BALANCING THE DEMANDS OF TWO TASKS: AN INVESTIGATION OF COGNITIVE-MOTOR DUAL-TASKING IN RELAPSING REMITTING MULTIPLE SCLEROSIS

AND CLINICAL RESEARCH PORTFOLIO

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CHAPTER ONE: SYSTEMATIC REVIEW

Divided Attention in Relapsing Remitting Multiple Sclerosis: A Systematic Review of the Evidence

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Prepared in accordance with authors instructions for the Journal of the International Neuropsychological Society (see Appendix 1.1)

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Chapter One: Systematic Review Contents

Divided Attention in Relapsing Remitting Multiple Sclerosis: A Systematic Review of the Evidence

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Abstract

Background: One form of attention suggested to be impaired in Multiple Sclerosis (MS) is divided attention (DA), or the ability to attend to more multiple tasks or streams of information simultaneously; also referred to as dual-tasking. The ability to dual-task is required for everyday situations including cognitive-motor combinations such as walking and talking. Several studies have reported a disproportionate difficulty in combining walking with cognitive tasks in people with MS. Various explanations for this difficulty have been proposed, with a DA deficit being one. Consequently, it is important to determine whether a DA deficit is evident in MS. **Objective:** To examine the literature that has investigated performance of people with Relapsing-Remitting MS on tasks of DA. **Methods:** Two hundred and fifteen potentially relevant articles were initially identified. Eight met inclusion criteria. Studies were rated using a methodological quality rating protocol developed from SIGN Methodology Checklists 3 and 4 and a narrative review was conducted. **Results:** Six of the eight included studies reported a DA deficit in the RRMS group in comparison to controls. Effect sizes were calculated for seven of the eight papers with a median effect size of 0.69. Several methodological limitations of included studies were identified. **Conclusions:** It was not possible to conclude that a DA deficit is evident in individuals with RRMS. This was due to varying methodologies of measures of DA, lack of adherence to a dual-task paradigm, and limited control for potential confounding variables across the included studies.

Key words: Multiple Sclerosis, Divided Attention, Dual-Task

Introduction

Worldwide, it is estimated that approximately 2,500,000 people have a diagnosis of Multiple Sclerosis (MS) [MS Trust, 2015]. MS is an autoimmune disease wherein the body's immune system attacks the myelin sheath of nerves, resulting in scarring [Gontkovsky & Golden, 2008]. MS is characterised by progressive and changeable episodes of demyelination and transaction resulting in axonal damage and loss of neurons [Farooqui, 2011]. Enduring axonal and grey matter tissue damage, *inter alia*, can contribute to atrophy within the brain [De Stefano, Battaglini, & Smith, 2007]; this underlies neurological disability and associated loss of motor or cognitive functions [Fisher, Lee, Nakamura, & Rudick, 2008]. Variation in the amount of axonal damage and atrophy, as well as the locations of lesions in the brain, results in a wide variation in symptom presentation [McDonald et al., 2001]. Over the last decade, neuroimaging research has demonstrated loss of axons and cell bodies in very early stages of MS [DeLuca, Ebers, & Esiri, 2004; Davies et al., 2004]. Therefore, it is imperative to investigate associated impairment as early in the disease process as possible.

There are three forms of MS that have differing disease courses: Relapsing-Remitting (RRMS); Secondary Progressive (SPMS); and Primary Progressive (PPMS). Imaging and histopathological findings suggest that inflammation is dominant in the disease course of RRMS, whereas in SPMS and PPMS neurodegeneration predominates [Kuhlmann, 2013]. RRMS is characterised by episodes of acute worsening followed by partial or complete recovery. Conversely, SPMS and PPMS are characterised by unremitting worsening. RRMS is not only the most prevalent type of MS but the majority of individuals diagnosed with MS start with this disease course [Kuhlmann, 2013]. Consequently, this review focuses on the RRMS subtype.

Cognitive impairment in MS is reported to occur in 40-65% of patients [Julian, 2011]. Typically, impairments start early in the disease process, deteriorate over time, and are independent of physical disability [Julian, 2011]. Although there is not a consistent profile of cognitive impairment in MS, the cognitive domains most commonly affected in MS are memory, attention, executive functioning and information processing speed. This is a result of predominantly subcortical white

matter aetiology in the brain [DeSousa, Albert, & Kalman, 2002]. This review focuses on the domain of attention.

One form of attention suggested to be impaired in MS is divided attention (DA) [Bobholz & Rao, 2003; Ferreira, 2010]. DA refers to the ability to attend to more than one task or stream information simultaneously; sometimes also referred to as dual-tasking [Lezak, 1995]. The cognitive skill of DA is complex, utilising dedicated cortical areas which need reciprocal intact white matter connections. Axonal changes seen in MS make white matter connections vulnerable to damage. The common format for investigating dual-tasking involves tasks being carried out independently and then combined. In a number of groups (e.g. older adults and people with various neurological conditions) it has been shown that when two tasks are combined, the decrement in performance from single to dual-task conditions is greater than in healthy controls [Yang, Chen, Lee, Cheng, & Wang, 2007; Muir et al., 2012]. A particularly important everyday 'dual-task' is walking and talking. Several studies have found evidence for a disproportionate difficulty in combining walking with cognitive tasks in people with MS [Hamilton et al., 2009; Kalron, Dvir, & Achiron, 2010]. There are several possible explanations for why walking and talking might be impaired; and these relate to theories of attentional control.

Models of attentional control include Baddeley and Hitch's Working Memory Model [Baddeley & Hitch, 1974; Baddeley, 1996]. The central executive of this model is viewed as an attentional controller. What is not explicit in this model is whether the central executive can divide attention between the two slave systems simultaneously or only move attention flexibly from one to another. Other recent models of working memory [Oberauer, 2002; Oberauer, 2009] describe models that have a focus of attention which has a capacity of one unit, suggesting that the focus of attention can only be on one thing at a time. This idea is consistent with theories of dual-task performance, including the response-selection bottleneck model [Pashler, 1994], which suggests the process of selecting a response to a stimulus can only attend to one unit at a time and therefore dual-task demands will create a cost compared to single task performance. Another explanation for dual-task decrements [Tsang, 2013] is resource theory, which suggests that resources needed for task processing are limited, and if the tasks demands are not met by sufficient supply of resources, performance degrades.

In relation to walking and talking in a condition such as MS, it would appear that there are several potential reasons why we might see disproportionate decrements. One is that there is a central problem with DA so that tasks cannot be combined. The other is a resource limitation issue - tasks such as walking demand much greater resources than usual and these demands outstrip the capacity of the system, particularly where there are additional cognitive demands [Hamilton et al., 2009; Kalron et al., 2010]. It would therefore be useful to clarify whether a DA deficit is evident in MS, particularly in the early stages, and to examine whether there is evidence of a DA deficit on tasks that do not involve demanding motor tasks such as walking.

The aim of this review therefore was to examine the literature that has investigated performance of people with RRMS on tasks of DA. This review asks three questions: (1) is there a DA deficit in RRMS; (2) what methods are used to measure DA in RRMS; and (3) if there is a DA deficit, is this evident early in the disease course? As part of this review, the nature of the tasks used, and characteristics of the participants (early/late stage MS) will be described and the methodological quality of the literature determined.

Methods

All studies that scrutinised performance of people with RRMS on tasks of DA were eligible for inclusion in this systematic review. Dynamed, UpToDate, BMJ Best Practice and the Cochrane Database of Systematic Reviews were searched with the term “Multiple Sclerosis”. No ongoing or accessible, meta-analyses, systematic or literature reviews focusing on this topic were found.

Database Searches

The search terms “divided attention” and “multiple sclerosis”, with Boolean operator ‘AND’ in-between, were applied to the title, abstract and index fields of databases. The following search platforms and databases were used: Medline (via OVID Medline (R) 1946 to week 1 January 2016 and OVID Medline (R) in-process & other non-indexed citations); Embase (via OVID Embase, 1947 to present, updated daily on 28th January 2016); CINAHL, PsycInfo, Psychology and Behavioural Sciences Collection and Biomedical Reference Collection: Comprehensive (via

EBSCOhost 1987 until 28th January 2016); Cochrane Library (inception date of database until 28th January 2016); Web of Science (inception date of database until 28th January 2016). Subsequently, a hand search of the reference lists of included studies were examined to ensure no pertinent articles were missed from database searches.

Study Selection

Figure 1 outlines the search approach taken, number of references considered at each stage of the search process and exclusion criteria. Eight studies [Claros-Salinas et al., 2013; Devos, Brijs, Alders, Wets, & Feys, 2013; McCarthy, Beaumont, Thompson, & Peacock, 2005; Patanella et al., 2010; Paul, Beatty, Schneider, Blanco, & Hames, 1998; Ruet, Deloire, Charre-Morin, Hamel, & Brochet, 2013; De Sonneville et al., 2002; Stoquart-ElSankari, Bottin, Roussel-Pieronne, & Godefroy, 2010] met the following inclusion criteria: (i) peer-reviewed articles published in English; (ii) human, adult participants (aged 18-65); (iii) original published research; (iv) participants have a diagnosis of RRMS; (v) presence of a control group; (vi) study provides a measure of DA as characterised by the study authors; and (vii) studies do not involve a complex motor task that requires balance and/or walking. If suitability for inclusion was ambiguous, an independent researcher examined the article.

