype of MS. It was decided not to include people with Secondary or Primary Progressive MS as research has shown that the presentation of the progressive subtypes may have a different aetiology which could have resulted in confounding factors. The age group 18-65 was chosen to reflect the age range of most employed people.

8.3 Sample Size

Previous studies using the JEF© have not detailed power calculations in their reports. However, previous JEF© studies which have used a between groups design have found that comparisons of 19 people in both the clinical and control group, have been sufficient to show a significant difference in performance (Denmark et al., 2017).

Traditional pen and paper neuropsychological assessments usually show a large effect size for the difference in performance between people with MS and healthy controls. For example, $d = 1.1$ for the Symbol Digit Modalities Test (Benedict et al., 2016) and $d = 0.9$ for the California Verbal Learning Test, second edition (Parmenter, Testa, Schretlen, Weinstock-Guttman, & Benedict, 2010). It was therefore anticipated that there would be a large effect size for the comparisons carried out in this project.

An independent t-test was used to analyse the data in order to investigate the first hypothesis, that there is a significant difference in performance on the JEF© for people with MS. A priori power calculations were carried out to establish the number of participants needed to achieve a large effect size. A minimum of 26 participants would need to be recruited to each group to achieve a power of 0.8 and a large effect size of $d = 0.8$.

A Fisher's r to z transformation was carried out where necessary to investigate the second hypothesis, that the results of the JEF© will be more strongly correlated to employment performance. A priori power calculations were also carried out to ascertain the number of participants needed to have a

power of 0.8 and a large effect size for this analysis. 66 participants would need to be recruited to each group in order to have a large effect size of $d = 0.5$ and a power of 0.8.

These power calculations informed the decision to attempt to recruit 132 participants to each group in order to have a large effect size and sufficient power for both analyses.

Ethical approval for this study was obtained from the Royal Holloway Ethics Committee.

8.4 Materials

The neuropsychological and psychological measures used in this study were chosen because they have been well validated for use within the MS population. A number of neuropsychological tests were chosen in order to have as comprehensive an assessment of executive functions as possible.

8.4.1 The JEF©

The JEF© is a non-immersive, virtual reality test which takes place in an office environment. The JEF© assesses the following cognitive constructs: planning, prioritisation, selective thinking, creative thinking, adaptive thinking, multitasking, time-based prospective memory (TBPM), action-based prospective memory (ABPM) and event-based prospective memory (EBPM). A Total Score based on the averages of the other constructs can also be calculated. (Denmark et al., 2017; Jansari et al., 2014; Jansari, Agnew,

Akesson, & Murphy, 2004; Jansari et al., 2013; Montgomery, Ashmore, & Jansari, 2011; Montgomery et al., 2010; Montgomery, Seddon, Fisk, Mruphy, & Jansari, 2012; Soar et al., 2016).

The participant is asked to imagine that it is their first day as a new member of staff in the office. Since the manager is unable to meet them personally, they have left a list of instructions for what to do on their first day. The main task is to arrange the office so that it is ready for a meeting which is due to take place, however there are some other unexpected tasks that the participant must attend to. The participant is not given any cues for how to go about completing their tasks.

There are three areas which the participant can navigate between - the main meeting room, a side office and a corridor. In the meeting room there are objects which are necessary for the participant to be able to complete the tasks, as well as other everyday items there to create a sense of realism.

See figures 2 and 3 for screenshots of the JEF©.



Figure 2: Screenshot of the JEF© Meeting Room (taken from Denmark et al., 2017)



Figure 3: Screenshot of the JEF© office (taken from Denmark et al., 2017)

8.4.2 Traditional Neuropsychological Battery

8.4.2.1 Test of Premorbid Function (TOPF).

Healthy controls and participants with MS were matched according to age, sex and premorbid IQ to avoid an effect of confounding variables. As such, participants were asked to complete the TOPF to have an estimate of premorbid IQ.

The TOPF requires participants to read words which have atypical grapheme to phoneme translations. The TOPF is well correlated with full scale IQ as measured by the Wechsler Adult Intelligence Scale, Fourth Edition, $r = 0.7$ (Berg, Durant, Banks, & Miller, 2016).

8.4.2.2 The Behavioural Assessment of the Dysexecutive Syndrome (BADs).

The BADs is an ecologically valid battery which assesses planning, novel problem solving, multitasking, temporal awareness and cognitive flexibility (Norris & Tate, 2000; Wilson, Evans, Emslie, Alderman, & Burgess, 1998). Since one of the advantages of the JEF© is its ecological validity, it was decided to compare it to existing neuropsychological tests which are also known for being ecologically valid. The subtests of the BADs have been shown to be moderately correlated to other measures of executive function and have a Cronbach's alpha of 0.60 for the total score (Strauss, Sherman, & Spreen, 2006). Furthermore, the BADs has been used successfully in other

studies which have assessed executive function in this population (Grech et al., 2017b; Honan, Brown, & Batchelor, 2015).

The BADS is comprised of six tests: The Rule Shift Cards Task, The Action Program Test, Key Search, Zoo Maps, Temporal Judgement and Modified Six Elements. For this study, only Key Search and Zoo Maps were administered in order to keep the battery to a reasonable length of time. These particular subtests were chosen as both use real world scenarios to assess executive function, which is similar to the premise of the JEF©. Together these subtests assess planning, problem solving and self-monitoring abilities (Norris & Tate, 2000).

For the Key Search test, the participant is asked to imagine that they have lost their keys in a field represented by a 100mm square drawn on a piece of A4 paper. The participant is asked to draw a line from a black dot located outside the square to indicate how they would walk around the field to ensure that they find their keys.

The Zoo Maps test has two parts to it. In the first, high cognitive demand version, participants are given the map of a zoo and asked to draw which route they would take in order to successfully visit designated areas, whilst following specific rules about which paths they can use. In the second version, participants are simply required to follow a list of instructions in order to visit designated areas of the zoo.

8.4.2.3 Verbal fluency task.

This task assesses semantic fluency and is a test of executive function as well as language. Participants are asked to list as many words as they can which are part of the same semantic group in 90 seconds (Henry & Beatty, 2006). There is a high level of internal reliability for verbal fluency tests, $r = 0.83$, as well as moderate levels of validity for different categories $r = 0.66-0.77$ (Strauss et al., 2006).

8.4.3 Cognitive Status Test

8.4.3.1 Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS).

The BICAMS is a battery created to provide clinicians a brief cognitive assessment for people with MS which is more sensitive than screening questionnaires, yet does not require specialist expertise to administer (Langdon et al., 2012). It is comprised of the California Verbal Learning Test (Second Edition) (trials 1-5) (CVLT-II), which measures verbal memory, The Symbol Digit Modalities Test (oral version) (SDMT), which measures processing speed, and the Brief Visuospatial Memory Test – Revised (BVMTR) (trials 1-3), which assesses visuospatial memory. The BICAMS has 14 validations already published and is fast becoming the international gold standard for assessing cognition in MS.

In the SDMT, the participant is given a coding table which has numbers that are associated with symbols. The participant is also given a table which

has a series of symbols without their corresponding numbers. The task requires the participant to say which number matches the symbol as quickly as possible within a 90 second time limit.

For the CVLT-II, the participant is asked to memorise a list of 16 words read by the examiner. The participant is then asked to immediately recall as many words as possible, in any order, from the list. The participant is given five trials and asked to recall words even if they have been said in previous trials. The examiner reads the words out in the same order each time.

For the BVMT-R, the participant is presented with a stimulus which contains a 2 x 3 arrangement of abstract geometrical shapes. The participant is allowed to look at the stimulus for ten seconds before being asked to draw the correct shape in the correct position. This is carried out a total of three times.

8.4.4 Psychological Measures

8.4.4.1 COPE Inventory.

The dispositional version of the COPE Inventory is a multidimensional questionnaire about coping styles which assesses the different ways in which people respond to stress (Carver et al., 1989). This is a 52-item, self-report questionnaire. Responses are measured on a 4-point Likert-scale with responses ranging from “I usually don’t do this at all” to “I usually do this a lot”. It has previously been used to assess coping styles in the MS population.

The authors of the questionnaire did not group the 15 scales into aggregates or composites such as “adaptive” or “maladaptive”. However other studies have created their own subscales “active”, “avoidant” and a combination of the two. This study will use the subscales used in previous research which showed a relationship between executive functions and avoidant coping strategies in the MS population (Grech et al., 2017b; Rabinowitz & Arnett, 2009).

Maladaptive coping strategies therefore considered to be: denial, mental disengagement and behavioural disengagement. Adaptive coping strategies are: active coping, planning and suppression of other activities. Since participants can score highly on both the adaptive and maladaptive coping scales, a third composite scale will be used to look at overall coping. This is calculated by subtracting the z score for maladaptive coping from the z score for adaptive coping.

The questionnaire has good internal validity, with an average Cronbach’s alpha of 0.79 (Measurement Instrument Database for the Social Sciences, n.d.).

8.4.4.2 Hospital Anxiety and Depression Scale (HADS).

As depression and anxiety are commonly reported by people with MS, it is necessary to ensure that this is not a confounding variable in this study. Participants will therefore complete the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). This is a 14-item questionnaire

which uses a 4-point Likert scale for its responses. The HADS has been reported to have moderate to strong ratings of validity for the depression and anxiety subscales, $r = 0.6 - 0.8$ (Bjelland, Dahl, Haug, & Neckelmann, 2002). It has been validated for use within the MS population and is regularly used as a screening questionnaire in clinics (Honarmand & Feinstein, 2009).

8.4.4.3 *Fatigue Severity Scale (FSS).*

As fatigue is a common symptom experienced by people with MS it is necessary to confirm that it is not a significant confounding factor for this study. Participants will therefore be asked to complete the Fatigue Severity Scale (FSS) (Krupp et al., 1989). This is a 9-item questionnaire asking participants to rate their experience of fatigue over the last week. It has good validity, $r > 0.5$ and moderate reliability, $ICC > 0.6$ (Learmonth et al., 2013).

8.4.5 Employment Measures

As there are many reasons why PwMS may decide to leave their job, it is important that the questionnaires used to investigate employment performance also reflect this. The following self-report questionnaires were chosen as together they cover a number of socioeconomic, environmental and disease related factors which can contribute to poor workplace performance and ultimately unemployment.

8.4.5.1 Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ).

This self-report questionnaire consists of 50 items answered on a 5-point Likert scale and is designed to cover work difficulties experienced by people with MS. It has good internal validity and reliability and has been shown to account for up to 40% of the variance in reduced hours of employment since diagnosis including expectations about leaving work, expectations of being able to reduce one's working hours and expectations about having to change jobs (Honan et al., 2012).

8.4.5.2 Multiple Sclerosis Questionnaire for Job Difficulties (MSQ-Job).

This self-report questionnaire consists of 42-items and was designed to measure the impact of MS on workplace tasks using a 5-point Likert scale. The questionnaire measures six scales: tactile perception and fine movement, fatigue-related mental functions and symptoms, movement and fatigue-related body functions, psychological and relational aspects, time and organization flexibility in the workplace, company's attitudes and policies and an overall score (Schiavolin et al., 2016).

The questionnaire has a Cronbach's alpha of 0.86 and has moderate to strong correlations to other measures of disability and quality of life for people with MS (Raggi et al., 2015).

8.5 Procedure

The neuropsychological tests were administered before the questionnaires to reduce the impact of testing fatigue on performance. Participants were asked to complete the neuropsychological tests in the following order: the JEF©, the TOPF, the BICAMS, Key Search and Zoo Maps from the BADS and the verbal fluency test.

The JEF© software was run on a laptop with the 3D state software. Participants were administered the JEF© and the traditional, pen-and-paper neuropsychological test battery according to their respective administration manuals. Participants were given time to practise using the mouse to press the arrows on the screen which control movement and to pick up and move items within the JEF©.

Participants were able to ask for clarification as appropriate. For the JEF© in particular, clarification was given about how to use the mechanics of the system (for example, moving between rooms and picking up objects), however no further information about how to go about completing the tasks was provided.

Data collection was completed by as follows: 18 MS and 12 HC data collected by Laura Clemens (author), 5 HC data collected by Dr Gurpreet Reen (postdoctoral researcher, assisting) and 7 HC data collected by Zoe Mason (undergraduate psychology student, assisting). Both assistants received instruction and training in how to administer and score the neuropsychological tests from the author.