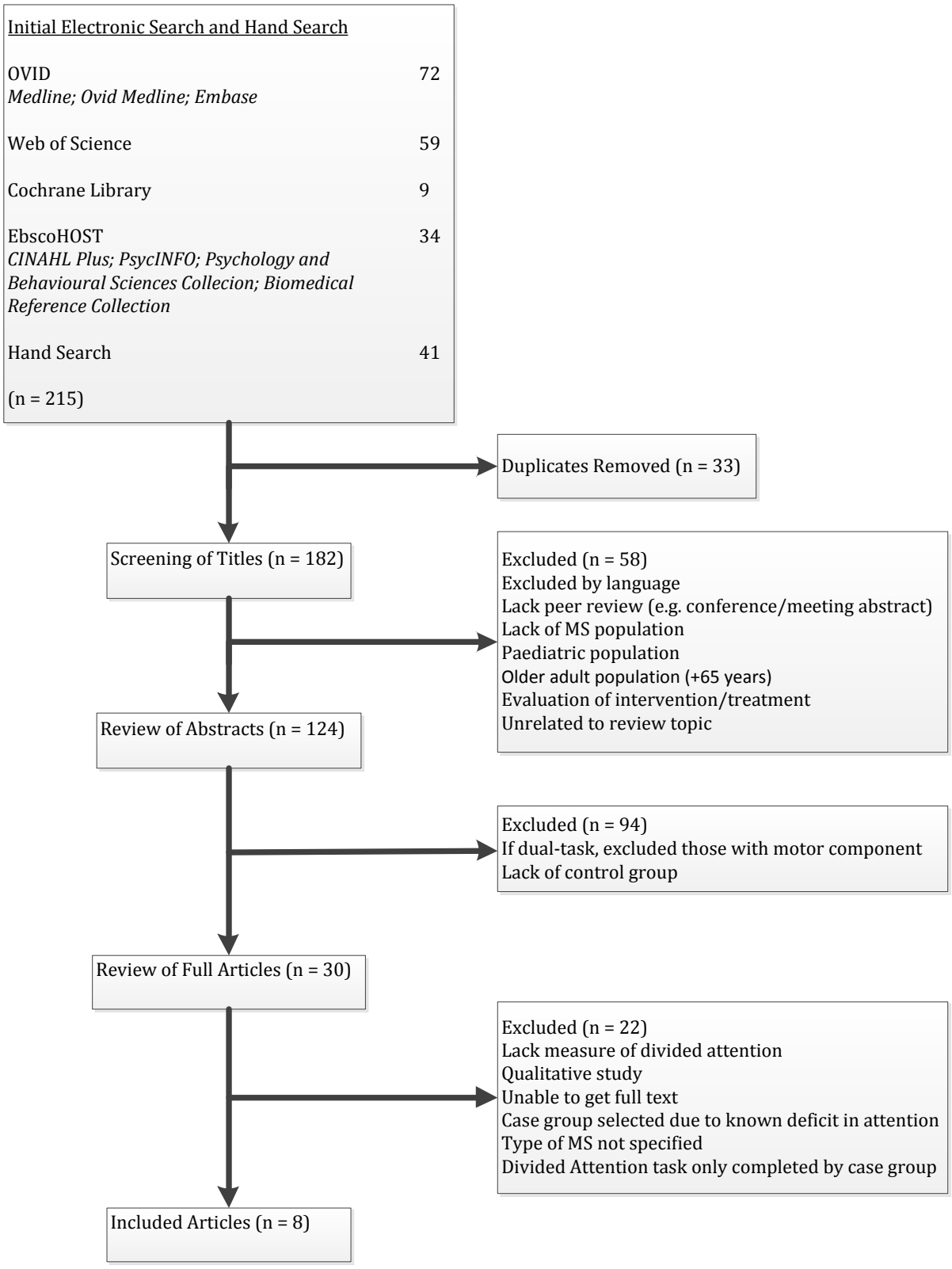

Figure 1: Article Search Strategy Flowchart

Quality Rating

A quality rating protocol was composed (appendix 1.2) based on the Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklists 3: Cohort Studies and 4: Case-control Studies [SIGN, 2007]. The protocol consists of 13 items separated into two sections that cover six methodological areas: study question, subject selection, assessment, confounding factors, statistical analysis and overall assessment. Each item in section one is answered with 'yes', 'no' or 'can't say'. Consistent with SIGN procedures, the overall methodological quality is rated as 'high quality' (++), 'acceptable' (+) or 'low quality' (0) based on the answers to the 10 items in section one. For the purposes of this review, a rating of ++ was given if the majority (seven or more) of the items in section one were answered 'yes'; a rating of + was given if most (five or six) of the items were answered 'yes'; and a rating of '0' is given if less than half (less than five) items were answered 'yes'. Ratings of each of the included studies are shown in appendix 1.3.

To ensure consistency in quality rating, a second independent rater also assessed all included papers. Each reviewer separately evaluated four papers then met to discuss individual ratings given. Agreement in overall quality was found for all four co-rated papers i.e. both gave the same overall quality rating for each paper (++, + or 0). If disagreement arose around individual items and what scored 'yes', 'no' or 'can't say', this was resolved through discussion and ratings were revised to the agreed rating. The remaining four articles were then rated independently.

Effect Sizes

Where feasible, effect sizes were calculated for differences between patients and controls on measures of DA within each study, irrespective of a statistically significant difference being found.

Data Synthesis and Extraction

It is important to consider overall findings of included studies in the context of their methodological strengths and limitations. Due to variation in methodology and measures of DA between studies, a meta-analysis was not considered appropriate and a narrative synthesis was therefore undertaken [Popay et al., 2006].

To systematically collect pertinent information from each included study, a data extraction form was developed (appendix 1.4). Using this tool, information regarding study characteristics, participant characteristics, recruitment, measures and results were extracted from each of the eight included papers.

Results

Study Characteristics

Eight studies met inclusion criteria for this review. Table 1 summarises the characteristics and quality ratings of included studies. Some studies also included participants with Primary or Secondary Progressive MS, but the review focused on results with RRMS.

Six of the eight included studies found significantly greater performance decrement in individuals with RRMS than with controls. One paper compared performance between groups on the DA measure, but no statistically significant difference was found. The other paper did not report a comparison between groups on DA task performance (despite including a control group) and therefore it could not be determined whether a DA deficit was present. Various DA measures were used across studies (see methodological limitations section below). Seven studies reported disease severity using the Expanded Disability Status Score (EDSS). Four reported EDSS scores as a range, which spanned from scores of 1.0 – 8.5. Three reported group mean EDSS scores of 1.4, 4.67 and 4.7. One study reported a mean Ambulatory Index (AI) score of 4.03.

Table 1: Summary of Included Studies with Sample Characteristics, Divided Attention Measures and Quality Ratings

ID	Study	Sample Size and Characteristics	Study Aim	Measures of DA	DA Deficit Reported in RRMS?	Quality Score
A	Claros-Salinas et al, 2013	*n* MS = 32 *n* Control = 20 MS participants recruited from a neurological rehabilitation unit in Germany. Study does not state how control participants were recruited. Type of MS: RRMS, PPMS, SPMS EDSS: Average score of 3.6 (range 1.0–6.5)	To investigate whether cognitive fatigue in MS patients is a spontaneous phenomenon or if it can be provoked or exacerbated through cognitive effort and motor exercise.	TAP-M: DA Subtest: Simultaneous Visual + Auditory tasks A visual task *(white crosses appeared in a quasi random configuration – participants were asked to press a response key when detected target configuration)* and an auditory task *(200 pure tones presented successively one after the other – participants were asked to press a response key when detected a repetition of tone frequency)* were performed simultaneously.	Unknown *(Control performance on TAP-M DA Subtest not commented on in results)*	+
B	Devos et al, 2013	*n* MS = 15 *n* Control = 17 Participants in both groups were recruited through advertisements or after attending a local information session. Type of MS: RRMS, SPMS, PPMS EDSS: score range of 1–6 (*n*7 = ≤3 & *n*8 = 3.5 – 6)	To investigate whether driving performance is impaired in persons with mild to moderate MS.	Two measures: 1. Driving simulator (DS) with DA task 2. Directions and Compass Tasks (DCT) *(MS only)* DS with DA: Driving scenario including daily traffic situations. Assessed driving skills such as adapting speed and avoiding hazardous situations. On top of these driving skills, DA symbols were randomly projected in the side mirrors. Participants responded e.g. by pressing the horn when seen a horn symbol.	Yes *(Significant difference between MS and controls on Driving Simulator DA task)*	++

				DCT: Subjects were given a deck of cue cards depicting vehicles travelling in different directions. They were instructed to position these cards on a 4x4 matrix so that each vehicle was travelling in the directions indicated by either arrows or compass cards.		
C	McCarthy et al, 2005	*n* MS = 30 *n* Control = 30 Study does not state how MS or control participants were recruited. Type of MS: RRMS, CPMS EDSS: Range 1–8.5	To consider the specific nature of attentional dysfunction in MS.	DAT: Visual, Auditory and Bimodal Divided Attention Task (designed by authors) Participants were presented with pairs of digits and asked to respond when target pairs were presented. Digits were presented under visual, auditory and bimodal (visual + auditory) conditions.	Yes *(Controls group significantly more hits, fewer false positives, greater percentage of correct responses and faster response times than MS group)*	0
D	Patanella et al, 2010	*n* MS = 30 *n* Control = 30 MS participants recruited from a MS Centre. Study does not state how control participants were recruited. Type of MS: RRMS EDSS: Mean 1.4 (SD of 1.2)	To investigate the role of Brain Derived Neurotrophic Factor and inflammatory factors in the development of cognitive dysfunction in MS.	Three Measures: 1. MFTC 2. SDMT 3. TMA MFTC: A visual task in which subjects are requested to identify a target item in an array of distractors. SDMT: Using a reference key, participants have 90 seconds to pair specific numbers with given geometric figures. TMA: Circles are numbered 1-25 and participants should draw lines to connect the numbers in ascending order as quickly as can.	Yes *(Significant difference between MS and controls on MFCT reaction time, SDMT and TMA)*	+

E	Paul et al, 1998	*n* MS = 39 *n* Control = 18 MS participants recruited from the practices of neurologists and regional support groups in Tulsa and Oklahoma City. Control participants were recruited from the community e.g. patients relatives. Type of MS: RRMS, CPMS, SPMS AI: Mean score of 4.03	To assess the status of attention in MS.	Three Measures: 1. Oral SDMT 2. PASAT 3. G-LAS Oral SDMT: Using a reference key, participants have 90 seconds to pair specific numbers with given geometric figures. Responses are given orally. PASAT: Single digits are presented every 3 seconds and the participant must add each new digit to the one immediately prior to it. G-LAS: Requires participants to detect a target consisting of either a large global or smaller local forms hat as a whole constitute a global stimulus. Participants hit a response key when seen the target letters 'S' or 'H'.	Yes *(Significant difference between groups on all DA measures)*	+
F	Ruet et al, 2013	*n* PPMS = 41 *n* RRMS = 60 *n* Control = 415 MS participants were recruited from the MS Centre of Bordeaux. Study does not state how control participants were recruited. Type of MS: PPMS, RRMS EDSS: 1.5 - 7.0 (mean 3.5)	To characterise the cognitive abilities of patients with PPMS and RRMS. To compare the cognitive patterns in PPMS and RRMS.	TAP: DA Subtest: Simultaneous performance of visual and auditory tasks A visual task *(white crosses appeared in a quasi random configuration – participants were asked to press a response key when detected target configuration)* and an auditory task *(200 pure tones presented successively one after the other – participants were asked to press a response key when detected a repetition of tone frequency)* were performed simultaneously.	No *(No significant difference between RRMS and controls on TAP: DA Subtest)*	++

G	De Sonneville et al, 2002	*n* MS = 53 *n* Control = 58 MS participants randomly selected at a secondary/tertiary referral centre for MS. Control participants recruited from the community. Type of MS: SPMS, PPMS, RRMS EDSS: Mean 4.7 (SD=2.0) *[RRMS mean 3.0; SD=1.2]*	To evaluate information processing characteristics in patients with MS.	ANTP: Visuo-spatial Processing (VSP) and Memory Search (MemS) subtests ANTP – VSP: After memorisation of a pre-defined target pattern participants have to detect this target pattern in a signal consisting of four patterns. Press either 'yes'-key or 'no'-key. ANTP – MemS: Employs a display load of four letters and consists of three parts in which target set size (memory load) is increased from one to three target letters. Press either 'yes'-key or 'no'-key.	Yes *(Significant differences found between groups on both DA measure for speed of processing only – not for accuracy)*	0
H	Stoquart-ElSankari et al, 2010	*n* MS = 20 *n* Control = 20 MS participants were admitted in the Department of Neurology of Amiens University Hospital. Study does not state how control participants were recruited. Type of MS: SPMS, PPMS, RRMS EDSS: Mean 4.67	To examine mechanisms accounting for action slowing in MS patients.	SRT task *(dual-task condition aimed to assess DA)* Imperative stimuli were letters randomly chosen among four letters. They appeared with a randomly varying interval (100, 150, 200, 250 and 300 ms) after the extinction of a warning visual stimulus (fixation cross). Subjects had to depress as fast as possible the response key with their index finger, regardless of the letter.	Yes *(Significant differences found between groups on SRT task for reaction time – not for omissions)*	+

Note: Quality Rating Scoring: ++ = High quality; + = Acceptable; 0 = Low quality. **Abbreviations:** DA = divided attention; MS = Multiple Sclerosis; RRMS = Relapsing-Remitting MS; SPMS = Secondary Progressive MS; PPMS = Primary Progressive MS; CPMS = Chronic Progressive MS; EDSS = Expanded Disability Status Score; SD = Standard Deviation; TAP-M = Test of Attentional Performance (mobile version); TAP = Test of Attentional Performance; PASAT = Paced Auditory Serial Addition Test; SDMT = Symbol Digit Modalities Test; DAT = Divided Attention Task; MFTC = Multiple Features Target Cancellation Test; TMA = Trail Making Part A; AI = Ambulatory Index; G-LAS = Global-Local Attention Shift; ANTP = Amsterdam Neuropsychological Tasks Program; SRT = Simple Reaction Time.

Quality Ratings

Overall quality ratings ranged from low quality (0) to high quality (++) with a median rating of acceptable (+). A summary of quality scores for each study can be found in appendix 1.3. All eight studies had a clear aim or purpose, ensured cases and controls were taken from comparable populations, confirmed cases were clearly defined and differentiated from controls, and reported disease severity using a standardised measure which ensured that exposure status was measured in a valid and reliable way. The two studies with the lowest overall quality ratings tended not to have reported exclusion criteria for controls; did not compare participants and non-participants; did not clearly establish that controls were non-cases; did not provide validity and reliability information for measures used; did not control for key confounders; and did not report confidence intervals.

Studies were considered to have identified the main potential confounders if they included measures of, and controlled for, the following six key variables in their design or analysis: age, gender, IQ or education, depression, anxiety and fatigue. It is important to control for such confounders as they may explain why some of the dual-tasking difficulties found are common in MS. Only two studies controlled for all six variables. All studies controlled for age and gender. Six also controlled for education or IQ level. One study did not include any measures to control for depression, anxiety or fatigue variables. Seven studies controlled for one of these three variables. More specifically, six of the seven studies included a measure of depression, six included a measure of fatigue, and three included a measure of anxiety. Only three studies included measures of all three of these potential confounding variables. Two additional confounders were important to consider for one paper that used a driving simulator: visual acuity and motor ability. This paper controlled for seven potential confounders (excluding level of education).

Overall, it was difficult to ascertain whether study quality influenced findings, due to differences in measures used to assess DA, discrepancy between the key potential confounders controlled for and methodological limitations (outlined below). For example, although all eight studies utilised neuropsychology tests to assess DA, the measures used varied and in one particular study [Devos et al., 2013] one of the two DA measures was only used in the MS group. This meant performance on that measure could not be compared with control subjects.

Effect Sizes

Effect sizes could not be calculated for one paper, but were calculated for each measure of DA for the seven remaining studies. Two of the seven studies had reported effect sizes. For the five studies that did not report effect sizes, Cohen's *d* or *r* was calculated for differences between groups on all measures of DA. One of the five studies reported median and interquartile-ranges (IQR) [Devos et al., 2013], and therefore an estimated mean and variance (standard deviation) was calculated using the formulas (below) [Hozo, Djulbegovic, & Hozo, 2005]; Cohen's d was then calculated using the estimated figures. For both formulas: median (m); low end of IQR (a); and high end of IQR (b).

$$\bar{x} \approx \frac{a + 2m + b}{4}$$

Formula 1: Calculating estimated mean

$$S^2 = \frac{1}{12}\left(\frac{(a - 2m + b)^2}{4} + (b - a)^2\right).$$

Formula 2: Calculating estimated variance

Table 2 summarises effect sizes for all DA measures used where effect size calculations were possible. An overall weighted effect size was not calculated given the heterogeneity of the measures used. Calculated individual effect sizes ranged from 0.00 to 5.77 across studies, with a median individual effect size of 0.69, which is in the medium–large effect size range [Cohen., 1988].

Table 2: Summary of Individual Effect Sizes for Divided Attention Tasks in Studies

ID	Study	ES Calculated (Y/N)	DA Test	Effect Size
A	Claros-Salinas (2013)	N	-	-
B	Devos (2013)	Y	Driving Simulator (RT) Driving Simulator (AR)	*d* = 5.35 *d* = 5.77
C	McCarthy (2005)	Y	Bimodal Task (RT) Bimodal Task (AR)	*d* = 1.18 *d* = 0.50
D	Patanella (2010)	Y	MFTC (RT) MFTC (AR) SDMT (AR) TMA (RT)	*d* = 1.07 *d* = 0.00 *d* = 0.71 *d* = 0.83
E	Paul (1998)	Y	SDMT (AR) PASAT 2.4s (AR) PASAT 1.6s (AR) G-LAS: NB/GT (RT) G-LAS: NB/LT (RT) G-LAS: LB/GT (RT) G-LAS: LB/LT (RT) G-LAS: GB/GT (RT) G-LAS: GB/LT (RT)	*d* = 1.33 *d* = 0.89 *d* = 0.77 *d* = 1.21 *d* = 0.67 *d* = 1.16 *d* = 0.96 *d* = 1.23 *d* = 0.93

F	Ruet (2013)	Y	*PPMS vs. C*	
			TAP (RT): Visual	*d* = 0.40
			TAP (RT): Auditory	*d* = 0.20
			TAP (AR): Visual	*d* = 0.00
			TAP (AR): Auditory	*d* = 0.00
			RRMS vs. C	
			TAP (RT): Visual	*d* = 1.40
			TAP (RT): Auditory	*d* = 0.30
			TAP (AR): Visual	*d* = 0.00
			TAP (AR): Auditory	*d* = 0.00
G	Sonneville (2002)	Y	ANTP: V-SP (RT)	*r* = 0.44
			ANTP: V-SP (Errors)	*r* = 0.32
			ANTP: M-S (RT)	*r* = 0.59
			ANTP: M-S (Errors)	*r* = 0.28
H	Stoquart-ElSankari (2010)	Y	SRT dual-task (RT)	*d* = 0.92
			SRT dual-task (%A)	*d* = 0.12
			SRT dual-task (%O)	*d* = 0.27

Note: Effect size (Cohen's *d* or *r*) of difference between Multiple Sclerosis (MS) and Control groups. Effect size calculated when studies reported both MS and Control performance data for Divided Attention measures.

Abbreviations: ES = Effect Size; RT = Reaction Time; AR = Accurate Responses; MFTC = Multiple Features Target Cancellation Test; SDMT = Symbol Digit Modalities Test; TMA = Trail Making Test A; PASAT = Paced Auditory Serial Addition Test; G-LAS = Global-Local Attention Shift; NB = Neutral Bias; LB = Local Bias; GB = Global Bias; GT = Global Target; LT = Local Target; PPMS = Primary Progressive Multiple Sclerosis; RRMS = Relapsing Remitting Multiple Sclerosis; C = Controls; TAP = Test of Attentional Performance; ANTP = Amsterdam Neuropsychological Tasks Program; V-SP = Visuo-spatial processing; SRT = Simple Reaction Time; %A = percentage anticipations; %O = percentage omissions; M-S = Memory-Search.

Methodological Limitations of Reviewed Studies

Several methodological limitations were identified. Firstly, there was considerable variability in the tests used to measure DA (see table 1).

Five of the eight studies used a single measure of DA. Of these five studies, one study used the Test of Attentional Performance (TAP), a test used to examine different aspects of attention. Another study used the mobility version of the TAP test namely TAP-M, which was developed to test aspects of attention in driving abilities [Zimmerman & Fimm, 2005]. The third study used the Divided Attention Task (DAT), which uses visual, auditory and bimodal tasks. The fourth study used the 'Visuo-spatial Processing' and 'Memory Search' subtests of the Amsterdam Neuropsychological Tasks Program (ANTP). Finally, the fifth used a Simple Reaction Time (SRT) task under single and dual-task conditions. The three remaining studies used multiple measures of DA in their studies. One used a Driving Simulator with DA task and the Directions and Compass Tasks. Another used the Multiple Features Target Cancellation Test (MFTC), the Symbol Digit Modalities Test (SDMT) and the Trail Making Test – Part A (TMA). The final study used the oral version of the SDMT, the Paced Auditory Serial Addition Test (PASAT); and the Global-Local Attention Shift (G-LAS) test.

A critical issue was whether the tests used actually measured DA. Dual-tasking paradigms have been utilised to study DA and the fundamental properties of the central executive system in several populations [Baddeley, Bella Sala, Gray, Papagno, & Spinnler, 1997]. A measure was deemed to have successfully measured DA if it adhered to a dual-task paradigm, which requires participants to perform two different tasks individually and then simultaneously, with DA being examined in relation to the dual-task cost (i.e. level of decrement in performance from single to dual-task conditions). Two of the eight studies included a measure of DA that met this criteria and statistically examined interactions of single and dual-task performance between MS and control groups [McCarthy et al., 2005; Stoquart-ElSankari et al., 2010]. These studies used the following tests: DAT and SRT Task. Both studies found a significant dual-task cost in the MS group compared to controls. However, only one paper assessed DA performance by type of MS (RRMS and PPMS) as opposed to MS group as a whole [Stoquart-ElSankari et al., 2010]. This paper found a significant decrement in performance from single to dual-task in both

forms of MS compared to controls, with PPMS individuals performing worse than RRMS.