9 Results

All neuropsychological tests were scored according to their administration manuals. Since scaled scores cannot be calculated for the BADS subtests, raw scores for neuropsychological tests have been used throughout. On all neuropsychological tests, higher scores reflect lower levels of impairment. On employment, mood and fatigue questionnaires, higher scores reflect a greater level of difficulties. Standard deviations are presented in parentheses in tables. With the exception of the correlations between composite variables (table 10), all variables are analysed by group, i.e MS and HC.

All data were checked for normality and parametric tests were used where possible. Data were considered normally distributed if Z scores for skew and kurtosis were non-significant at $p \leq 0.01$.

The mean and standard deviation of scores from the HC group from this study were used for the calculation of Z scores for any variable that was standardised in this manner.

As this is an exploratory study with a small sample size, a less conservative p-value of $p \leq 0.05$ was used despite multiple analyses being conducted.

9.1 Group Demographics

A total of 42 participants were recruited for this study - 18 participants with MS and 24 HCs. A summary of demographic data can be found in Table 5.

Table 5: Demographic Information (means and standard deviations where appropriate)

	<u>MS</u>	<u>HC</u>
Total number	18	24
(Women : Men)	(14 : 4)	(13 : 11)
Age (years)	45.33 (9.46)	44.41 (9.26)
Years of Education	15.56 (2.89)	16.29 (2.98)
Estimated Premorbid IQ (TOPF)	104.56 (10.98)	105.60 (10.79)
Years Post Diagnosis	8.33 (5.89)	N/A
<i>Note. *$p < 0.05$, **$p = 0.01$, ***$p < 0.001$</i>		

ANOVAs were carried out to determine if there were significant differences in the demographics of the two groups. The ANOVAs found that there was no significant difference between groups on age ($p = 0.78$), years of education ($p = 0.43$) or premorbid IQ ($p = 0.76$).

There were more women than men in both groups, however this reflects the gender demographics of people with RRMS. A Chi-Square analysis found that there were no significant differences in gender between the groups ($p = 0.11$). 15 people in the MS group were ambulant, two people walked using crutches for aids and one person required the use of a self-propelled wheelchair.

All control participants except one person were in some form of employment. The unemployed participant had last been in work 4 years ago

and took voluntary early retirement. All participants in the MS group were employed or involved in some sort of voluntary work.

9.2 Disease-Related Variables

Table 6: Means and Standard Deviations of MS Related Disease and Psychological Variables

	<u>MS</u>	<u>HC</u>
HADS: depression***	6.22 (4.43)	2.33 (2.63)
HADS: anxiety	7.22 (5.56)	5.08 (3.41)
FSS**	4.81 (1.85)	3.67 (1.72)
<i>Note. *$p < 0.05$, **$p = 0.01$, ***$p < 0.001$</i>		

Means and standard deviations for scores on the HADS questionnaire and the FSS can be found in Table 6. Independent t -tests were carried out and separate variance estimates were used as homogeneity of variance estimates were not met (HADS anxiety: $F = 8.54$, $p = 0.01$, FSS: $F = 9.46$, $p = 0.004$). T -tests found that there was no significant difference between the groups on measures of anxiety, however there was a significant difference between groups on fatigue ($t(24.11) = 4.18$, $p < 0.001$).

HC scores for HADS depression were significantly positively skewed and a Mann-Whitney U test was therefore carried out. This showed that PwMS were significantly more depressed than the HC group ($U = 90.50$, $p = 0.01$).

Although fatigue and low mood could be considered confounding factors, it was decided not to covary these variables as fatigue and low mood are

physical or neuropsychiatric symptoms of MS (Murphy et al., 2017; Wicks et al., 2016). Furthermore, studies have found that subjective reports of cognition in MS are mediated by depression and other psychological factors which is not the case for objective measurements (Bruce et al., 2010; Van der Hiele et al., 2012).

9.3 Neuropsychological Battery Test Scores

9.3.1 The JEF©

Table 7: Means and Standard Deviations of JEF© Scores

	<u>MS</u>	<u>HC</u>
Total Score*	58.40 (14.20)	68.80 (14.90)
Planning	56.50 (25.70)	69.40 (28.80)
Prioritisation	81.90 (24.00)	88.50 (19.50)
Selective-Thinking	70.80 (32.40)	77.10 (28.50)
Creative Thinking*	41.70 (30.90)	64.60 (32.90)
Adaptive-Thinking	51.40 (27.70)	58.30 (31.90)
Action-Based Prospective Memory*	30.60 (31.60)	49.00 (23.90)
Event-Based Prospective Memory	75.00 (19.20)	80.20 (24.40)
Time-Based Prospective Memory	59.70 (34.00)	63.50 (28.50)
<i>Note: All JEF© scores are percentages</i> <i>Total score is the mean of the JEF© subtests</i> <i>*p < 0.05, **p = 0.01, ***p < 0.001</i>		

Means and standard deviations for the JEF© subscales and JEF© Total Score can be found in Table 7. A graphical representation of this data can be found in Appendix II. HC scores for the prioritisation subscale on the JEF©

were significantly negatively skewed. A Log10 transformation on reflected scores was carried out to achieve a normal distribution for the use of parametric tests.

A *t*-test found that the HC group had significantly better JEF© Total Scores than the MS group ($t(40) = -2.26, p = 0.03$).

ANOVAs were carried out on JEF© subscale scores to accommodate testing multiple dependent variables. Homogeneity of variance was not met for the event-based prospective memory subscale ($F = 4.29, p = 0.05$) so separate variance estimates were used and a *t*-test conducted. Out of the eight subscales, significant differences were only seen on the creative-thinking subscale ($F(1, 40) = 5.25, p = 0.03$) and action-based prospective memory subscale ($F(1, 40) = 5.07, p = 0.03$).

The JEF© therefore appears to be able to discriminate between the HC and MS population and is sensitive to deficits as proposed in the first hypothesis.

9.3.2 Executive Function and BICAMS

Table 8: Means and Standard Deviations of Executive Function and BICAMS Tests

<u>Test</u>	<u>MS</u>	<u>HC</u>
BADS: Zoo Maps*	10.56 (3.87)	13.83 (2.85)
BADS: Key Search	13.67 (2.77)	12.58 (2.83)
Semantic Fluency	25.67 (6.20)	22.92 (6.23)
BICAMS: SDMT	52.83 (12.59)	51.79 (12.45)
BICAMS: BVMT-R	22.44 (4.68)	24.38 (5.72)
BICAMS: CVLT-II	53.11 (12.66)	49.41 (10.27)
<i>Note. *$p < 0.05$, **$p = 0.01$, ***$p < 0.001$</i>		

The descriptive statistics for the traditional neuropsychological test battery and the BICAMS can be found in Table 8 above. With the exception of Zoo Maps, ANOVAs found that there were no significant group differences on the executive function test battery, or the BICAMS (Zoo Maps: $F(1, 40) = 10.01$, $p = 0.003$).

9.3.3 Employment and COPE Questionnaires

Table 9: Means and Standard Deviations of Employment and COPE Questionnaires

<u>Questionnaire</u>	<u>MS</u>	<u>HC</u>
MSQ-Job***	87.78 (32.68)	57.86 (18.26)
MSWDQ***	119.83 (49.05)	69.58 (15.83)
Adaptive Coping	36.22 (6.38)	34.13 (5.24)
Maladaptive Coping*	20.06 (4.52)	23.83 (6.40)
Total Coping*	1.00 (1.25)	0.00 (1.62)
<i>Note. Total Coping scores are Z scores</i>		
<i>*p < 0.05, **p = 0.01, ***p < 0.001</i>		

The means and standard deviations for the employment and coping questionnaires can be found in Table 9. Higher scores on the employment questionnaires represent greater levels of work difficulties. Maladaptive Coping and Adaptive Coping scales were created by combining the scores of specific scales on the COPE as outlined in previous studies (for example, Grech et al., 2017). Higher scores on the Adaptive and Maladaptive Coping scales represent greater use of these types of coping strategies.

HC scores for the MSQ-Job were significantly positively skewed. A fractional transformation was carried out to achieve a normal distribution of data. A Total Coping Score was created by converting the Adaptive Coping and Maladaptive Scales to Z scores and subtracting the new standardised Maladaptive Coping score from the standardised Adaptive Coping score as outlined in previous studies.

An ANOVA was initially conducted on MSWDQ and MSQ-Job data. However, separate variance estimates needed to be used for MSWDQ data as homogeneity of variance assumptions were not met ($F = 29.86, p < 0.001$). Therefore, a separate t -test was carried out for this data. There were significant differences between groups on both employment questionnaires ($F(1, 40) = 20.11, p < 0.001$ and $t(19.67) = 4.19, p < 0.001$ for the MSWDQ and MSQ-Job respectively), with PwMS consistently reporting a greater number of work difficulties.

There was no significant difference between groups on the Adaptive Coping scale ($p = 0.25$), however an ANOVA showed that the HC group used significantly fewer maladaptive coping strategies in comparison to the MS group ($F(1, 40) = 4.56, p = 0.04$). A t -test found that the MS group had better overall coping strategies ($t(40) = 2.18, p = 0.04$).

PwMS scored higher on Total Coping- as this score reflects the combination of both maladaptive and adaptive coping styles, this may be explained by PwMS using fewer maladaptive coping strategies.

9.4 Relationships between Executive Function, Employment and Coping

A composite score for the traditional executive function tests was created by converting the raw scores of the individual subtests to Z scores which were then added together (Executive Function Index). A composite score for the employment tests was created in the same way (Employment

Index). Pearson's correlations were carried out to assess the relationship between the Executive Function Index, Employment Index and Adaptive, Maladaptive and Total Coping scales. Pearson's correlations were also carried out to establish if there was a relationship between the JEF© Total Score, Executive Function Index, Adaptive, Maladaptive and Total Coping Scales. Participants were not separated according to group for these correlations. The results of these correlations can be found in Table 10 below. Only significant relationships will be discussed further.

Table 10: Correlations between JEF© and Executive Function Index and Coping Scales

	JEF© Total Score (<i>r</i>)	Executive Function Index (<i>r</i>)	Fisher's <i>r</i> to <i>z</i> ratio (<i>z</i>)
Executive Function Index	0.65***	-	-
Employment Index	-0.32*	-0.15	-0.8
Maladaptive Coping	-0.04	-0.18	0.63
Adaptive Coping	0.32*	0.38**	-0.3
Total Coping	0.25	0.38**	-0.64
<i>Note: N = 42</i> <i>*p < 0.05, **p = 0.01, ***p < 0.001</i>			

There was a significant, moderate correlation between the JEF© Total Score and the Executive Function Index which suggests that the JEF© is able to measure and assess executive function. There was also a weak, but

significant negative correlation between the JEF© total score and Employment index. However, there was no significant relationship between the Executive Function Index and the Employment Index. A Fisher's r to z calculation found that there was no significant difference in the strength of these correlations. Therefore, it is not possible to accept the second hypothesis that the JEF© is more closely correlated to employment outcomes in comparison to the traditional neuropsychological tests used.

There were weak, significant correlations between both the JEF© total score and the Executive Index and the Adaptive Coping Scale. A Fisher's r to z transformation was carried out to ascertain if there was a significant difference in the strength of any of the correlations including coping variables, however this returned a non-significant result for all variables. It is therefore not possible to accept the third hypothesis, that the scores from the JEF© would be more strongly correlated to coping styles in comparison to the traditional neuropsychological tests.

10 Discussion

10.1 Summary of Relevant Findings

A cross-sectional study was conducted to investigate whether the JEF© device is able to detect difficulties in executive function in the MS population and to find out how this compared to traditional, pencil and paper methods of executive function.

As the JEF© aims to be an ecologically valid assessment of cognition it was also decided to see if there were relationships between the scores of the JEF©, employment outcomes and coping styles – both of which have been shown to be related to executive function within the MS population (Grech et al., 2017b; Honarmand et al., 2011; Jansari et al., 2014; Morse et al., 2013; Van der Hiele et al., 2015).