The remaining six studies used a range of other test formats. One study used the TAP-M test and stated that their participants completed visual and auditory tasks simultaneously, however, did not state whether the two tasks also had to be performed under single task conditions. Another study that used a driving simulator with a DA task did not ask participants to complete tasks individually, only simultaneously. A further study used the TAP test and although tasks were completed individually then simultaneously, DA decrement was not examined in relation to the dual-task cost. The remaining three studies used the following tests: MFTC, SDMT, TMA, PASAT, G-LAS and ANTP. None of these tests meet dual-task paradigm criteria, as they do not require individuals to attend to two tasks or streams of information simultaneously. The SDMT and TMA tests ask individuals to attend to one task and complete it as quickly and accurately as they can. The MFTC, PASAT, G-LAS and ANTP tests require persons to attend to one task and select target items amongst distractor items.

A third factor was the lack of control for potential confounding variables. Studies were considered to have identified the main potential confounders if they controlled for six key variables in their design or analysis (see above quality rating section). Six of the eight included studies did not control for all aforementioned potential confounding variables. This made it difficult to determine if relationships found between independent and dependent variables in these studies were confounded by other variables.

A final methodological limitation was a lack of statistical exploration of disease severity range and performance on DA tasks. The most routinely used tool to measure MS disease progression in research trials is the Expanded Disability Status Score (EDSS) [Goldman, Motl, & Rudick, 2010], which is a 10-point scale. A score of 0–3.5 indicates that MS disease progression is in the low range and is based on changes in one or more functional system e.g. ambulation. A score of 4.0–6.0 is in the moderate range and is based on gait dysfunction. Scores of 6.0–7.5 is the moderate–severe range and is based on walking function. Scores over 7.5 are in the severe range and are based on loss of ambulation (score 8.0), loss of upper

extremity function (score 8.0–9.0), loss of bulbar function (score 9.0–9.5) and finally death (score 10) [Goldman et al., 2010].

Seven of the eight included studies reported EDSS scores. Six of the seven used Kurtzke's (1983) version of EDSS and one used a French adapted version of this tool. EDSS scores were reported as range, mean or both. The remaining study used the Ambulatory Index (AI) to measure disease progression. The AI is a 9-point scale which measures overall physical disability. A score of zero indicates no physical disability whilst a score of nine indicates wheelchair-dependency [Paul et al., 1998].

To establish if a DA deficit is present early in the MS disease course, it is important to determine whether DA deficits are present in individuals with low-range EDSS scores. Two studies [Claros-Salinas et al., 2013; Devos et al., 2013] reported EDSS but did not explore DA task performance in terms of disease severity range. Both studies had EDSS scores ranging from 1.0–6.0 (low–moderate severity). One found a DA deficit in the MS group as a whole compared to controls whilst the other did not report necessary data to determine if a DA deficit existed. One of the six remaining studies included solely RRMS participants [Patanella et al., 2010], had a mean EDSS of 1.4 (low range) and found a significant difference between RRMS and controls on reaction time but not accuracy for the DA tasks used.

Five studies reported EDSS scores for the different forms of MS, which further allowed for consideration of the relationship between EDSS severity range and DA task performance. One of the five studies [McCarthy et al., 2005] had an EDSS score range of 1.0–8.5 but found no significant differences in EDSS scores between MS subtypes (RRMS and CPMS). However, this study did find a DA deficit in the MS group as a whole compared to controls. Conversely, the remaining four studies found a significant difference in EDSS/AI scores between MS subtypes. In all four studies, RRMS participants scored within the low disease progression range whilst other forms of MS (PPMS; SPMS) scored 3.5–6.1 across studies (moderate range). One of the four studies did not differentiate between MS subtype and DA task performance but did find a DA deficit in the MS group as a whole compared to controls [Paul et al., 1998]. The remaining three studies explored DA task performance between the control group and both the entire MS group and MS subtypes. Two studies found a significant difference in DA performance between the MS and control groups and

also between RRMS and PPMS subgroups and the controls. Both studies also found that progressive subtypes performed worse than RRMS participants. The final study found no significant differences on DA task performance between either MS subtype, RRMS and PPMS, and their matched controls.

The differing approaches to exploration of the relationship between disease severity and performance on DA tasks made it difficult to ascertain if the DA deficits reported were seen early in disease course or not. More specifically, when entire MS groups were compared to controls, if a DA deficit was found, it was difficult to determine what range(s) of disease severity contributed to this. For example, it could be that those with higher EDSS scores are strongly influencing DA scores. Three studies examined DA task performance in the MS subtypes and compared them to controls. In these studies participants with RRMS had an EDSS in the low range. Two of the three studies found a DA deficit in the RRMS group; one did not. Two of these three studies controlled for all confounding variables (outlined above), one found a deficit [Stoquart-ElSankari et al., 2010] and one did not [Ruet et al., 2013]. This discrepancy in results could be due to different tests of DA being used.

Discussion

This review asked three questions: (1) is there a DA deficit in RRMS; (2) what methods are used to measure DA in RRMS; and (3) if there is a DA deficit, does this seem to be evident early in the disease course? Firstly, six of the eight included studies found a DA deficit in the RRMS group in comparison to control subjects. Secondly, various methods were used to measure DA; this was a methodological limitation. Lastly, due to a lack of statistical exploration of the relationship between level of disease severity and performance on DA tasks, it was difficult to ascertain if the DA deficits found were seen early in disease course or not.

Two of the eight included papers did not find a DA deficit in RRMS participants. One paper did not report a comparison between groups on DA task performance and therefore it could not be determined whether a DA deficit was present, despite including a control group in their study and reporting comparisons on other cognitive domains [Claros-Salinas et al., 2013]. The other paper compared performance between groups on the DA measure but no statistically significant difference was found [Ruet et al., 2013]. The latter paper reported ratio scores for the

DA task used (TAP: DA Subtest) which gave a form of decrement score. Results suggested that for most patients and controls no decrement was found. For example, controls had a ratio score of 1.0 on several measures with a standard deviation of 0.0 indicating no variation in scores at all. This means that the distributions were not normally distributed and therefore the use of parametric t-tests was inappropriate. This may partly explain why a DA deficit was not found in this paper.

Several methodological limitations were identified in the eight included studies, which made it difficult to answer the three review questions. When considering the concept of DA and how best to measure this ability, it is important to consider cognitive models of attention. Arguably, the most frequently referenced theory of attention is Baddeley's (1986) working memory model [Baddeley et al., 1997]. This multi-structure model proposes that a central executive regulates and allocates limited attentional resources to two slave systems: phonological loop and visuospatial sketchpad. A pivotal role of the central executive system is to efficiently apportion and manage attentional resources when two or more tasks are being performed simultaneously or when attention is divided between the two slave systems. Dual-tasking or DA paradigms have been utilised considerably to study the fundamental properties of the central executive system in several patient populations [Baddeley et al., 1997]. Of the eight included studies, only two adhered to a dual-task paradigm when measuring DA.

The two studies that adhered to a dual-task paradigm used the following tests: DAT and SRT Task. The six remaining studies utilised a variety of different tests with dissimilar designs. For example, the PASAT asks participants to listen to digits presented at either 2 or 3-second intervals and add each new digit to the number presented immediately beforehand. In contrast, the SDMT requires participants to quickly and accurately pair numbers and figures using an index key. Whether these tests truly measure DA is questionable. The designs of such tests arguably involve different cognitive abilities such as sustained attention, working memory and processing speed as opposed to DA. The PASAT and SDMT have commonly been used and have been proven to be sensitive to information processing speed and working memory deficits in individuals with MS [Skelly, Dettori, & Brodt, 2012; Wood et al., 2012]. However, it is debateable whether these tests satisfy Baddeley and colleagues suggested methodological criteria for comprehensively measuring DA.

Given the varying methodologies of the included measures of DA used across the eight studies, and that a significant number did not adhere to a dual-task paradigm, the DA deficits reported are called into question.

Another factor that made it difficult to determine if a true DA deficit existed was the lack of control for potential confounding variables. This potentially leads to flawed conclusions regarding the association between independent and dependent variables [Wood et al., 2012]. Controlling for all potential confounding variables ensures that if a relationship between the independent and dependent variables are found, this is a true association [Skelly et al., 2012]. Looking solely at the two studies that controlled for all six potential confounding variables (age, gender, education/IQ, anxiety, depression, fatigue) [Ruet et al., 2013; Stoquart-ElSankari et al., 2010], although both studies controlled for confounders and included measures of DA that adhered to a dual-task paradigm, only one found a deficit in DA when comparing RRMS performance with controls [Stoquart-ElSankari et al., 2010]. Overall, it is unclear if mood or fatigue levels have contributed to the reported DA deficits seen in the MS groups and therefore whether a true DA deficit exists in RRMS.

With regard to confounders, whilst one might want to control for these variables to understand whether there is a direct link between MS pathology and DA deficits, it is still important to know whether there is an uncontrolled difference between groups because it may be that a ‘confounder’ is actually a moderator, or even a mediator of the effect. For example, it may be that anxiety is a mediator such that anxiety depletes attentional resources making dual-tasking more difficult and that people with MS are more likely to be anxious than healthy controls. Thus controlling for anxiety would potentially remove the difference between people with MS and controls, but that does not mean that people with MS do not have a DA deficit.

The final factor that made it difficult to answer the third review question was a lack of statistical exploration of disease severity range and performance on DA tasks. It is important to consider if DA difficulties occur early in MS so that interventions, which may ameliorate deficits in attention, can be introduced in a timely manner. If we know deficits in DA are relatively common in these earlier stages clinicians will be in a better position to inform patients to try to be aware of them and seek help in managing them. As MS progresses, the more wide ranging cognitive difficulties may be present including DA problems but it is less certain that such difficulties are

present earlier in the disease course. Although all studies incorporated a standardised measure of disease progression (EDSS or AI), there was a lack of consideration given to level of disease severity and cognitive performance. However, in three studies participants with RRMS had an EDSS in the low severity range. Two of the three studies found a DA deficit in the RRMS group; one did not. Two of these three studies controlled for all confounding variables, one found a deficit [Stoquart-ElSankari et al., 2010] and one did not [Ruet et al., 2013]. This discrepancy in results could be due to different tests of DA being used. Overall, it remains unclear whether a DA deficit exists early in MS disease progression.

Future Research

None of the included studies aimed to solely assess DA in MS. Future research should be conducted to answer this specific question in order to clearly ascertain whether decrement found under dual-task conditions is a result of a central problem with DA or if it is a resource limitation issue. Below are recommendations for future researchers to consider when designing a study.

Recommendations

1. Methodology should include a justification of sample size based on power calculations.
2. Study design should incorporate clear inclusion and exclusion criteria for both case and control subjects.
3. All potential confounders should be taken into consideration at the study design level. Principally: age, gender, education or IQ level, mood and fatigue. Matching case and control subjects by age, gender and education/IQ level will control for these potential confounders. It is also important to explore the possible contribution of mood and fatigue levels on performance of DA measures using valid and reliable measures.
4. Careful consideration should be given to test selection to ensure DA is accurately measured. Incorporating tests that adhere to Baddeley and colleagues' dual-task paradigm.
5. Study design should incorporate a standardised tool of disease severity such as EDSS to measure disease progression and severity.

Conclusion

It was not possible to definitively conclude that a DA deficit is evident in individuals with RRMS. This was due to the varying methodologies employed and varying measures of DA used, a lack of adherence to a dual-task paradigm, and limited control for potential confounding variables across the eight included studies. Two of the eight studies used a measure of DA that met dual-task paradigm criteria and statistically examined interactions of single and dual-task performance between MS and control groups. Both studies found a significant dual-task cost in the MS group compared to controls. However, one study had a 'low quality' rating and did not assess DA performance by type of MS i.e. RRMS. The remaining study used a measure of DA that met dual-task paradigm criteria, controlled for all confounding variables, and had 'acceptable' quality rating. This study found that RRMS participants performed significantly more poorly than controls on the DA task (SRT Task). This suggests that a DA deficit may exist in RRMS and warrants further investigation. Future studies should address outlined methodological issues.

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CHAPTER TWO: MAJOR RESEARCH PROJECT

Balancing the Demands of Two Tasks: An Investigation of Cognitive-Motor Dual-Tasking in Relapsing Remitting Multiple Sclerosis

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Prepared in accordance with authors instructions for the Journal of the International Neuropsychological Society (see Appendix 2.1)

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Plain English Summary

Background: Impairments in memory and thinking abilities (cognition) and problems with balance are common in Multiple Sclerosis (MS). Such difficulties can impact on a person's ability to take part in meaningful everyday activities, maintain a job and are associated with reduced quality of life. Although evidence shows there are shortfalls in memory and thinking abilities and balance performance in MS, few studies have examined the link between these factors in people with MS. A small number of studies that use 'dual-task designs', where people are asked to perform a cognitive task by itself, a balance task by itself, and to do the cognitive and balance tasks at the same time, have found that people with MS have difficulty doing the two tasks at the same time. In contract, other studies have found people with MS can perform the two tasks together with little difficulty. **Objective:** To investigate: (1) Whether individuals with MS have more difficulty performing balance and cognitive tasks at the same time compared to healthy control subjects; (2) If there is a connection between how people perform when doing two tasks at the same time and scores on a questionnaire that ask how able people are doing two things at the same time in everyday life. In addition, levels of anxiety and depression, tiredness and severity of MS were examined to see if they impacted a person's ability to do a cognitive and a balance task at the same time. **Methods:** Thirty-four participants with Relapsing Remitting MS (RRMS) and thirty-four healthy controls took part. Participants completed cognitive and balance tasks separately and at the same time. The cognitive task required participants to listen to pre-recorded numbers and repeat them back in reverse order to how they heard them (e.g. heard 5-2-4; answer 4-2-5). The balance task required participants to stand barefoot on a metal or foam surface and hold their balance as best they could. When doing the two tasks at the same time, participants had to listen to the numbers and repeat them back in reverse order at the same time as holding their balance as best they could. **Results:** Participants with RRMS had more difficulty doing the balance and cognitive tasks at the same time compared to controls. Tiredness and severity of MS did not impact a person's ability to do the two tasks at the same time. However, it appears that when a person with RRMS is more anxious or depressed this influences their ability to perform the two tasks at the same time. **Conclusions:** RRMS causes difficulties doing a cognitive and a balance task at the same time, impacting particularly on ability to

maintain balance. This may contribute to an increased risk of walking difficulties and falls. The striking relationship between anxiety/depression and dual-task performance suggests that worry may be contributing to difficulties doing two tasks at the same time. This raises the possibility that Psychological interventions aimed at managing worry may improve a person's ability to do a cognitive and a balance task at the same time.

Abstract

Background: People with relapsing remitting MS (PwRRMS) suffer disproportionate decrements in gait under dual-task conditions, when walking and a cognitive task are combined. There has been much less investigation of the impact of cognitive demands on balance. This study investigated whether: (1) PwRRMS show disproportionate decrements in postural stability under dual-task conditions compared to healthy controls; (2) dual-task decrements are associated with everyday dual-tasking difficulties. In addition, the impact of mood, fatigue and disease severity on dual-tasking were also examined. **Methods**: 34 PwRRMS and 34 matched controls completed cognitive (digit span) and balance (movement of centre of pressure on a Biosway, on stable and unstable surfaces) tasks under single and dual-task conditions. Everyday dual-tasking was measured using the DTQ. Mood was measured by the HADS. Fatigue was measured via the MFIS. **Results**: No differences in age, gender, years of education, estimated pre-morbid IQ or baseline digit span between the groups. Compared to healthy controls, PwRRMS showed a significantly greater decrement in postural stability under dual-task conditions on an unstable surface (p=0.007), but not a stable surface (p=0.679). PwRRMS reported higher levels of everyday dual-tasking difficulties (p<0.001). Balance decrement scores were not correlated with everyday dual-tasking difficulties, or with fatigue. Stable surface balance decrement scores were significantly associated with levels of anxiety (rho=0.527, p=0.001) and depression (rho=0.451, p=0.007). **Conclusion**: RRMS causes difficulties with dual-tasking, impacting balance, particularly under challenging conditions, which may contribute to an increased risk of gait difficulties and falls. The striking relationship between anxiety/depression and dual-task decrement suggests that worry may be contributing to dual-task difficulties.

Key words: Adult, attention, memory, neuropsychological tests, postural stability, balance, multiple sclerosis, nervous system disorders

Introduction

Cognitive impairment is common in Multiple Sclerosis (MS), occurs at all disease stages and can be a primary source of social dysfunction, occupational disability and diminished quality of life [Rodgers & Panegyres, 2007]. Estimated prevalence of cognitive impairment in people with MS (PwMS) ranges between 43% and 65% [Denney, Sworowski, & Lynch, 2005] typically involving difficulty with attention, memory, information processing speed and executive functions [Goretti et al., 2014; Whelan et al., 2010].

Balance and gait difficulties and associated risk of falling in PwMS are well documented [Cattaneo et al., 2002; Leone, Patti, & Feys, 2015]. Where balance or gait is impaired, greater attention allocation may be required to maintain effective stability. Postural control has been defined as, "the control of the body's position in space for the purposes of balance and orientation" [Shumway-Cook & Woolacott, 2000]. Conventionally it has been considered a reflex or automatic controlled task, with the implication that minimal attentional resource is used by postural control systems [Woolacott & Shumway-Cook, 2002]. Recent research contradicts this hypothesis, suggesting there are substantial attentional requirements for postural control [Donker, Roerdink, Greven, & Beek, 2007; Yogev-Seligmann et al., 2008].

Dual-task designs, where participants perform cognitive and motor tasks concurrently, have been used to investigate the possible interaction of cognitive functioning and posture [Andersson, Hagman, Talianzadeh, Svedberg, & Larsen, 2002]. Boes and associates (2012) investigated the effects of dual-tasking on postural control in PwMS with mild or moderate disability. Participants undertook posturography testing under a single-task and cognitive dual-task condition. Results showed that postural control was compromised by dual-task demands and declined with disability status. Moreover, a small number of studies further suggest that PwMS display a significant decrement in balance or gait under dual-task conditions when compared to control subjects [Hamilton et al., 2009; Cameron & Lord, 2010; Kalron, Dvir, & Achiron, 2010; Jacobs & Kasser, 2012]. Additionally, some research concludes that poor postural control contributes to increased risk of falling for PwMS [Cattaneo et al., 2002; Cameron & Lord, 2010]. However, other studies indicate no decrement in gait and cognition under dual-task conditions [Andersson et al., 2002; Allali, Laidet, Assal, Armand, & Lalive, 2014]. Varying results within the evidence-

base warrant further investigation of balance and gait decrement in PwMS, particularly focused on understanding the impact of dual-tasking on cognitive functioning [Wajda, Motl, & Sosnoff, 2014] and to explore further possible causal factors of dual-task deficits [Leone et al., 2015].

There have been relatively few attempts to explain the presence of dual-tasking decrements. One possibility is that there is a central problem with divided attention so that tasks cannot be combined. Another is that damage to motor systems leads to greater demand for conscious attention while performing motor tasks, and as a result, insufficient attentional resource is available for secondary tasks [Kalron et al., 2010]. A further alternative is that in certain neurological disorders working memory capacity is reduced. This results in more attentional resource being required when performing previously low attentionally demanding cognitive and motor tasks. This increase in attentional demand causes the attentional system to be overloaded, resulting in reduced cognitive capacity [Kalron et al., 2010] and poor balance/gait [Leone et al., 2015]. The evidence so far does not conclusively point to one or other of these possible explanations.

In summary, emerging evidence suggests that deficits in attention and balance/gait are present in MS. However, there is paucity in evidence regarding the interaction of demands on these systems in PwMS. If it is true that for some PwMS, balance/gait difficulties are either only apparent or disproportionally impaired under dual-task conditions, then it may be prudent to measure this routinely in clinical practice. The twofold aim of this study is to investigate: (1) if people with Relapsing Remitting MS (PwRRMS) have increased difficulties with balance and cognitive-motor dual-tasking compared to control subjects; (2) if there is a relationship between dual-task performance and everyday functioning measured by scores on a self-report questionnaire, the Dual-Task Questionnaire (DTQ) [Evans, Greenfield, Wilson, & Bateman, 2009]. In addition, the impact of mood, fatigue and disease severity (EDSS) on dual-tasking will also be examined. Estimated prevalence rates for depression range from 10% to 41.8%; anxiety 23.5% to 41%; and fatigue 60% to 92% [Wood et al., 2012]. In order to determine whether dual-task decrements, if present, are caused by MS disease pathology it is important to consider the impact of potential confounders such as mood, fatigue and level of disease severity.