18 participants with MS and 24 healthy controls were recruited who were matched on all demographic variables and anxiety but not low mood or fatigue which are common symptoms of MS. There were no significant differences between the MS and HC group on BICAMS measures which assess cognitive domains frequently affected in MS. This may be due to the recruitment criteria and/or sample size of the study.

PwMS who are employed frequently out-perform their unemployed peers on measures of cognition (see section 5.1, p. 70 for further details). It is therefore possible that the sample of this study represents a selection of PwMS who are less severely impaired by the condition by virtue of their being

in work. Nevertheless, PwMS who are employed often perform worse in cognitive testing than a healthy control population. It may be that the small sample size of this study meant that there was insufficient power to detect this difference.

10.1.1 Hypothesis 1

The first hypothesis stated that the JEF© would be sensitive to deficits in executive function in the MS population. Although there were no significant differences between groups on several of the JEF© subscales (namely: planning, prioritisation, selective-thinking, adaptive-thinking, event-based prospective memory and time-based prospective memory), there were significant between group differences on JEF© total score, creative thinking and action-based prospective memory. The only traditional executive function test which showed differences between the HC and MS group was Zoo Maps. This may be explained by the test already being considered to be ecologically valid (Wilson et al., 1996).

The JEF© Total Score was also correlated with the composite score of Executive Index. This found that there was a moderate, positive significant relationship between the JEF© and existing executive function tests. This provides further evidence which suggests that the JEF© is indeed assessing executive function.

Taken together, these results would suggest that the JEF© is sensitive to executive functioning within the MS population as initially predicted.

10.1.2 Hypothesis 2

The second hypothesis stated that the JEF© would be more strongly correlated to employment outcomes than traditional neuropsychology tests. Correlations between the composite Employment Index, the JEF© Total Score and the Executive Function Index were carried out.

There was a weak, but significant negative correlation between the JEF© and the Employment Index where greater levels of work difficulty were associated with poorer total score on the JEF©. There was no significant relationship between the Executive Index and the Employment Index. Fisher's r to z calculations were carried out to determine if there was a significant difference in the strengths of the correlations between the Employment Index composite and the JEF© total score or Executive Index composite and returned non-significant results. Therefore, the second hypothesis that the JEF© is more strongly correlated to employment outcomes than the existing executive function tests cannot be supported by the outcome of this study. Power calculations outlined in section 8.3 (p.91) indicated that 66 people in each group would be needed if there was a large effect size. Unfortunately, this was not achieved and the actual power for this analysis was 0.13. It is therefore unclear as to whether no difference in the strength of these correlations was found due to not having enough power or because there is no actual difference between the populations.

10.1.3 Hypothesis 3

The third hypothesis stated that the results of the JEF© would be more strongly correlated to coping styles in comparison to existing neuropsychological tests.

Correlations were carried out between the three coping subscales: Adaptive Coping, Maladaptive Coping and Total Coping, JEF© Total Score and the Executive Function Index.

There were no significant correlations between Maladaptive Coping and JEF© Total Score and Executive Index. A significant, weak correlation was found between Total Coping and the Executive Index, but not between Total Coping score and the JEF© Total Score. There were significant, weak positive correlations between both the JEF© Total Scale and Executive Index and Adaptive Coping. A Fisher's r to z transformation was carried out to assess whether there was a significant difference between these correlations, however none was found.

The impact of having a small sample and subsequent power achieved cannot be discounted as a reason for not finding significant differences in the strength of these correlations. The power achieved for the Fisher's r to z transformation the coping variables are as follows: for Maladaptive Coping, the power achieved was 0.10. The power achieved for Adaptive Coping was 0.06. The power achieved for Total Coping was 0.10.

Taken together, the results indicate that the JEF© Total Score is not significantly related to Maladaptive Coping Styles, or Total Coping. Although

the JEF© Total Score and traditional executive function battery are both significantly related to Adaptive Coping styles, results are inconclusive as to whether there is a significant difference in the strength of these correlations due to the low level of power achieved for the Fisher's r to z transformation, therefore Hypothesis 3 cannot be accepted.

10.2 Relationship to Existing Literature

This study adds to the existing body of literature about the JEF© which shows that it is sensitive to deficits in executive function in clinical populations such as frontal lobe brain injury and acquired brain injury. It also adds to the evidence showing the JEF© to be capable of detecting deficits which may not be found in the performance on other traditional executive tests, such as the Stroop (Denmark et al., 2017; Jansari et al., 2014, 2013, Montgomery et al., 2011, 2010; Soar et al., 2016).

The results further highlight the need for the use of ecologically valid tests which also have a high level of experimental control for clinical and research settings (Chaytor & Schmitter-Edgecombe, 2003). This is one of the 2 studies which compares data from the JEF© against subtests from the BADS, an ecological valid battery which is well used in clinical practice (Wilson et al., 1996).

Reports of executive function (assessed on conventional tests) affecting employment are patchy in the MS population, with some studies finding significant differences between groups whilst others not finding any. These

results provide support to the theory that difficulties with executive function seen in MS are related to negative work events. Similar results have been found by Van der Hiele and colleagues (2015), Morse and colleagues (2013) and Honarmand's group (2011).

As previously mentioned, executive function is not a singular construct. Instead it is an umbrella term used to describe a series of complex cognitive abilities needed to successfully carry out goal-orientated behaviours (Miyake et al., 2000). It may therefore be necessary to ensure that these different subcomponents are adequately assessed in research make sure a thorough understanding of how executive function as a whole affects employment in this population. The JEF© is a more comprehensive assessment, evaluating many aspects of executive function. It takes approximately 40 minutes to complete, which is a similar length of time to the BADS, and therefore could be feasibly used in a clinical setting to assess several aspects of executive function in the same amount of time, or less, than a traditional executive function battery.

An unexpected finding was that people in the Healthy Control group used more Maladaptive Coping strategies in comparison to the MS group. It is possible that PwMS who are able to remain in employment represent a subgroup who use more Adaptive Coping strategies in order to manage the difficulties that accompany their diagnosis, including difficulties with employment. On the other hand, healthy individuals who do not have to manage the stresses which come with a chronic health condition may be able to utilise more maladaptive coping strategies with less negative effects.

10.3 Limitations

10.3.1 Neuropsychological Measures

One of the limitations of this study is that only two subtests from the BADS were used rather than all six subtests. This meant that it was not possible to calculate scaled scores for the BADS as this requires the profile scores of all six subtests.

This difficulty was side-stepped by using raw scores for all the tests rather than scaled scores. However, the subtest profile scores take into account the length of time taken to complete the task – successfully or otherwise. This means that whilst two people might both score the maximum number of raw score points on Zoo Maps and Key Search, they may have different profile scores. This subsequent profile score would reflect not just performance, but how effortful the individual may have found the task. Furthermore, using total profile scores would have meant that it would have been possible to calculate individual standard scores which would have accounted for age as well as effort.

Although there were no significant differences in the mean ages of the two groups, it is worth noting that the youngest participant in the HC and MS group were 29 and 30 respectively, and the oldest participants were 55 and 62. Despite obtaining the same profile score on the BADS, there could have been a difference of 10 standard points between the 29 year old and the 62 year old participants (Burgess, Alderman, Evans, Emslie, & Wilson, 1998).

In addition, whilst the JEF© may simultaneously measure different components of executive function, the traditional neuropsychological measures used do not reflect the full range of executive functions. For example there is no test which assesses cognitive set-shifting or mental flexibility, such as the Sorting Task or Trail Making from the Delis Kaplan Executive Function System (DKEFS) (Delis, Kaplan, & Kramer, 2001).

A more robust selection of tradition executive function measures which are able to produce age or standardised scores for comparison against the JEF© would improve this research.

10.3.2 The JEF©

One of the limitations of the JEF© is that it requires the participant to read out loud after the in-program timer has started. This is a particular problem as the participant needs to take note of a fire-alarm which sounds 5 minutes into the task. On occasion, it was noticed by the administrator that people had not finished reading the list of instructions as required when this first alarm went off. There is a possibility that a person did not hear the alarm as they were speaking over the top of the noise. Depending on the individual's reading speed, there may even be a possibility that they have not reached the instructions regarding the fire alarm and therefore ignored it. Conversely, people who are able to read aloud quickly may come to the end of this task ahead of time, thus allowing them more time to plan and proceed with the rest of the test.

There is, therefore, a potentially undesirable effect of reading speed on performance. An improvement may be to start the in-program timer *after* the participant has finished reading their list of tasks and instructions. This is similar to how Zoo Maps is administered, where the participant reads aloud the instructions and receives clarification *before* timing begins.

Ceiling effects on the JEF© are another limitation of the test which needs to be considered. On three subtests, prioritisation, selection and event-based prospective memory, over 50% of participants in the control group managed to score 100%. Similarly, 55.6% of people in the MS group were also able to score full marks on the prioritisation subscale. It is therefore difficult to know whether ability on these subscales has been accurately measured (Salkind, Frey, Dougherty, Rasmussen Teasdale, & Hill-Kapturczak, 2010).

10.3.3 Sample and Recruitment

As previously mentioned, it was not possible to recruit the number of participants needed to have a power of 0.8. Whilst previous studies using the JEF© have been able to see an effect similar to those reported in this study (Denmark et al., 2017; Jansari et al., 2014; Montgomery et al., 2012), it is necessary to mention that this study was under powered, particularly for the analyses needed to investigate Hypothesis 3. However, the effect size was sufficient to demonstrate a difference on Total JEF© Score between groups.

It is important to consider how representative the sample in this study in comparison to the general population. Firstly, participants who took part, primarily lived in London and the South East which could have resulted in a more biased demographic.

Secondly, the MS group was comprised solely of people who reported having RRMS, therefore leaving out two thirds of the MS subtypes. Although RRMS is the most common subtype of MS, excluding the other two main subtypes means that the disease as a whole is not represented in this study. On one hand, this is an exploratory pilot study and it is necessary to reduce the impact of differences in disease and demographic variables on the results. There is evidence that the cognitive and disease profiles of the progressive subtypes of MS are significantly different to those seen in RRMS which supports the decision to exclude two subtypes (Dickens et al., 2014; Ntoskou et al., 2018; Ruet, Deloire, Charre-Morin, Hamel, & Brochet, 2013). However, it is possible that the outcome would not be the same if people with SPMS and PRMS were included and therefore results should not be generalised to the other two subgroups.

Furthermore, given that this is a cross-sectional study, it is not possible to determine causality and the possibility of employment difficulties leading to cognitive impairment cannot be excluded. It should also be mentioned that the effects of fatigue and depression on cognitive performance cannot be eliminated as confounding factors in this study.

Participants with MS were recruited via MS charity websites and through advertising at MS Therapy Centres. MS Therapy Centres are standalone

charity organisations which provide complementary therapies such as physiotherapy, oxygen therapy and counselling. They also allow people with MS to access peer support. It is not mandatory for people with MS to access these centres and they may not be as easily accessible as more local NHS MS clinics.

Recruiting from MS websites and their associated social media platforms also means that adverts may not have reached people who are less technologically literate or choose not to use social media for various reasons. Therefore, the population from which the sample was taken may not be representative of the wider MS population.

Since participants were not recruited from the NHS, it was not possible to confirm that they had a diagnosis of clinically definite RRMS using neurology reports or to have access to health records to confirm that they did not have other conditions which may have excluded them from testing, despite having checked this verbally with participants during screening.

In addition, information regarding employment difficulties was gained through self-report questionnaires only, and there were no external or objective reports of performance at work.

Another limitation is that no tests were carried out to assess sensorimotor difficulties, such as visual acuity or motor functioning which are areas that are frequently affected by MS (Wicks et al., 2016). These are also problems which could affect using the JEF© in a practical manner as it requires sustained viewing of a computer screen and the use of a mouse or

mousepad. However, the author has considerable experience as a clinician and researcher and closely monitored the level of sensorimotor difficulties to minimise these confounds.

10.4 Clinical and Research Implications

This study was an exploratory study which aimed to pilot new technology in this clinical group. It has provided further support to the theory that cognitive difficulties, including executive dysfunction, negatively impact employment outcomes for people with MS. The results of the employment questionnaires also demonstrate that people with MS report experiencing a greater number of work difficulties in comparison to the general population. It adds weight to the need to continue to research this area so that people with MS who want work can continue to do so. Nevertheless, there were some difficulties which arose from the design of the study and future studies should aim to mitigate these as much as possible in order to ensure that difficulties observed are due to executive dysfunction and not unfamiliarity with the JEF© program and its interface.