Hypotheses

1. Compared to healthy controls, PwRRMS will show greater decrement under dual-task conditions compared to single-task conditions on measures of balance, digit span, and a combined decrement score.
2. There will be a significant correlation between measures of dual-task decrement and scores on the DTQ.

Methods

Ethical Approval

Ethical approval was obtained from NRES Committee East Midlands – Nottingham 2 (Appendices 2.2 and 2.3). NHS Highland Research and Development Department granted management approval (Appendix 2.4). Participation in the study was voluntary and all participants provided written informed consent.

Justification of Sample Size

Few studies have examined dual-tasking with postural measures as outcomes. Kalron et al (2011) considered the effect of a cognitive task on postural control in individuals with a clinically isolated syndrome suggestive of MS and control subjects [Kalron, Dvir, & Achrion, 2011]. They found that controls showed greater decrement from single to dual-task conditions than PwMS, but the very mild sample was unrepresentative of PwMS. Jacobs and Kasser (2012) reported that PwMS showed significantly greater decrement compared to controls on a postural task but provided insufficient data to calculate an effect size. Wajda, Motl and Sosnoff (2014) investigated the demographic, cognitive and clinical correlates of dual-task-cost of balance in PwMS but had no control group.

In their study of gait under dual-task conditions, Hamilton et al (2009) found medium-large effect sizes for a number of dual-task decrement measures (ranging from d=0.7 to d=1.5). In the present study we took a number of approaches to try to maximise effect sizes, such as inclusion of a wider range of disability levels of MS participants and use of a backward digit span task which is more challenging than the previously used forward digit span tasks. However, given that the nature of the motor task is different from that used by Hamilton et al, we took a conservative approach and powered the study on the basis of the lower of the effect sizes (d=0.7). Using

G*Power 3.1 [Faul, Erdfelder, Buchner, & Lang, 2009], with power set at 0.8, alpha at 0.05 (two-tailed), d=0.7, a minimum of 34 participants per group was required.

Participants

Thirty-five RRMS participants were recruited through NHS Highland Neuropsychology, Neurology, MS Nurses and MS Therapy Centre services. Inclusion criteria for RRMS participants were: (i) diagnosis of RRMS; (ii) aged between 17-65 years; (iii) free of relapse 30 days prior to task administration; (iv) an Expanded Disability Status Scale (EDSS) Score of up to 6.5 [Multiple Sclerosis Trust., 2013] (v) capacity to consent. A Consultant Neurologist sub-specialising in MS confirmed diagnosis and EDSS Score based on standardised investigation and in alignment with the revised McDonald diagnostic criteria [Polman et al., 2010]. Thirty-four control participants included a convenience sample of family of the MS participants and volunteers recruited through poster advertisement in local hospitals. Volunteers were accepted as control participants if they matched an RRMS participant by age and gender. Exclusion criteria for all participants were: (i) presence of major psychiatric disorders; (ii) history of neurodegenerative disease (other than MS) or brain injury; (iii) significant sensory deficits e.g. visual impairment; and (iv) severe co-morbid health condition affecting motor abilities e.g. diabetes; (v) inability to stand (for whatever reason).

Design

A between-subjects design was used to compare balance and dual-tasking performance amongst RRMS and control participants under single and dual-task conditions. A within-subjects design was used to examine the association between self-reported scores on mood and the divided attention questionnaire and dual-tasking performance.

Measures

Demographic information was collected from all participants (gender, age, education) and in addition for RRMS participants, disease onset, years of illness and EDSS score.

Baseline Assessment

Hospital Anxiety and Depression Scale (HADS) [Zigmond & Snaith., 1983] (all participants)

Anxiety and depression were screened using the HADS. This self-report measure was designed for use with non-psychiatric hospital patients. The HADS reliability and validity has been described as being good to very good with internal consistency coefficients of 0.8, concurrent validity of 0.6–0.8 and both specificity and sensitivity of 0.8 [Bjelland, Dahl, Haug, & Neckelmann, 2002]. An exclusion criterion of this study was the presence of major psychiatric disorders. The authors of the HADS recommend that, for depression and anxiety scales alike, raw scores of 8-10 identify mild cases, 11-15 moderate, and 16+ severe [Zigmond & Snaith, 1983]. Therefore, if participants scored 16+ on either the anxiety or depression items of the HADS they would be excluded from the study.

Modified Fatigue Impact Scale (MFIS) [MSCCP., 1998] (all participants)

This 20-item self-report measure was used to assess fatigue. It is a recommended measure of fatigue in MS [MSCCP., 1998] with good reliability and validity. It has an intra-class correlation coefficient of 0.91, internal consistency coefficient of 0.92 and a convergent validity coefficient of 0.67 [Kos et al., 2005].

Multiple Sclerosis Impact Scale (MSIS-29) [Hobart, Lamping, Fitzpatrick, Riazi, & Thompson, 2001] (RRMS participants only)

This 29-item self-report measure was used to assess quality of life in PwRRMS. It has been shown to have good variability, small floor and ceiling effects, high intra-class correlation coefficient of 0.87, and high internal consistency coefficients of 0.91 [Hobart et al., 2001].

Dual-Task Questionnaire (DTQ) [Evans et al., 2009] (all participants)

The 10-item DTQ was used to measure self-reported ability to divided attention. This questionnaire asks PwMS to rate how often they experience certain dual-task difficulties in day-to-day life. For example, “do you need to stop an activity to talk?” There are 5 response options ranging from *very often* to *never, or not*

applicable. Evans et al. reported a test-retest correlation of 0.690 ($p<0.04$) [Evans et al., 2009].

Test of Premorbid Function (TOPF) [Wechsler., 2011] (all participants)

Premorbid intellectual functioning was assessed using the TOPF. It has been shown to have a high level of internal reliability (0.95) and high test-retest stability (correlations ranging from 0.89 to 0.95) [Pearson Education Ltd, 2010].

Addenbrooke's Cognitive Examination (ACE-III) [Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013] (all participants)

The ACE-III, a short cognitive test designed to screen for dementia, was utilised to assess general cognition. It has not been validated specifically with an MS population but has been used in one prior MS study [Hamilton et al., 2009] to describe basic cognitive functioning of MS and control subjects. Sensitivity is reported to be 0.94 and specificity 0.89 for the optimal cut-off in relation to distinguishing people with dementia from controls. This is with a cut-off score of 88/100 [Hodges., 2007].

Cortical Vision Screening Test (CORVIST) [James, Plant, & Warrington, 2001] (all participants)

This 10-subtest measure was used to assess visuoperceptual ability. Each subtest measures a different aspect of visual processing and identifies cortical based visual problems. The CORVIST was used to ensure participants did not have significant visual impairment.

Backwards Digit Span [Cocchini et al., 2004] (all participants)

Individual digit span assessments were completed based on a method developed by Cocchini et al (2004) (see appendices 2.10–2.13). At baseline, digit span was established for each individual. Participants heard digit lists at a rate of one per second and were asked to repeat these back in reverse order (e.g. heard: 5-2-4; answer: 4-2-5). Initial span length was two digits and participants were presented with six sequences at each span length. If five out of six digits were accurately recalled, the digit sequence was lengthened by one digit. Individual digit span was

determined as the last sequence length at which five out of six responses were correct. Established individual span length was then used during single and dual-task conditions.

Balance Tasks

BioSway [Biodex., 2015] (all participants)

Postural stability was measured using the BioSway, which is a flexible balance assessment device. It measures neuromuscular control and capability to balance on firm and unstable surfaces. It has good reliability with an intra-class correlation coefficient of 0.81 [Biodex., 2015]. The dimensions of the platform are 21.25”w x 19.00”l x 2.56”h. Sensors embedded in the platform produce an Anterior/Posterior Stability Score (APSS), a Medial/Lateral Stability Score (MLSS) and a person’s Overall Stability Index (OSI). These indexes are standard deviations assessing flux around the zero or central point (i.e. horizontal). The OSI is a composite of the MLSS and APSI and was the primary stability score used in this study.

During the four balance tasks participants stood barefoot on the BioSway with eyes open and hands by their sides. To ensure measurement of normal balance, if a participant used a walking aid to balance day-to-day they were asked to use this aid whilst undertaking all study-related balance tasks. Foot position was taken in a comfortable position on the unstable surface prior to task commencement and the same foot position was used for each task. Participants stood on a stable surface during tasks 2 and 4 and an unstable surface for tasks 3 and 5. They were instructed to focus on holding their balance throughout single-task conditions (2 and 3) and to simultaneously focus on holding balance and saying aloud, in reverse order, numbers heard during dual-task conditions (4 and 5). OSI scores were calculated under single and dual-task conditions and dual-task decrement score calculated in terms of percentage change from single to dual-task conditions.

Cognitive Task

During one single and two dual-task conditions participants listened to sequences of digits at their individualised digit span length. Pre-recorded digit sequences were played aloud and participants were required to repeat each sequence in reverse order. Responses were recorded manually. Scores were

calculated by allocating one point for each digit in the correct place in a sequence. The total correct was then calculated. To obtain percentage correct scores, the total score was divided by the total possible correct score and multiplied by 100.

Procedure

At routine appointments, PwRRMS who met the study criteria were informed about the study by their Neuropsychologist, Neurologist, MS Nurse or MS Therapy Centre Manager. Those who expressed an interest were provided with the participant information sheet. If consent and contact information was provided, after 24 hours, the researcher contacted potential participants by telephone to provide further information regarding the study and answer any questions. Control participants contacted the researcher using contact details on the poster. If verbal consent was given, arrangements were made to meet and written consent was obtained.

All participants completed baseline assessment measures as previously described. Subsequently, all participants undertook three single and two dual-tasks. Task 1 required participants to complete a titrated backward digit span task. Task 2 involved participants standing on the BioSway platform, stable surface, for a total of 80 seconds with a 15 second break half way. Task 3 involved participants standing on the BioSway platform, unstable surface, for 80 seconds with a 15 second rest half way. For Task 4, participants stood on the BioSway platform, stable surface, whilst simultaneously completing the backwards-span task. Task 5 required participants to stand on the BioSway platform, unstable surface, whilst completing the backwards-span task. To ensure consistency of delivery, instructions for balance tasks were pre-produced by the researcher and instructions for digit span were based on the backwards digit span subtest in the WAIS-IV [Pearson Education Ltd, 2008]. To control for order effect, task order was randomly assigned. A simple function in Excel was used to produce different combinations of 1-5 to ensure that the 68 participants completed the three single and two dual-tasks in a different order from one another.