Although fatigue over the preceding week had been measured, state fatigue was not taken in to account on the day. Nor were participants formally asked about how anxious they felt in using a new software programme, although participants were provided with appropriate reassurance if they expressed any anxiety at the thought of being assessed or using the programme. Replication of this study should include measurement of state

fatigue and anxiety. This could be achieved by asking participants to subjectively rate how fatigued they felt on the day and how anxious they felt at using the test. If participants rated themselves as being highly anxious they could have been invited to do some breathing exercises or progressive muscle relaxation until they could report a reduction in how anxious they felt.

Future research should also include a way to ensure that participants have sufficient practice so that they are competent and well adapted to the JEF© program to ensure that difficulties which arise are due to executive dysfunction and not problems with using new software with an unfamiliar interface.

Subsequent research could focus on replicating this study with a larger sample size, a more extensive battery of ecologically valid executive function tests, and tests which are less ecologically valid, but which assess other subcomponents of executive function. Objective reports of work performance could also be gathered from a participant's colleague or employer to add to the self-reported information from employment questionnaires.

Following this, the study could be broadened by extending the inclusion criteria to allow for all subtypes of MS. Results could be analysed both by individual subtypes as well as a mixed sample. Recruiting from multiple NHS sites as well as from third sector agencies would access more people who might be more representative of the MS population. As well as allowing for confirmation of MS diagnosis, it would also be an opportunity to investigate whether the JEF© can be used effectively in a clinical setting.

There was anecdotal feedback from participants stating they felt that the difficulties they faced completing tasks during the JEF© test reflected real life difficulties they experienced at work and at home. It would be interesting to see if this is shared experience. A mixed methods qualitative and quantitative approach could be used to investigate this, both within the MS community, and other clinical populations. Due to potential difficulties with insight into deficits, it may be helpful to have a reliable informant present when the participant is completing the JEF© so they can also provide feedback.

As the results show that executive function difficulties are related to negative work outcomes, it may be beneficial for psychologists to include executive function tests, particularly ecologically valid tests such as the BADS, as part of their assessment to see whether there are any difficulties in this domain. This would allow clinicians to be able make recommendations regarding work accommodations that could be implemented.

11 Conclusion

This study found that the JEF© is capable of assessing executive function for people with RRMS and is able to discriminate between them and a healthy control population. This was also the case for the Zoo Maps test, but none of the other tests of executive function.

There was a significant difference in reported work difficulties experienced, with people with MS reporting a greater number of problems in comparison to the control sample.

There was a correlation between the work difficulties experienced and scores on the JEF©, which suggests that the executive function difficulties detected are relate to real world consequences.

Whilst there were significant correlation between the Total JEF© score, the Executive Index and adaptive coping, there was no significant difference in the strength of these correlations.

The utility of ecologically valid tests of executive function are highlighted by the results of this study. Further research could focus on replicating the results with a larger sample size, as well as a mixed group of PwMS and a more robust traditional executive function battery.

12 Paper 3: Integration, Dissemination and Impact

12.1 Integration

This thesis has a strong focus on how cognition is linked to work difficulties in Multiple Sclerosis (MS). The systematic review was chosen to give a broader overview and understanding of the relationship between cognition and employment within this population. The findings of the review were very consistent. People with MS (PwMS) who were unemployed performed poorly in cognitive tests in a number of domains in comparison to PwMS who managed to remain in some form of employment. In addition, PwMS who were employed were still out performed on these tests by healthy control groups.

Significant group differences were not seen in every cognitive domain, for example attention-concentration. However, deficits were seen in several cognitive domains, such as delayed memory recall, immediate memory recall and information processing speed as well as executive function. However, a significant impact of executive dysfunction on negative work events or unemployment was not consistently found amongst the studies which assessed this area. A relationship between the executive functions of idea generation and set shifting and employment was seen.

The inconsistent relationship between outcome on traditional executive function tests and employment served as further basis for the empirical study, which could add to the body of literature about the role of executive function in

employment. The empirical study, using the Jansari Assessment of Executive Function (JEF©), also built on the literature by including more ecologically valid measures of executive function - only one study in the systematic review included ecologically valid measures of executive function, namely Zoo Maps and the Modified Six Elements Test (Morse et al., 2013).

The results of the empirical study were in line with the results of the systematic review. Namely, that there is a relationship between executive function as measured by the JEF© and negative work events. Whilst there was a between group difference on the JEF© Total Score, there was also a between group difference seen on the subscales of Creative thinking and Event-Based Prospective Memory. It is possible that differences in these areas are similar to the differences found in set shifting and idea generation in the systematic review.

Creative thinking involves finding solutions to problems using unspecified methods, whilst Action-Based Prospective Memory requires the participant to remember to take action after a specific stimulus. It is possible that these subscales are analogous to idea generation and set shifting. Creative thinking on the JEF© involves unprompted idea generation, whilst Action-Based Prospective Memory requires cognitive flexibility in order to move between tasks successfully.

The results of the systematic review and empirical study, therefore provide a coherent narrative regarding the relationship between cognitive impairment in MS and workplace difficulties and employment outcomes.

12.1.1 Challenges and Improvements

Despite the successful outcome of the empirical study, its final design was not its original incarnation. The challenges and difficulties are described below, as well as potential improvements that could have been made.

12.1.1.1 Test battery.

It was initially hoped that a larger test battery, which included more ecological tests of executive function, would be administered. This would have included the remaining subtests from the Behavioural Assessment of Dysexecutive Syndrome Battery (BADS) – Rule Shift Cards Test, Temporal Awareness, Action Programming and The Modified Six Elements Test. It would have also used the Sorting Task from the DKEFS as an additional measure of cognitive flexibility and idea generation. However, this would have extended the battery to 2.5 hours which may have led some people to become fatigued. Given that fatigue is a symptom of MS, it was important to consider how and if people would manage a long battery of neuropsychological tests. It was therefore decided to reduce the test battery so that it could be completed in 2 hours which is typical of other studies assessing cognition in MS.

In fact, it was frequently the case that whilst the healthy control population was able to complete the study in two hours, people with MS took longer - this may be due to difficulties with information processing speed seen in this population. In hindsight, a pilot version could have been carried out to

get a more accurate idea of how long the test battery would take and to get feedback from participants as to whether it was manageable or whether they felt fatigued by the process. I would also build in breaks between participants to provide a buffer in case a participant was particularly slow so that the next participant could be seen promptly.

One way of overcoming the issue of fatigue might have been to conduct testing over two separate sessions. However, this would have required more time and was not feasible and within the scope of a Clinical Psychology research project. Furthermore, trying to access a population who are still in employment meant that it was difficult to find time the individual would be able to spare, unless self-employed or had flexible working hours. Whilst this was managed with a single 2-hour testing session, people may have been less willing to participate with a greater time commitment.

The test battery did not include tests of visual and contrast acuity or tests of motor function which are areas often affected by MS, but which could also affect how an individual was able to use the JEF©. An improvement would be to include appropriate tests, such as the Nine-Hole Peg Test or the Snellen Test. The Nine-Hole Peg Test is a measure of arm and hand function where the individual is required to place nine pegs into holes as quickly as possible. It is frequently used for clinical and research purposes in the MS population and forms part of the Multiple Sclerosis Functional Composite measures (MSFC) (Fischer, Rudick, Cutter, & Reingold, 1999). The Snellen Visual Acuity test requires people to read a series of letters at a distance of 6m and is well used by opticians and ophthalmologists. In addition, the Multiple

Sclerosis Vision Test Battery could be used to assess contrast acuity (Bullimore, 2016).

12.1.1.2 Recruitment.

Recruiting from websites meant that there was no way to risk assess participants prior to meeting them and all testing needed to be carried out in a public space. For this reason, testing took place either at Senate House Library or Royal Holloway. However, not being able to have more flexible or local testing sites may have limited the level of interest that was generated.

One participant mentioned that a friend with MS had wanted to take part but had been put off by the need to come into Central London. If it had been possible to recruit from the NHS as planned, MS participants would have been given the option to do the study at home as discussions could have taken place with their MS nurse or team regarding any risks they were aware of.

On one hand, it is difficult to guarantee that a participant will have an environment that is suitable for testing, despite making explicit requests, as I have noticed doing cognitive testing in my clinical role, however offering the possibility of a home visit might have allowed more people to take part. Still, this would have not resolved the problem of having people who were from a specific geographical location.

12.1.1.3 *The JEF©.*

12.1.1.3.1 Medical device status.

The nature and use of the JEF© frequently posed a number of challenges for this project. Whilst applying for proportionate ethical review by HRA, it was brought to our attention that the JEF© was actually considered to be a medical device. The formal definition of a medical device is “an instrument, apparatus, appliance, material or other article, whether used alone or in combination, together with any software necessary for its proper application, which is intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease” (“Medical Device Regulation 2002,” 2002). The creator of the JEF© reported never having encountered this problem in the past. Since the JEF© has no CE marking it was not eligible for proportionate review and full HRA and REC ethics was sought. This led to some delay with starting recruitment.

Whilst the study went through HRA and REC review without issue, the NHS trust originally approached felt the study could not be considered “in-house” despite involving a member of staff as a supervisor and that the JEF© would need to get a CE marking. It was eventually decided to recruit participants through MS Therapy Centres and Charities rather than through the NHS. The need to obtain CE marking for the JEF© for use in NHS setting was also brought to the attention of its creator.

12.1.1.3.2 *Difficulties using the program.*

There were several difficulties noted in using the program. One of these is related to its interface and how people move around, pick up and put down objects in the system.

Whilst many people were able to use the program without difficulty following the initial instructions, other people did struggle to use the interface. Since computer and technological literacy is not being assessed by the JEF©, it is important to have a design which is simple enough for an individual with little or no computer experience to use. However, the method of moving around, that is clicking directional arrows on the screen, is different to how people are currently accustomed to moving around in games or programs such as “Google Maps”. In these programs, people are able to use a “double-click” function to move to where they want to go, and people often tried to do this on the JEF©.

In addition, the left and right arrows serve to change the field of vision left and right, rather than moving the individual laterally in that direction. In effect, clicking the left and right arrow keys in the JEF© is similar to turning left and right on the spot in real life. Again, people found this challenging given that it is somewhat counter-intuitive to how we expect to use arrows to move around in other programmes and games. On two occasions, participants became “stuck” in the door and were unable to leave the office or move anywhere else. As this was early on during testing, it was possible for the programme to be restarted, however this would not have been feasible later in the assessment.

Similarly, the movement of objects in the JEF© is unlike how an individual would expect to move objects within a computer programme. Although, the individual is given instructions and specifically told not to “click and drag” objects, people frequently did this by accident and appeared to be having to inhibit well learnt responses. This posed further difficulties as objects sometimes “disappeared” when a participant accidentally tried to drag it. This problem broke the illusion of the “semi-immersive” experience.

Whilst this was not a problem if a non-essential item disappeared, it was more problematic if it was an item crucial for completing a task. For example, losing one of the virtual memos is of very little consequence as the participant has a hard copy on the table with more information on it than the virtual memo. However, losing either of the overhead projectors means that the participant is unable to either switch on the project or replace the broken one with the spare. When this happened, the assessor had to ask the participant what they were planning to do with the object. This also meant that the assessor had unintentionally indicated whether a particular item was important.

One of the participants brought to my attention the fact that there are no large print versions of the instructions, memos and paper tasks. As previously mentioned, difficulties with visual acuity are a problem for people with MS, however this issue may be encountered with other populations, or simply with people who do not have good eyesight.

These problems could be overcome by creating an update for the JEF© software to reflect how we currently use technology in 2018, for example

using a “click and drag” function to move objects and a “double-tap” function to move the individual around in the virtual space. In addition, coding the software in such a way the objects cannot disappear if the participant makes a mistake. It may also be helpful to have a way to measure how well participants are able to use the interface before starting the assessment. Perhaps with a few practice tasks which simply require the participant to move objects and navigate around the environment. The actual assessment would begin once participants were able to achieve these tasks in an optimum number of mouse clicks.

12.1.2 Personal Reflections

Although this was a challenging undertaking, I found this topic to be incredibly thought-provoking and stimulating. I have long been interested in the use of technology as a method of research and clinical assessment of psychological phenomena or difficulties. My undergraduate research involved using a computer program to assess differences in perception of 3D objects and faces. My Master’s research project involved administering the computerised human adaptation of a mouse battery originally designed to investigate fear, in a population who reported having difficulties with anxiety. This project has been a fascinating opportunity to see how technology can be used in both a research and potentially clinical capacity.

Aside from gathering data, I also provided teaching and training to two members of the research team in how to run and administer the JEF© as well

as the neuropsychological battery. I first taught the undergraduate student and upon reflection was struck by how quickly I had become familiar with the test materials, something that was developed both through this project but also my clinical placement.

Whilst I thought that the administration of certain tasks was fairly straightforward, I had to be reminded that this was not the case for people who had little experience of using neuropsychological tests. I was then more careful to explain things more thoroughly as needed. This experience encouraged me to reflect on the idea of becoming an “unconsciously competent” practitioner, both as a researcher and a clinician, and the amount of learning I have done over these two and half years of training. Overall, I enjoyed working as part of a team with the data collections assistants and were I to do this study again would definitely consider including more assistants.

One of the difficulties I encountered with testing, was trying to balance the need to build rapport for administering the tests and questionnaires with the need to move the patient quickly and efficiently through the test battery. Participants often wanted to clarify their responses on questionnaires or tell anecdotes related to their experiences of employment. Whilst on the one hand, I hoped that engaging in some of these conversations would serve to build rapport, facilitate engagement and convey to the individual that their participation was valued, I was also acutely aware that this might affect punctuality, making me late in seeing the next participant.

Whilst this something that I occasionally struggle with in clinical practice, it felt more marked and difficult to manage in my role as a researcher. In my clinical practice, clients would have been encouraged to adhere to the task and reassured that there would be an opportunity to share this information at a later date. However, I was aware that there was no other opportunity for this in this study and “cutting off” participants who were volunteering their time felt uncomfortable and invalidating of their experience and effort.

As I tested more participants, I learnt from this experience and as part of the introduction would inform them that there was a lot to get through and that there may be occasions when I would need to move through subtests quickly in the interest of time. This seemed to be received well by the participants.

During this project I attended a pop-up event in London organised by Shift.MS, an online charity who had agreed to help with recruitment. The event, held in Shoreditch, was very different to what I expected and was an eye-opening experience into the variety of charity events available to people with MS. The event clearly catered to a young, urban demographic of people with MS and the positive response and turn out showed me the importance of having a variety of charities and organisation which could cater for the different sub-groups of people with MS.

The event included the premier of a short video called “The Commute”. This video followed three people with MS on their routes to work in various parts of the country. It was also a great experience to hear some real-life, qualitative accounts of the difficulties people with MS experience with regards to employment, as well as why they felt it was important to remain employed

some of which I had not considered. For example, one man spoke about how he hoped remaining employed would be a symbol of resilience in the face of adversity to his children.

I used the event as an opportunity to reflect on my own thoughts and beliefs around employment and whether it was something I take for granted. This thesis and the degree in general have been challenging experiences, and at times it has been hard to find pleasure in it. Nevertheless, being amongst people who felt uncertain about their own careers and employment future made me realise how unhappy I would feel if I felt forced or unable to continue working and allowed me to empathise with their experience.

Attending this event reminded me that neuropsychological data is only one part of formulating why a person with MS may end up leaving employment, of the importance of listening to the person and their narrative and considering the impact of other difficulties such as mental health.

The reasons for remaining in employment presented in the video also made me consider the variety of reasons why someone with MS may choose to leave work. During the development of the project, service users were asked to provide their feedback about its design. One service user acknowledged that employment was important for some people, but also expressed his concern that this research, and similar studies, could be used to coerce people with MS into remaining employed. These experiences highlighted the need for a person-centred approach when working clinically, and that perhaps employment is used as a clinical indicator only if the client considers it to be an important value.

12.2 Dissemination

A presentation of the research has already been delivered to Trainee Clinical Psychologists at Royal Holloway in May 2018.

It is hoped a shortened version of the systematic review will be published in a peer reviewed journal. At this point it is anticipated that the paper will be submitted to the Journal of Multiple Sclerosis and Related Disorders (MSARD). This journal was chosen as it is an international journal which aims to publish a variety of articles including reviews, in order to teach and enhance the practice of clinicians, including psychologists, who are involved in the care of people with MS. The journal also provides summaries of key articles in a way that is accessible to a lay audience and had an impact factor of 2.35 in 2016. If the review is not accepted by this journal, then an alternative publication with a similar audience and impact factor will be approached.

It is anticipated that the empirical report will be published in Neuropsychological Rehabilitation. This is the same journal which published a paper on the JEF© with participants with acquired brain injury and focal frontal lobe lesions (Denmark et al., 2017; Jansari et al., 2014). The journal had an impact factor of 2.80 in 2016 and aims to publish material on experimental and clinical research related to neurorehabilitation and neuropsychological assessment. Previous papers published on neuropsychological research in

this journal include studies regarding the development of the BADS (Norris & Tate, 2000; Wilson et al., 1998). Similarly, if the report is not accepted an alternative journal with a similar readership and impact factor will be approached.

A brief summary of the empirical article will also be sent to the MS Therapy Centres and MS charity websites which provided support with recruitment. These organisations would be encouraged to publish these reports in a newsletter which could be circulated to their members.

Several MS Therapy Centre staff members pointed out that that their service users found it disheartening when they took part in research but did not hear anything about the results or see how it impacted their care or the understanding of their difficulties.

Hearing feedback of results seems to be important for people with MS - in fact all participants with MS indicated on their consent form that they would like to have a summary of the results sent to them once available. Participants from the MS group will therefore receive a one-page summary of the results which will have more references to specifics of the program as they will be more familiar with it.

A longer article, which will aim to encourage discussion around this topic, will be co-written with a service user with MS and published on an appropriate charity website such as Shift.MS. Collaborating with a service user will ensure that information that service users consider relevant is shared and that it is written in an accessible format for a lay audience. Shift.MS

currently have a plan to carry out and disseminate research on employment in MS over the next 18 months. It is possible that the empirical research undertaken as part of this thesis would complement the existing research they have and provide additional information about the role of executive function and cognitive impairment more generally in employment difficulties.

12.3 Impact

As a result of the plan for dissemination described above, it is hoped that this thesis will lead to further research and development of ecologically valid tools for the assessment of cognition across a variety of populations, and that these tools will be available for use in clinical practice. The empirical study has demonstrated that ecologically valid tests are able to detect difficulties which may not be found when using less ecologically valid measures of executive function, such as the Stroop Test (Chaytor, Schmitter-Edgecombe, & Burr, 2006). This outcome may encourage clinicians to use ecologically valid tests as part of their assessment batteries more routinely.

This is the ninth study to use the JEF© in research and it is hoped the outcome of this study will contribute to its development and use as a neuropsychological assessment tool within clinical populations. Suggestions have been made regarding how to improve the interface and these could be shared with its creator to see if this is the first time these problems have been encountered, whether suggested changes could feasibly be implemented or

whether alternative solutions could be found. The positive results of this study also provide further support for the use of virtual reality to assess cognition.

Approximately 50% of PwMS with low levels of physical disability are unemployed across Europe, resulting in significant individual and societal costs (Kobelt et al., 2017). It is a subject that therefore warrants further investigation in order to reduce the negative impact caused. To the best of my knowledge, the systematic review is the first which investigates the link specifically between objective cognitive ability and employment outcomes in MS. Hopefully the outcome of the review will provide information which new researchers could use as a base for understanding and exploring the literature and be an informative synthesis of information for more experienced researchers and clinicians working with PwMS.

Furthermore, it is hoped that additional evidence of the relationship between cognition and work outcomes for people with MS will encourage policy makers to consider what steps they could take to ensure that PwMS can remain in employment for as long as they choose. This may include creating or strengthening initiatives that provide businesses with the means to acquire or implement accommodations which would help people with MS stay in work.

Ensuring that this research is appropriately disseminated to service users means that the knowledge will be held by people who are already campaigning for changes to policy. This will hopefully be achieved not only through collaborating with service users to write an article specifically for PwMS, but also through disseminating this information in an accessible

manner to service users who may not have considered the potential impact of cognitive changes on their employment. It is hoped that this will lead to increased awareness of the challenges faced by people with MS within the general population, as publication on websites with social media links may reach people who know very little about the disease. Increased awareness may result in more support for this group to gain the tools it needs to reduce the impact of cognition on employment.

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14 Appendices

14.1 Appendix I: Questionnaires

14.1.1 Multiple Sclerosis Work Difficulties

Questionnaire (MSWDQ)

Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ)

Instructions

People with MS often experience difficulties in the workplace that are either directly or indirectly related to their symptoms. The following questions describe several difficult or problem situations that a person with MS may encounter at work. Please circle the appropriate response (0, 1, 2,...) based on your everyday experience over the last four weeks in your current or most recent job. Please answer every question, and if you are not sure which answer to select, please choose the one that comes closest to describing you.

During the past four weeks whilst working in your current or most recent job, please indicate how frequently you experienced the following as a result of your MS.

	Never	Rarely	Sometimes	Often	Almost Always
1. I felt that I had to work because of my financial position	1	2	3	4	5
2. I hesitated to proceed on an everyday task	1	2	3	4	5
3. I experienced a lack of coordination with my movements	1	2	3	4	5
4. I felt social isolated	1	2	3	4	5
5. I thought that my employer was not very understanding of my needs	1	2	3	4	5
6. I forgot about a deadline I had to meet	1	2	3	4	5
7. I felt I was not appropriately recognised for my work	1	2	3	4	5
8. I found it difficult to learn something new	1	2	3	4	5
9. I found it difficult to use my hands	1	2	3	4	5
10. I had problems with walking	1	2	3	4	5
11. I thought that my manager or work colleagues were not	1	2	3	4	5

supportive of me					
12. I felt that I was not valued by my work colleagues	1	2	3	4	5
13. I feared that I might be too tired to deal effectively with others	1	2	3	4	5
14. I felt that disturbances in my bowel or bladder function distracted me from doing a task	1	2	3	4	5
15. I experienced difficulties getting to and from my workplace	1	2	3	4	5
16. I had trouble remembering something I recently read	1	2	3	4	5
17. I thought that work was interfering with my home responsibilities	1	2	3	4	5
18. I needed to be reminded to do a task at a particular time	1	2	3	4	5
19. I forgot to do a task that someone asked me to do	1	2	3	4	5
20. I felt that I could not perform to the level that was expected of me	1	2	3	4	5
21. I found it difficult to tolerate the temperature at work	1	2	3	4	5
22. I feared that I was going to let my work colleagues down	1	2	3	4	5
23. I found accessing my office or worksite difficult	1	2	3	4	5
24. I feared that I would break wind in front of other people	1	2	3	4	5
25. I struggled to remember a recent conversation	1	2	3	4	5
26. I felt embarrassed by my bladder/bowel problems	1	2	3	4	5
27. I experienced pain whilst undertaking a task	1	2	3	4	5
28. I feared that I would not be able to support myself if I could no longer work	1	2	3	4	5
29. I felt too tired to undertake a task	1	2	3	4	5
30. I became sleepy whilst trying to undertake a task	1	2	3	4	5
31. I forgot to attend a meeting or appointment	1	2	3	4	5
32. I felt that the amount of pay I received was not adequate for my needs	1	2	3	4	5
33. I found it difficult to maintain my balance	1	2	3	4	5
34. I had to read something more	1	2	3	4	5

than once to understand it					
35. I had trouble concentrating on a task	1	2	3	4	5
36. I felt I did not have easy access to facilities (e.g. bathroom, kitchen, elevators)	1	2	3	4	5
37. I had difficulty with communicating my thoughts to co-workers	1	2	3	4	5
38. I felt that it was more difficult to balance work and home duties	1	2	3	4	5
39. I found it hard to think clearly	1	2	3	4	5
40. I found it difficult to write or type	1	2	3	4	5
41. I found it hard to do my work because my muscles or joints were hurting	1	2	3	4	5
42. I found it difficult to stand for long periods of time	1	2	3	4	5
43. I felt unable to manage stairs	1	2	3	4	5
44. I did not have adequate access to devices to assist me (e.g. electric wheelchair)	1	2	3	4	5
45. I found it difficult to interact with people	1	2	3	4	5
46. I thought that I was being discriminated against	1	2	3	4	5
47. I feared that I would be incontinent	1	2	3	4	5
48. I found it difficult to reduce my work hours because my pay would also be reduced	1	2	3	4	5
49. I forgot what task I had to do	1	2	3	4	5
50. I felt that work was becoming harder due to responsibilities at home	1	2	3	4	5

14.1.2 Multiple Sclerosis Questionnaire for the Evaluation of Job Difficulties (MSQ-Job)

The Multiple Sclerosis Questionnaire for the evaluation of Job Difficulties (MSQ-Job)

The following statements are on your health, on your workplace and on the context in which you carry out your working activities. For each item, please think to the degree to which your health or the context in which you work had an impact over your difficulties in carrying out your working activities.