Results

Data Analysis

Distributions of all variables were examined for normality. All scores apart from age and DTQ were not normally distributed. Where appropriate, a parametric

approach was used and a non-parametric approach was adopted for all other scores. Descriptive statistics were produced to describe the data. Independent samples T-tests and Mann-Whitney U tests were used as appropriate to compare groups on demographic information, baseline clinical features, and on single-task and dual-task performance. Using Mann-Whitney U-Test, measures of dual-task decrement (for balance and digit span tasks) were compared for both groups. Spearman correlations were used to examine whether there was a relationship between DTQ scores and individual dual-task decrement scores. Spearman Correlation coefficients *(r)* were used firstly to explore relationships between self-reported anxiety and depression and dual-task decrement scores and secondly, to examine disease severity (EDSS Score) and dual-task decrement scores in the MS group only. To balance risk of type I and II errors, a Bonferroni correction was applied - the level of significance was reduced by the number of correlations calculated for each factor. More specifically, four different correlations were derived for each factor; therefore the p-value was divided by four to reduce the likelihood of type I errors, whilst maintaining reasonable power. Therefore, the significance level became 0.0125 for these correlations. All effect sizes were reported as Cohen's *r* for consistency.

Descriptive Characteristics

Data were collected for 35 RRMS and 34 control participants. Data for one RRMS participant could not be used due to a leg tremor during balance testing. Data included in statistical analysis were therefore taken from 34 PwRRMS and 34 healthy control participants. Demographic and clinical characteristics of each group are outlined in Table 1. There were no significant differences in age (t (df 66) = 0.207), gender (t (df 66) = 0.000), years of education (z=-1.101), estimated pre-morbid IQ (z=-1.695) or baseline digit span (z=-1.108) between the groups. A significant difference was found between groups for self-reported DTQ scores (p<0.001; d=2.30; r=0.75; t (df 66) = 9.476) - PwRRMS reported greater difficulty dual-tasking day-to-day compared to controls. RRMS performance was significantly poorer on the ACE-III compared to healthy controls (p<0.001; r=-0.76; z=-6.306). All thirty-four control subjects scored above the two clinical cut-offs compared to twenty-five RRMS participants. Five PwRRMS scored below the first cut-off (score of 88) and four scored below the second cut-off (score of 82). PwRRMS self-reported greater levels

of fatigue (p<0.001; r=-0.69; z=-5.683), depression (p<0.001; r=-0.55; z=-4.543) and anxiety (p<0.001; r=-0.43; z=-3.548) compared to controls.

Performance under single and dual-task conditions

Data was analysed to establish performance on digit span and balance tasks under single and dual-task conditions. Significant differences were found between groups on all digit span tasks (single-task: z=-3.236, u=330, p<0.001, r=-0.39; dual-task stable: z=-4.596, u=210, p<0.001, r=-0.56; dual-task unstable: z=-6.536, u=50, p<0.001, r=-0.79). Significant differences were also found between groups on all balance tasks (single stable: z=-4.683, u=204, p<0.001, r=-0.57; single unstable: z=-5.189, u=159, p<0.001, r=-0.63; dual-task stable: z=-3.828, u=269, p<0.001, r=-0.46; dual-task unstable: z=-5.888, u=101, p<0.001, r=-0.71). Table 2 and Figure 1 summarise RRMS and control participant performance on all single and dual-tasks.

Table 1: Participant Demographic and Clinical Characteristics

	MS Participants *n* = 34	Control Participants *n* = 34	*P* value**
Demographic variables			
Age	43.06 ± 9.92	42.56 ± 10.05	0.837
Gender			
- Female	28	28	
- Male	6	6	1.000
Years of Education	15.00 [12.875–18.250]	16.50 [13.375–19.00]	0.271
Clinical Variables			
Dual-Task Questionnaire Score	22.85 ± 7.37	7.76 ± 5.65	<0.001*
HADS Score			
- Depression	5.00 [2.00–9.00]	1.00 [0.00–3.00]	<0.001*
- Anxiety	8.50 [5.00–10.00]	4.00 [2.00–6.25]	<0.001*
MFIS Score	47.00 [37.50–58.75]	11.50 [2.00–25.00]	<0.001*
TOPF Score	47.00 [31.75–57.00]	56.00 [40.75–65.00]	0.090
ACE-III Score	92.00 [86.50–96.00]	99.00 [98.00–100.00]	<0.001*
Backwards Digit Span Baseline Score	4.00 [3.00–4.00]	4.00 [3.00–5.00]	0.268
MS Participants Only			
EDSS Score	4.0 [3.0–4.0]	-	-
MSIS-29 Score	78.50 [63.00–99.25]	-	-
Using MS Medication	17 (50%)	-	-

Note: Values are mean ± standard deviation, median [lower–upper interquartile range] or *n*.

**p value for difference between RRMS versus healthy control participants

*Statistically significant difference for RRMS versus healthy control participants.

Table 2: RRMS and Control Participant Performance on all Single and Dual-tasks

	MS Participants *n* = 34	Control Participants *n* = 34	*P* value**	effect size (r)^
Cognitive Task				
Digit Span %C Single Task	96.00 [93–100]	100.00 [97–100]	<0.001*	0.39
Digit Span %C Dual-task 1 (stable)	88.00 [79.50–95.25]	98.50 [94-100]	<0.001*	0.56
Digit Span %C Dual-task 2 (unstable)	78.00 [60–82.25]	100.00 [92–100]	<0.001*	0.79
Balance Task				
OSI Single Task (stable)	0.550 [0.300–0.800]	0.300 [0.200–0.300]	<0.001*	0.57
OSI Single Task (unstable)	0.800 [0.575–1.125]	0.400 [0.300–0.600]	<0.001*	0.63
OSI Dual-task 1 (stable)	0.550 [0.400–1.225]	0.300 [0.200–0.500]	<0.001*	0.46
OSI Dual-task 2 (unstable)	1.050 [0.675–1.500]	0.500 [0.300–0.600]	<0.001*	0.71

Note: Values are median [lower–upper interquartile range]

**p value for difference between RRMS versus healthy control participants

*Statistically significant difference for RRMS versus healthy control participants

^ effect size (r) of difference between RRMS and Controls

Abbreviations: OSI = Overall Stability Index; %C = Percentage Correct

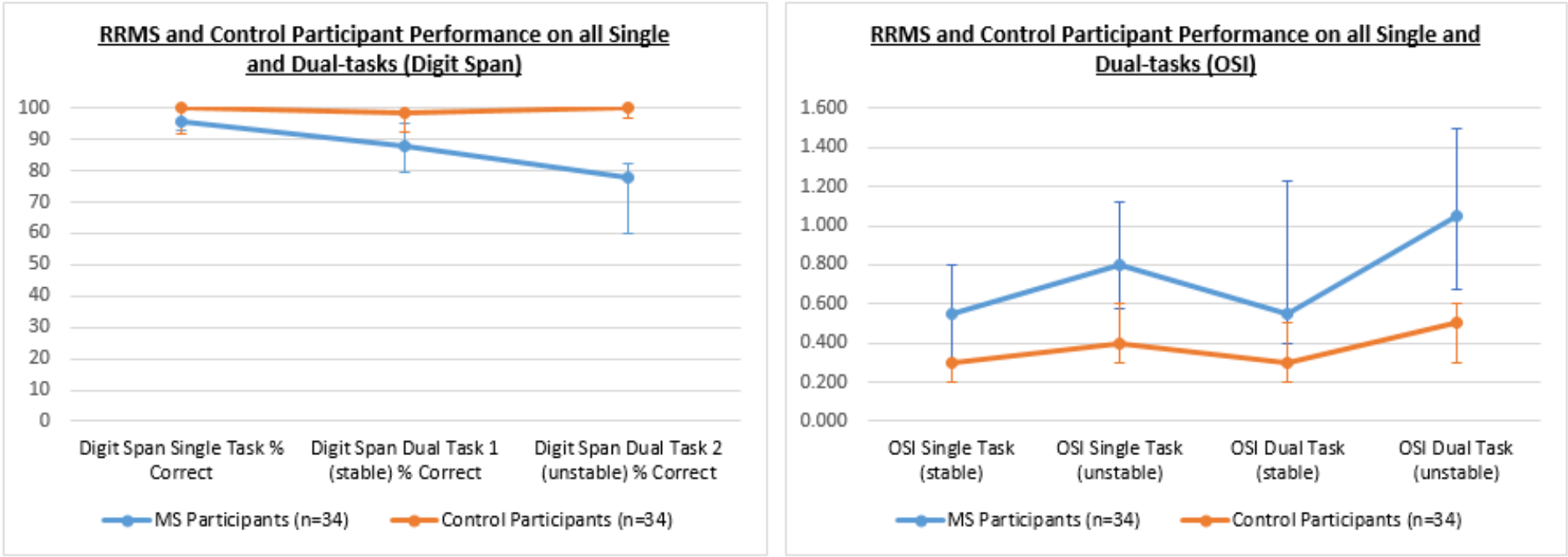

Figure 1: RRMS and Control Participant Median Performance on all Single and Dual-tasks

Note: Error bars represent lower-upper interquartile ranges for each of the median scores

Dual-task decrement

Baddeley et al.'s (1997) formula was used to calculate percentage change (decrement) in performance from single to dual-task conditions [Baddeley, Della Sala, Gray, Papagno, & Spinnler, 1997].

$$\text{Percentage of change task A} = \frac{\text{Single-Task A} - \text{Dual task A}}{\text{Single-Task A}} \times 100$$

Percentage changes (decrements) in performance from single to dual-task conditions are outlined in Table 3 and Figure 2.

Digit Span Performance

Statistically significant differences were found between RRMS and control participants in digit span performance *decrement* in stable (z=-3.417; p<0.001 two-tailed; r=0.41) and unstable (z=-6.556; p<0.001 two-tailed; r=0.80) dual-task conditions. In the stable dual-task condition, RRMS participants' performance decreased by 7% compared to 0% for controls. In the unstable dual-task condition, performance decreased by 20% in the RRMS group compared to 0% in the control group.

Balance Task Performance

Statistically significant differences were found between RRMS and control groups in balance task performance *decrement* in unstable (z=-2.715; p=0.007 two-tailed; r=0.33), but not stable (z=-0.413; p=0.679 two-tailed; r=0.05) dual-task conditions. A medium-large effect size was found for the unstable condition with overall stability decreasing by 25% in the RRMS group compared to 0% in the control group. No effect was found for the stable condition with RRMS overall stability decreased by 29% compared to 50% for controls.