Each item has to be rated on a 1-5 scale reflecting how much of an impact did it have on work difficulties: No – Mild – Moderate – Severe – Complete

1. Tactile perception and fine movement	How much of an impact did the following issues had on work difficulties?				
	No	Mild	Moderate	Severe	Complete
1.1) Difficulties in perceiving tactile stimuli					
1.2) Difficulties in using computer					
1.3) Difficulties in fine hand movements					
1.4) Physical impairments affecting hands/arms (e.g. poor sensitivity, lack of strength...)					
1.5) Sensitivity to warmth/cold (e.g. loss of sensitivity, effect of temperature on sensitivity)					
1.6) Physical impairments affecting legs/feet (e.g. poor sensitivity, lack of strength...)					

2. Fatigue-related mental functions and symptoms	How much of an impact did the following issues had on work difficulties?				
	No	Mild	Moderate	Severe	Complete
2.1) Difficulties in understanding					
2.2) Difficulties with memory					
2.3) Difficulties in learning new tasks					
2.4) Difficulties in pronouncing specific words					
2.5) Visual disturbances					
2.6) Feeling sad, blue or depressed					
2.7) Feeling anxious or overly worried					
2.8) Difficulties with sleeping					
2.9) Feeling of being not productive or					

efficient					
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3. Movement and fatigue-related body functions	How much of an impact did the following issues had on work difficulties?				
	No	Mild	Moderate	Severe	Complete
	e				
3.1) Movement difficulties (e.g. moving around, walking)					
3.2) Problems with balance or dizziness					
3.3) Difficulties in standing for a long period					
3.4) Difficulties related to getting easily tired					
3.5) Difficulties with movement coordination					
3.6) Bowel problems					
3.7) Difficulties related to fatigue					

4. Psychological and relational aspects	How much of an impact did the following issues had on work difficulties?				
	No	Mild	Moderate	Severe	Complete
	e				
4.1) Lack of motivation					
4.2) Sense of isolation					
4.3) Poor self-confidence					
4.4) Difficulties in relating with others					
4.5) Poor confidence in one's own working future					
4.6) Sense of inadequacy					

5. Time and organization flexibility in the workplace	How much of an impact did the following issues had on work difficulties?				
	No	Mild	Moderate	Severe	Complete
	e				
5.1) Poor or no flexibility in working hours					
5.2) Poor opportunities to get part-time working hours					
5.3) Having to work on shifts or work overtime frequently					
5.4) Poor opportunities to take breaks during working hour					
5.5) Poor opportunities to obtain paid leaves					
5.6) Poor opportunities to make changes (of task, role or working hours)					
5.7) Poor opportunities to work at home/do teleworking					

6. Company's attitudes and policies	How much of an impact did the following issues had on work difficulties?				
	No	Mild	Moderate	Severe	Complete
	e				
6.1) Lack of information on disability and work rules, and on the rights of workers					

with disabilities in the workplace					
6.2) Lack of knowledge on national disability laws					
6.3) Poor knowledge on the disease and its symptoms in the workplace					
6.4) Poor opportunities to obtain psychological support					
6.5) Lack of good relationships with the employer or lack of comprehension and appreciation					
6.6) Poor career growth opportunities					
6.7) Uncertain or inadequate financial and/or social security perspectives					

14.1.3 COPE Inventory

COPE Inventory

We are interested in how people respond when they confront difficult or stressful events in their lives. There are lots of ways to try to deal with stress. This questionnaire asks you to indicate what you generally do and feel, when you experience stressful events. Obviously, different events bring out somewhat different responses, but think about what you usually do when you are under a lot of stress.

Then respond to each of the following items by writing the number that corresponds with your answer next to the statement. Please try to respond to each item separately in your mind from each other item. Choose your answers thoughtfully, and make your answers as true FOR YOU as you can. Please answer every item. There are no "right" or "wrong" answers, so choose the most accurate answer for YOU--not what you think "most people" would say or do. Indicate what YOU usually do when YOU experience a stressful event.

- 1 = I usually don't do this at all
- 2 = I usually do this a little bit
- 3 = I usually do this a medium amount
- 4 = I usually do this a lot

1. I try to grow as a person as a result of the experience.
2. I turn to work or other substitute activities to take my mind off things.
3. I get upset and let my emotions out.
4. I try to get advice from someone about what to do.
5. I concentrate my efforts on doing something about it.
6. I say to myself "this isn't real."
7. I put my trust in God.
8. I laugh about the situation.
9. I admit to myself that I can't deal with it, and quit trying.
10. I restrain myself from doing anything too quickly.

11. I discuss my feelings with someone.
12. I use alcohol or drugs to make myself feel better.
13. I get used to the idea that it happened.
14. I talk to someone to find out more about the situation.
15. I keep myself from getting distracted by other thoughts or activities.
16. I daydream about things other than this.
17. I get upset, and am really aware of it.
18. I seek God's help.
19. I make a plan of action.
20. I make jokes about it.

21. I accept that this has happened and that it can't be changed.
22. I hold off doing anything about it until the situation permits.
23. I try to get emotional support from friends or relatives.
24. I just give up trying to reach my goal.
25. I take additional action to try to get rid of the problem.

26. I try to lose myself for a while by drinking alcohol or taking drugs.
27. I refuse to believe that it has happened.
28. I let my feelings out.
29. I try to see it in a different light, to make it seem more positive.
30. I talk to someone who could do something concrete about the problem.
31. I sleep more than usual.
32. I try to come up with a strategy about what to do.
33. I focus on dealing with this problem, and if necessary let other things slide a little.
34. I get sympathy and understanding from someone.
35. I drink alcohol or take drugs, in order to think about it less.
36. I kid around about it.
37. I give up the attempt to get what I want.
38. I look for something good in what is happening.
39. I think about how I might best handle the problem.
40. I pretend that it hasn't really happened.
41. I make sure not to make matters worse by acting too soon.
42. I try hard to prevent other things from interfering with my efforts at dealing with this.
43. I go to movies or watch TV, to think about it less.
44. I accept the reality of the fact that it happened.
45. I ask people who have had similar experiences what they did.
46. I feel a lot of emotional distress and I find myself expressing those feelings a lot.
47. I take direct action to get around the problem.
48. I try to find comfort in my religion.
49. I force myself to wait for the right time to do something.
50. I make fun of the situation.
51. I reduce the amount of effort I'm putting into solving the problem.
52. I talk to someone about how I feel.
53. I use alcohol or drugs to help me get through it.
54. I learn to live with it.
55. I put aside other activities in order to concentrate on this.
56. I think hard about what steps to take.
57. I act as though it hasn't even happened.
58. I do what has to be done, one step at a time.
59. I learn something from the experience.
60. I pray more than usual.

14.1.4 Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)

Instructions: Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction is best.

I feel tense or 'wound up':	A	I feel as if I am slowed down:	D
Most of the time	3	Nearly all of the time	3
A lot of the time	2	Very often	2
Time to time, occasionally	1	Sometimes	1
Not at all	0	Not at all	0
I still enjoy the things I used to enjoy:	D	I get a sort of frightened feeling like 'butterflies in the stomach':	A
Definitely as much	0	Not at all	0
Not quite so much	1	Occasionally	1
Only a little	2	Quite often	2
Not at all	3	Very often	3
I get a sort of frightened feeling like something awful is about to happen:	A	I have lost interest in my appearance:	D
Very definitely and quite badly	3	Definitely	3
Yes, but not too badly	2	I don't take as much care as I should	2
A little, but it doesn't worry me	1	I may not take quite as much care	1
Not at all	0	I take just as much care as ever	0
I can laugh and see the funny side of things:	D	I feel restless as if I have to be on the move:	A
As much as I always could	0	Very much indeed	3
Not quite so much now	1	Quite a lot	2
Definitely not so much now	2	Not very much	1
Not at all	3	Not at all	0
Worrying thoughts go through my mind:	A	I look forward with enjoyment to things:	D
A great deal of the time	3	As much as I ever did	0
A lot of the time	2	Rather less than I used to	1
From time to time but not too often	1	Definitely less than I used to	2
Only occasionally	0	Hardly at all	3
I feel cheerful:	D	I get sudden feelings of panic:	A
Not at all	3	Very often indeed	3

Not often	2
Sometimes	1
Most of the time	0

Quite often	2
Not very often	1
Not at all	0

I can sit at ease and feel relaxed:	A
Definitely	0
Usually	1
Not often	2
Not at all	3

I can enjoy a good book or radio or TV programme:	D
Often	0
Sometimes	1
Not often	2
Very seldom	3

14.1.5 Fatigue Severity Scale (FSS)

Fatigue Severity Scale

Instructions: Circle the number that best represents your response to each question.

Scoring Range: 1= strongly disagree with the statement. 7= strongly agree with the statement

During the past week, I have found that:	Disagree <-----> Agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

14.2 Appendix II

14.2.1 Graph of JEF© Results

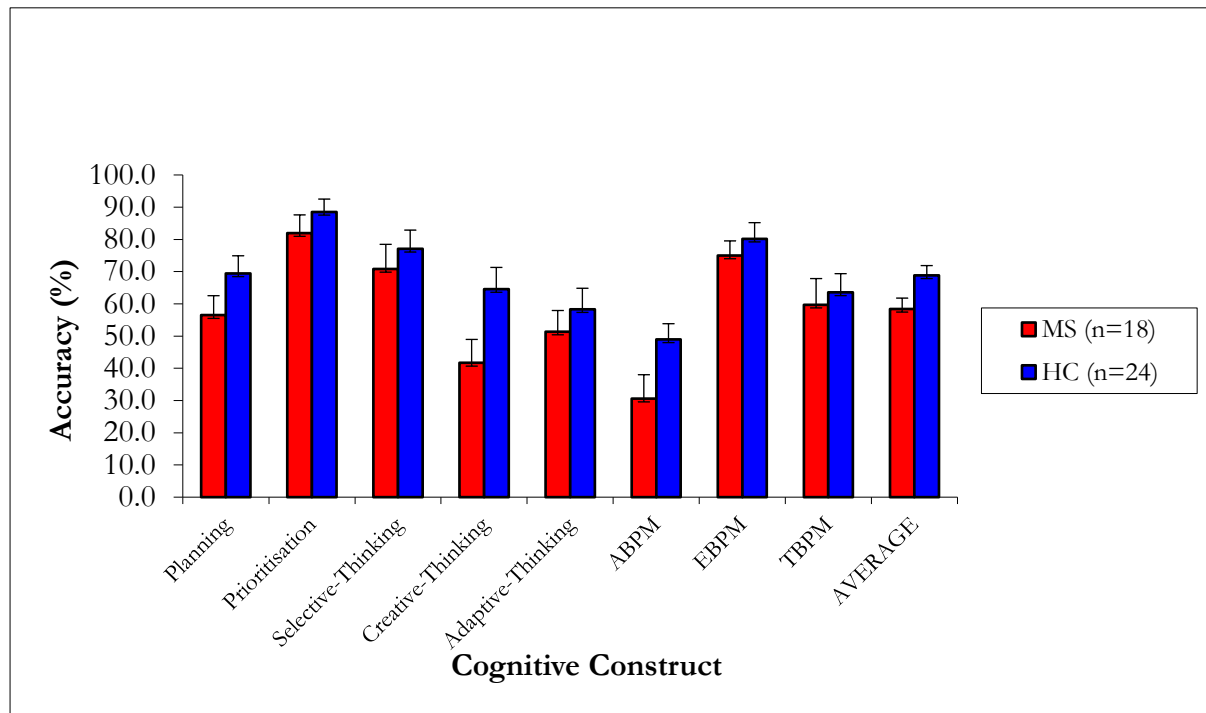


Figure 4: JEF© Performance as a Function of Group (error bars represent one standard error)

14.3 Appendix III: Information Sheets and Consent Forms

14.3.1 Information Sheet for People with Multiple Sclerosis



Participant Information Sheet

Study Title: Investigation of Executive Function in Multiple Sclerosis and employment performance.

We would like to invite you to take part in a research study. The study aims to assess higher brain functions, collectively known as “executive function”, using a new, computer-based test known as the Jansari assessment of Executive Function (JEF©) in the Multiple Sclerosis (MS) population. We are interested in seeing how this new test compares to other traditional, pen-and-paper tests of executive function and if the JEF© is more reflective of experiences in the workplace.

Before you decide whether or not to take part it is important that you understand why the research is being done and what it would involve for you. Please take time to read the following information carefully and discuss it with relatives or friends, or your GP.

What is the purpose of the study?

Multiple Sclerosis is a long term neurological disease which affects approximately 2.3 million people worldwide. A significant number of people with MS are unemployed because of the disease despite only having mild to moderate physical disabilities. It is likely that this is due to invisible symptoms of MS, such as problems with cognition (thinking, memory and other mental skills). As many people are diagnosed when they are of working age, unemployment can have a negative impact on quality of life.

Difficulties with memory and concentration are frequent for people with Multiple Sclerosis. They can be one of the earlier symptoms noticed and have been linked to unemployment. “Executive function” is an umbrella term for a set of complex mental skills needed to successfully plan and complete a chosen task. These abilities, which include planning, organisation and memory, are often needed in the workplace as well

as in daily life. Impairment in this area can therefore have significant consequences for individuals including their ability to use effective coping strategies.

A thorough assessment of an individual's cognitive problems can inform management plans. However, some traditional, pen-and-paper neuropsychological tests do not reflect real world tasks and can miss cognitive impairments which can affect everyday functioning.

The Jansari assessment of Executive Function (JEF©) is a new, computer-based test which takes place in a virtual office environment. It has been shown to detect executive function difficulties in other patient groups which have gone undetected by traditional, pen-and-paper neuropsychological tests. This test has yet to be used in the MS population. As the JEF assesses skills which are more closely related to real life, it may be a better way of assessing and monitoring these difficulties in the MS population and provide further information about how these difficulties affect employment. This study would therefore investigate whether the JEF© is sensitive to difficulties in this group and see how it compares to traditional, pen-and-paper neuropsychological tests.

Who is organising and conducting the research?

The research is being supervised by Professor Dawn Langdon PhD, a Clinical Neuropsychologist and Professor in Neuropsychology at Royal Holloway, University of London. The study is being carried out by Laura Clemens BSc MSc, who is a psychology graduate and Trainee Clinical Psychologist at Royal Holloway, University of London.

Why have I been invited?

You have been given this information sheet as you have indicated that you are interested in taking part in this study and may be a suitable participant.

Do I have to take part?

No. It is up to you to decide whether or not to take part.

What will happen to me if I take part?

You will speak to the researcher Laura Clemens, on the telephone. She will describe the study in more detail, go through this information sheet and check whether you want to take part or not. If you would like to take part she will ask you a few questions to confirm your eligibility. You would be free to withdraw from the study at any time, without giving a reason.

If you agree and are eligible to take part, a testing time and location will be agreed between you and the researcher. You will be asked to sign a consent form which states that you have read the information sheet, been given time to ask questions, understand that you are free to withdraw at any time and that you agree to take part.

The study will involve you completing a number of neuropsychological tests which should take no more than 1.5 hours to complete. You will then be asked to complete some questionnaires related to: employment performance, coping strategies, mood

and fatigue. We anticipate that the questionnaires will take no more than 30 minutes to complete.

There are no right or wrong answers, and you are free to decline to answer any question you do not feel happy to answer.

Expenses and payments

We regret that we are unable to cover expenses or offer payment for participation in this study.

What are the possible disadvantages or risks of taking part?

We do not anticipate that there will be any disadvantages to taking part, except for the time commitment needed to complete the study. We anticipate that the neuropsychological tests will not take longer than 1.5 hours and it is unlikely, but possible that you may feel fatigued during testing. We will monitor you closely for signs of fatigue and you will be able to have short breaks at appropriate points during testing if necessary.

What are the possible benefits of taking part?

We hope that this research will contribute to the validation of the JEF© as a measure that can produce results which are representative of real life experiences and difficulties and in turn improve disease monitoring and management. We will not be able to give you feedback on your performance as the testing battery does not constitute a full clinical assessment and therefore would not give us a fully accurate representation of your strengths and weaknesses.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice, and all information about you will be handled in confidence.

What will happen if I don't want to carry on with the study?

You are free to withdraw at any point, without giving a reason. You have the right to withdraw consent after it has been given, and to ask that your own data be destroyed.

What if there is a problem?

If you have any queries or concerns about the study please contact the researcher, Laura Clemens, on 07707 207992 or Laura.Clemens.2006@live.rhul.ac.uk in the first instance, or Prof Dawn Langdon, Clinical Neuropsychologist on D.Langdon@rhul.ac.uk. Any complaints about the way you have been dealt with during the study or any possible harm you might have suffered will be addressed.

If you remain unhappy and wish to complain formally about any aspect of the way you have been approached or treated during the course of this study, you may contact Prof Dawn Langdon on the details above.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for legal action for compensation, but you have to pay your own legal costs. Royal Holloway,

University of London, is providing negligent and non-negligent indemnity cover for this research.

Will my taking part in this study be kept confidential?

Yes. All data collected during the course of the study will be held according to the Data Protection Act (1998). All data collected will be anonymised and given a unique identification number. This means that only the researcher will know whose data belongs to whom. Your name will not be disclosed to anyone else, nor will you be identified in any report or publication.

All anonymised paper data will be stored securely in a locked filing cabinet that only Laura Clemens or Prof Dawn Langdon will have access to. All electronic data will be stored on a secure encrypted electronic storage device. On completion of the study, a copy of anonymised results from the JEF© will be given to Prof Ashok Jansari, the creator of the JEF©, and added to the existing dataset for use in future research. Signed consent forms will be stored securely at Royal Holloway University, and destroyed after two years.

What will happen to the results of the research study?

The results of the study will be written up as part of a Doctorate in Clinical Psychology. The results may also be published in a journal, presented at a conference or shared through an appropriate forum for people with MS. All published results will be anonymised and you will not be identified in any way. If you indicate your interest, we will also supply a summary of the findings.

Who has reviewed the study?

This study has been reviewed and given approval by the research subcommittee and ethics committee at Royal Holloway, University of London.

What do I do next if I wish to take part?

- Please contact the researcher, Laura Clemens, Trainee Clinical Psychologist either by emailing her on Laura.Clemens.2006@live.rhul.ac.uk or leaving a telephone message on 07707 207992. If leaving a message please make sure to say that you wish to speak with Laura Clemens and leave a contact number and best day/time to contact you.
- The researcher will then contact you by telephone and give you the chance to ask questions before you decide whether to participate. Please ask if there is anything that is not clear, or if you would like more information.

Thank you for considering taking part and/or taking time to read this sheet.

14.3.2 Consent Form for People with Multiple Sclerosis



CONSENT FORM FOR PEOPLE WITH MS

Study Title: Investigation of Executive Function in Multiple Sclerosis and employment performance.

- | | | Please
initial |
|----|--|---------------------------|
| 1. | I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. | <input type="checkbox"/> |
| 2. | I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. | <input type="checkbox"/> |
| 3. | I understand that information concerning my task performance, and questionnaires will be used by the researchers solely for the purpose of this study and will be stored coded and confidentially. | <input type="checkbox"/> |
| 4. | I understand that unidentifiable information about my results on the computer based task (the JEF) will be given to its creator, Professor Ashok Jansari, to be used in further research. | <input type="checkbox"/> |
| 5. | I would like to receive a brief summary of the outcome of this study. I understand that this summary will not detail my individual results. | <input type="checkbox"/> |
| 6. | I agree to take part in the above study | <input type="checkbox"/> |

Name of Participant

Signature

Date

Name of Researcher

Signature

Date

14.3.3 Information Sheet for Healthy Control

Participants



Healthy Control Participant Information Sheet

Study Title: Investigation of Executive Function in Multiple Sclerosis and employment performance.

We would like to invite you to take part in a research study. The study aims to assess higher brain functions, collectively known as “executive function”, using a new, computer-based test known as the Jansari assessment of Executive Function (JEF©) in the Multiple Sclerosis (MS) population. We also need to recruit and assess healthy volunteers to compare their results to those of people with MS. We are interested in seeing how this new test compares to other traditional, pen-and-paper tests of executive function and if the JEF© is more reflective of experiences in the workplace.

Before you decide whether or not to take part it is important that you understand why the research is being done and what it would involve for you. Please take time to read the following information carefully and discuss it with relatives or friends if you wish.

What is the purpose of the study?

Multiple Sclerosis is a long term neurological disease which affects approximately 2.3 million people worldwide. A significant number of people with MS are unemployed because of the disease despite only having mild to moderate physical disabilities. It is likely that this is due to invisible symptoms of MS, such as problems with cognition (thinking, memory and other mental skills). As many people are diagnosed when they are of working age, unemployment can have a negative impact on quality of life.

Varying degrees of impairment in cognitive abilities (thinking) are relatively common within this population. They can be one of the earlier symptoms noticed and have been linked to unemployment. “Executive function” is an umbrella term for a set of complex mental skills needed to successfully plan and complete a chosen task. These abilities, which include planning, organisation and memory, are often needed in the workplace as well as in daily life. Impairment in this area can therefore have significant consequences for individuals including their ability to use effective coping strategies.

A thorough assessment of an individual’s cognitive problems can inform management plans. However, some traditional, pen-and-paper neuropsychological tests do not

reflect real world tasks and can miss cognitive impairments which can affect everyday functioning.

The Jansari assessment of Executive Function (JEF©) is a new, computer-based test which takes place in a virtual office environment. It has been shown to detect executive function difficulties in other patient groups which have gone undetected by traditional, pen-and-paper neuropsychological tests. This test has yet to be used in the MS population. As the JEF assesses skills which are more closely related to real life, it may be a better way of assessing and monitoring these difficulties in the MS population and provide further information about how these difficulties affect employment. This study would therefore investigate whether the JEF© is sensitive to deficits in this group and see how it compares to traditional, pen-and-paper neuropsychological tests. We are collecting our own healthy control data as there is no existing normed control data for the JEF©

Who is organising and conducting the research?

The research is being supervised by Professor Dawn Langdon PhD, a Clinical Neuropsychologist and Professor in Neuropsychology at Royal Holloway, University of London. The study is being carried out by Laura Clemens BSc MSc, who is a psychology graduate and Trainee Clinical Psychologist at Royal Holloway, University of London.

Why have I been invited?

We need to recruit a healthy control group to compare their results to those of people with MS. You have been given this information sheet as you may be suitable for the study and may be interested in taking part.

Do I have to take part?

No. It is up to you to decide whether or not to take part.

What will happen to me if I take part?

You will speak to the researcher Laura Clemens, on the telephone. She will describe the study in more detail, go through this information sheet and check whether you want to take part or not. If you would like to take part she will ask you a few questions to confirm your eligibility. You would be free to withdraw from the study at any time, without giving a reason.

If you agree and are eligible to take part, a testing time and location will be agreed between you and the researcher. You will be asked to sign a consent form which states that you have read the information sheet, been given time to ask questions, understand that you are free to withdraw at any time and that you agree to take part.

The study will involve you completing a number of neuropsychological tests which should take no more than 1.5 hours to complete. You will then be asked to complete some questionnaires related to: employment performance, coping strategies, mood and fatigue. We anticipate that the questionnaires will take no more than 30 minutes to complete.

There are no right or wrong answers, and you are free to decline to answer any question you do not feel happy to answer.

Expenses and payments

We regret that we are unable to cover expenses or offer payment for participation in this study.

What are the possible disadvantages or risks of taking part?

We do not anticipate that there will be any disadvantages to taking part, except for the time commitment needed to complete the study. We anticipate that the neuropsychological tests will not take longer than 1.5 hours and it is unlikely, but possible that you may feel fatigued during testing. We will monitor you closely for signs of fatigue and you will be able to have short breaks at appropriate points during testing if necessary.

What are the possible benefits of taking part?

We hope that this research will contribute to the validation of the JEF© as a measure that can produce results which are representative of real life experiences and difficulties and in turn improve disease monitoring and management. We will not be able to give you your test scores as the testing battery does not constitute a full clinical assessment and therefore would not give us a fully accurate representation of your strengths and weaknesses.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice, and all information about you will be handled in confidence.

What will happen if I don't want to carry on with the study?

You are free to withdraw at any point, without giving a reason. Refusal or withdrawal of consent will **not** affect any future care or treatment that you receive. You have the right to withdraw consent after it has been given, and to ask that your own data be destroyed.

What if there is a problem?

If you have any queries or concerns about the study please contact the researcher, Laura Clemens, on 07707 207992 or Laura.Clemens.2006@live.rhul.ac.uk in the first instance, or Prof Dawn Langdon, Clinical Neuropsychologist on D.Langdon@rhul.ac.uk. Any complaints about the way you have been dealt with during the study or any possible harm you might have suffered will be addressed.

If you remain unhappy and wish to complain formally about any aspect of the way you have been approached or treated during the course of this study, you may contact Prof Dawn Langdon on the details above.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for legal action for compensation, but you have to pay your own legal costs. Royal Holloway, University of London, is providing negligent and non-negligent indemnity cover for this research. The normal NHS complaints mechanisms will still be available to you.

Will my taking part in this study be kept confidential?

Yes. All data collected during the course of the study will be held according to the Data Protection Act (1998). All data collected will be anonymised and given a unique identification number. This means that only the researcher will know whose data belongs to whom. Your name will not be disclosed to anyone else, nor will you be identified in any report or publication.

All anonymised paper data will be stored securely in a locked filing cabinet that only Laura Clemens or Prof Dawn Langdon will have access to. All electronic data will be stored on a secure encrypted electronic storage device. On completion of the study, a copy of anonymised results from the JEF© will be given to Prof Ashok Jansari, the creator of the JEF©, and added to the existing dataset for use in future research. Signed consent forms will be stored securely at Royal Holloway University, and destroyed after two years.

What will happen to the results of the research study?

The results of the study will be written up as part of a Doctorate in Clinical Psychology. The results may also be published in a journal, presented at a conference or shared through an appropriate forum for people with MS. All published results will be anonymised and you will not be able to be identified in any way. If you indicate your interest, we will also offer you a summary of the findings.

Who has reviewed the study?

This study has been reviewed and given approval by the research subcommittee at Royal Holloway, University of London.

All NHS research is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests.

What do I do next if I wish to take part?

- Please contact the researcher, Laura Clemens, Trainee Clinical Psychologist either by emailing her on Laura.Clemens.2006@live.rhul.ac.uk or leaving a telephone message on 07707 207992. If leaving a message please make sure to say that you wish to speak with Laura Clemens and leave a contact number and best day/time to contact you.
- The researcher will then contact you by telephone and give you the chance to ask questions before you decide whether to participate. Please ask if there is anything that is not clear, or if you would like more information.

Thank you for considering taking part and/or taking time to read this sheet.

14.3.4 Consent Form for Healthy Control Participants



CONSENT FORM FOR HEALTHY VOLUNTEERS

Study Title: Investigation of Executive Function in Multiple Sclerosis and employment performance.

- | | | Please
initial |
|----|--|---------------------------|
| 1. | I confirm that I have read and understand the information sheet

for the above study. I have had the opportunity to consider the
information, ask questions and have had these answered satisfactorily. | <input type="checkbox"/> |
| 2. | I understand that my participation is voluntary and that I am free to withdraw

at any time, without giving any reason. | <input type="checkbox"/> |
| 3. | I understand that information concerning my task performance,

and questionnaires will be used by the researchers solely for the purpose
of this study and will be stored coded and confidentially. | <input type="checkbox"/> |
| 4. | I understand that unidentifiable information about my results on the

computer based task (the JEF©) will be given to its creator, Professor
Ashok Jansari, to be used in further research. | <input type="checkbox"/> |
| 5. | I would like to receive a brief summary of the outcome of this study. I

understand that this summary will not detail my individual results. | <input type="checkbox"/> |
| 6. | I agree to take part in the above study | <input type="checkbox"/> |

_____	_____	_____
Name of Participant	Signature	Date

_____	_____	_____
Name of Researcher	Signature	Date

14.4 Ethical Approval Documentation



Ethics Review Details

You have chosen to self certify your project.	
Name:	Clemens, Laura (2006)
Email:	ZRJT165@live.rhul.ac.uk
Title of research project or grant:	Investigation of Executive Function in Multiple Sclerosis and employment performance
Project type:	Royal Holloway postgraduate research project/grant
Department:	Psychology
Academic supervisor:	Prof Dawn Langdon
Email address of Academic Supervisor:	d.langdon@rhul.ac.uk
Funding Body Category:	No external funder
Funding Body:	
Start date:	09/04/2018
End date:	21/09/2018

Research question summary:

Multiple Sclerosis (MS) is a long-term, degenerative disease caused by structural changes to cells in the brain and spinal cord. In addition to physical impairments, MS can lead to difficulties related to complex abilities such as decision making, planning and switching between tasks. These abilities are collectively known as "executive function". Problems in executive function have been linked to unemployment in MS as well as the use of unhelpful coping strategies, which in turn affect employment performance. Assessing these abilities is important for the creation of effective treatment and management plans. Many of the traditional, pen and paper neuropsychological tests involve tasks which test executive function but are unrepresentative of real world tasks. For example, asking people to read the names of colours printed in the same, or a different colour to the actual name. A person therefore can score well on these traditional, pen and paper neuropsychological tests but still struggle with tasks requiring executive function in real life.

The Jansari assessment of Executive Function (JEF©) is a computer based test set in a virtual office environment which requires the participant to complete everyday tasks. For example, organising events or everyday objects in a logical manner. The JEF© has been shown to be sensitive to deficits in executive function in patient groups which report difficulties undetected by traditional, pen-and-paper neuropsychological tests. It is also portable and more engaging than traditional, pen-and paper neuropsychological tests.

This study would ascertain three things: whether the JEF© is sensitive to executive function deficits in the MS population, whether the JEF© is more closely related to work place performance in comparison to traditional pen-and-paper neuropsychological tests, and whether the JEF© scores are related to coping styles.

Research method summary:

53 people with Relapsing Remitting MS and 53 matched healthy volunteers aged 18-65 years and able to give informed consent will be recruited. This sample size was chosen following statistical power calculations. MS volunteers will be recruited through national MS charities and similar organisations. Adverts will be uploaded to the charities' websites and people who are interested will be asked to contact the Primary Investigator via email or telephone. Healthy Controls will be recruited from community groups. Potential participants will be given an information sheet and there will be a minimum of 24 hours before their interview. The researcher will check that they understand the project and answer any further questions. Participants will undergo a brief telephone screen to further ensure suitability. Once eligibility has been confirmed participants will be asked to sign the consent form prior to proceeding with testing. Testing will take place on university premises in London and other similar locations. The test battery will take a maximum of 2 hours to complete. The following validated tests will be administered: Test of Premorbid Functioning, (TOPF-UK), The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), Jansari Test of Executive Function (JEF©), Behavioural Assessment of Dysexecutive Syndrome (BADS), Delis-Kaplan Executive Function System (D-KEFS) – Sorting Test, Verbal Fluency Test, National Multiple Sclerosis Society Employment Preparation Survey (NMSS Survey), Multiple Sclerosis Questionnaire for Job Difficulties (MSQ-Job), Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ), The COPE inventory, Hospital Anxiety and Depression Scale (HADS), Fatigue Severity Scale (FAS). The performance of the two groups will be compared by creating a JEF index and executive index from the group scores and an appropriate statistical analysis. An index of work performance will be calculated from the employment questionnaires. Correlations will be carried out and statistical tests used to compare the strength of the correlations.

Risks to participants

Does your research involve any of the below?

Children (under the age of 16),

No

Participants with cognitive or physical impairment that may render them unable to give informed consent,

No

Participants who may be vulnerable for personal, emotional, psychological or other reasons,

Yes

Participants who may become vulnerable as a result of the conduct of the study (e.g. because it raises sensitive issues) or as a result of what is revealed in the study (e.g. criminal behaviour, or behaviour which is culturally or socially questionable),

No

Participants in unequal power relations (e.g. groups that you teach or work with, in which participants may feel coerced or unable to withdraw),

No

Participants who are likely to suffer negative consequences if identified (e.g. professional censure, exposure to stigma or abuse, damage to professional or social standing),

No

Details,

People with MS will be recruited as participants. Many studies of this kind have been completed without incident or upset, however there is a raised prevalence of psychiatric conditions in the MS population. As PI, I am a psychology graduate who has spent four and a half years in NHS mental health settings and so have some experience in this area. In addition, this issue will be covered in supervision.

Design and Data

Does your study include any of the following?

Will it be necessary for participants to take part in the study without their knowledge and/or informed consent at the time?,

No

Is there a risk that participants may be or become identifiable?,

No

Is pain or discomfort likely to result from the study?,

No

Could the study induce psychological stress or anxiety, or cause harm or negative consequences beyond the risks encountered in normal life?,

No

Does this research require approval from the NHS?,

No

If so what is the NHS Approval number,

Are drugs, placebos or other substances to be administered to the study participants, or will the study involve invasive, intrusive or potentially harmful procedures of any kind?,

No

Will human tissue including blood, saliva, urine, faeces, sperm or eggs be collected or used in the project?,

No

Will the research involve the use of administrative or secure data that requires permission from the appropriate authorities before use?,

No

Will financial inducements (other than reasonable expenses and compensation for time) be offered to participants?,

No

Is there a risk that any of the material, data, or outcomes to be used in this study has been derived from ethically-unsound procedures?,

No

Details,

Risks to the Environment / Society

Will the conduct of the research pose risks to the environment, site, society, or artifacts?,

No

Will the research be undertaken on private or government property without permission?,

No

Will geological or sedimentological samples be removed without permission?,

No

Will cultural or archaeological artifacts be removed without permission?,

No

Details,

Risks to Researchers/Institution

Does your research present any of the following risks to researchers or to the institution?

Is there a possibility that the researcher could be placed in a vulnerable situation either emotionally or physically (e.g. by being alone with vulnerable, or potentially aggressive participants, by entering an unsafe environment, or by working in countries in which there is unrest)?,

No

Is the topic of the research sensitive or controversial such that the researcher could be ethically or legally compromised (e.g. as a result of disclosures made during the research)?,

No

Will the research involve the investigation or observation of illegal practices, or the participation in illegal practices?,

No

Could any aspects of the research mean that the University has failed in its duty to care for researchers, participants, or the environment / society?,

No

Is there any reputational risk concerning the source of your funding?,

No

Is there any other ethical issue that may arise during the conduct of this study that could bring the institution into disrepute?,

No

Details,

Declaration

By submitting this form, I declare that the questions above have been answered truthfully and to the best of my knowledge and belief, and that I take full responsibility for these responses. I undertake to observe ethical principles throughout the research project and to report any changes that affect the ethics of the project to the University Research Ethics Committee for review.

Certificate produced for user ID, ZRJT165

Date:	09/04/2018 18:04
Signed by:	Clemens, Laura (2006)
Digital Signature:	Laura Clemens
Certificate dated:	4/9/2018 6:34:26 PM
Files uploaded:	Consent Form controls LC v4 for charities.docx Consent Form for people with MS LC v4 for charities.docx HC participant information sheet v6 for charities.docx MS information sheet v6 for charities.docx