Table 3: Percentage Change (decrement) in Performance from Single to Dual-task

Task	RRMS	Control	p- value**	effect size (r)^
Digit Span (Stable)	7% [0%–14%]	0% [0%–4%]	<0.001*	0.41
Balance Task (Stable)	29% [-20%–100%]	50% [0%–67.00%]	0.679	0.05
Digit Span (Unstable)	20% [14%–36%]	0% [0%–6%]	<0.001*	0.80
Balance Task (Unstable)	25% [0%–63.75%]	0% [-19%–27%]	0.007*	0.33

Note: Values are median [lower–upper interquartile range]

**p value for difference between RRMS versus healthy control participants

*Statistically significant difference for RRMS versus healthy control participants

^ effect size (r) of difference between RRMS and Controls

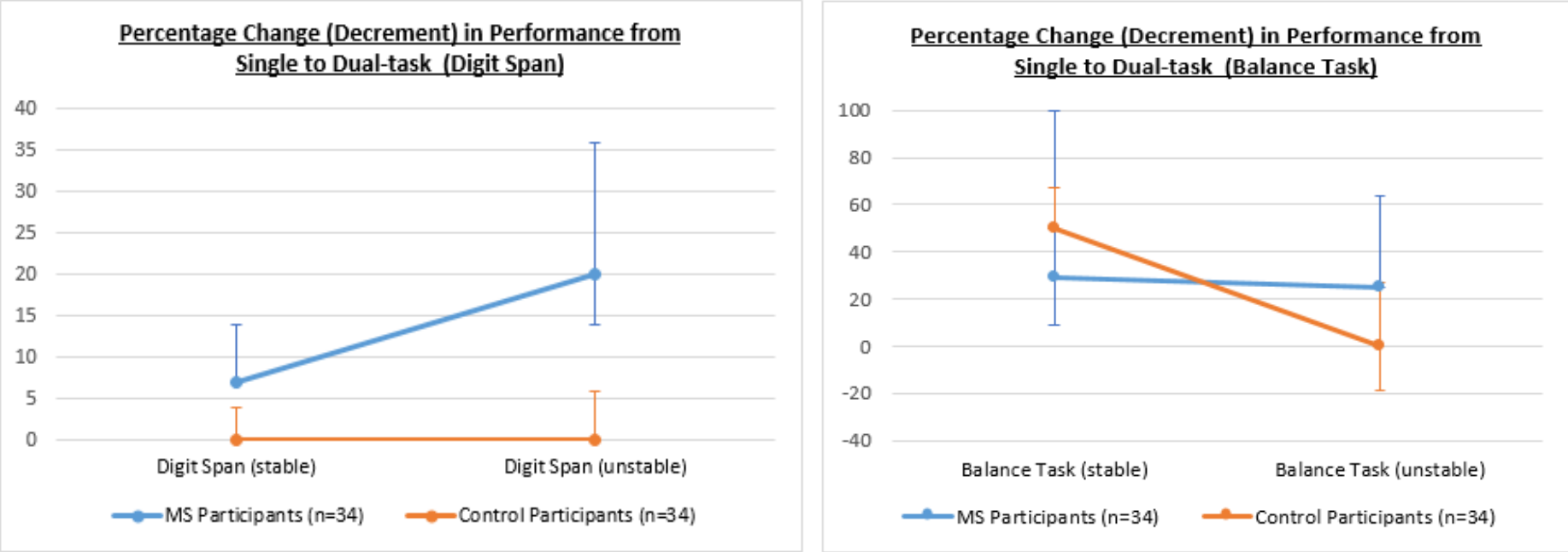

Figure 2: Percentage Change (decrement) in Performance from Single to Dual-task

Note: Error bars represent lower-upper interquartile ranges for each of the median scores

Correlational Analysis

The relation between a measure of everyday dual-tasking (DTQ), fatigue (MFIS), a cognitive screening measure (ACE-III) and decrement scores for digit span and balance tasks were explored. The results are outlined in Table 4. No significant correlations were found between self-reported DTQ scores, self-reported MFIS scores, ACE-III scores and decrement scores under any of the dual-task conditions.

The relation between disability status (EDSS), levels of anxiety and depression (HADS) and decrement scores were also explored. The results are outlined in Table 5. Stable surface balance decrement scores were significantly correlated with levels of anxiety (rho=0.527, p=0.001) and depression (rho=0.451, p=0.007). No significant correlations were found between EDSS and decrement scores under any of the dual-task conditions.

Table 4: Correlation Between Measure of Divided Attention (DTQ), Fatigue (MFIS), a Cognitive Screen (ACE-III) and Decrement Scores

	Digit Span Stable	Digit Span Unstable	Balance Task Stable	Balance Task Unstable
DTQ SCORE				
RRMS Participants				
P Value	0.355	0.271	0.552	0.160
Rho	-0.164	0.194	0.106	0.247
Control Participants				
P Value	0.082	0.283	0.778	0.684
Rho	-0.303	0.190	-0.050	0.073
MFIS SCORE				
RRMS Participants				
P Value	0.619	0.394	0.118	0.403
Rho	-0.088	0.151	0.273	0.148
Control Participants				
P Value	0.197	0.765	0.869	0.991
Rho	-0.227	0.053	0.029	-0.002
ACE-III SCORE				
RRMS Participants				
P Value	0.494	0.606	0.478	0.600
Rho	0.121	-0.092	0.126	0.093
Control Participants				
P Value	0.019	0.348	0.610	0.225
Rho	-0.401	-0.166	-0.091	-0.214

Note: Values are Pearson's *rho* and *p* value. *Statistically significant correlation

Table 5: Correlation Between Measure of Disability Status (EDSS), Levels of Anxiety and Depression (HADS) and Decrement Scores

	Digit Span Stable	Digit Span Unstable	Balance Task Stable	Balance Task Unstable
HADS ANXIETY				
RRMS Participants				
Rho	-0.083	0.174	0.527**	0.089
P Value	0.641	0.326	<0.001*	0.617
Control Participants				
Rho	-0.305	-0.042	-0.138	-0.074
P Value	0.079	0.812	0.435	0.676
HADS DEPRESSION				
RRMS Participants				
Rho	-0.184	0.220	0.451**	0.342
P Value	0.296	0.211	0.007*	0.168
Control Participants				
Rho	-0.190	0.111	-0.062	-0.216
P Value	0.282	0.534	0.729	0.220
RRMS Participants Only:				
EDSS SCORE				
Rho	-0.133	0.256	-0.048	0.360
P Value	0.455	0.144	0.789	0.036

Note: Values are Spearman's *rho* and *p* value.

*Statistically significant difference for RRMS versus healthy control participants

**Correlation is significant at the 0.0125 level (two-tailed)

Discussion

Consistent with hypothesis one, a main finding of the study was that PwRRMS show a greater decrement under dual-task conditions compared to single conditions on measures of balance, digit span and decrement scores when compared with controls. However, inconsistent with hypothesis one, with regard to balance, a significantly greater decrement was not found in the stable dual-task condition. Where statistically significant differences were found, effect sizes were medium–large.

On the stable balance condition, the percentage change in performance from single to dual-task conditions was higher in the control group (50%) compared to the RRMS group (29%) (see table 3), though this was not significant. One reason for the higher percentage change in the controls is that they started from a low baseline OSI level, so relatively modest changes (i.e. similar absolute level to those of the MS group), represent a higher percentage change. Somewhat anomalously, the median OSI scores were the same for controls and PwRRMS in both single stable and dual stable conditions, despite the median change scores being 50% and 29% respectively. This results from the skewed distributions, and the difference in distributions of absolute scores and percentage change scores.

Negahban et al. (2011) and Kalron et al. (2010) both found PwMS showed decreased postural control under dual-task conditions compared to controls. Two theoretical explanations have been proposed to account for the observed dual-task decrements in performance: The capacity model and the bottleneck model [Leone et al., 2015]. The capacity model proposes that the amount of cognitive resources available has a limit. Tasks are therefore completed within the capacity limits of those resources and dual-task decrements are apparent when the demands are greater than the resources. So when a cognitive task is added to a demanding motor task, then the system is overloaded and decrements occur. The question for this study though is why PwRRMS show greater decrements than controls. The cognitive task was titrated to individualised levels and so should have been requiring equal resources (unless we hypothesise that, due to working memory capacity being reduced in MS, the MS group require greater cognitive resources to produce a similar level of performance to that of the controls). For the motor task however, it may be argued that this was more difficult for the MS group, given that their performance

under single task conditions was poorer than controls. So if this task is demanding much higher level of cognitive resource, when a secondary cognitive task is added, the attentional capacity may be compromised to a greater extent than for controls.

The bottleneck model suggests that decrements in dual-tasking occur due to both tasks attempting to use the same neuronal resources. There is some evidence from fMRI studies that working memory, spatial attention and locomotive tasks use similar neuronal resources [LaBar, Gitelman, Parrish, & Mesulam, 1999; Malouin, Richards, Jackson, Dumas, & Doyon, 2003]. In the present study, although the digit span task is a verbal task, so potentially not drawing on visual/motor system resources, some participants self-reported mentally visualising digit sequences as they heard them and reading them backwards using the visual representation as a memory aid. This spatial aspect of digit span, combined with the visual feedback component of the balance task, suggests that shared neuronal resources were being used and if the capacity of these shared resources is reduced in MS, then this may have resulted in a disproportionate decrement under dual-task conditions.

Another potential explanation is that in MS there may be a central difficulty with dividing attention (even on tasks that are not making greater demands than usual) and that this makes it more difficult to efficiently allocate attention to two tasks simultaneously.

In the present study, whilst the most likely explanation for the disproportionate decrements for PwRRMS is the capacity model, some combination of all three potential explanations cannot be ruled out, something that could be explored in future research.

Factors affecting dual-tasking

Stable surface balance decrement scores were significantly associated with levels of anxiety and depression in PwRRMS, but this relationship was not evident on the unstable surface. Effect sizes were medium–large. The correlation between anxiety/depression and decrement in performance suggests that adding a cognitive task does not have any greater effect on the balance of PwRRMS than it does on controls when on a stable surface, unless participants are experiencing higher levels of anxiety/depression, in which case balance begins to deteriorate. On the unstable surface, there was a significant difference between PwRRMS and controls at a group

level, but no association with anxiety/depression. Perhaps it is the case that difficulties with dual-tasking on the unstable surface are so great as a result of limited cognitive resources, that variations in anxiety/depression do not have any additional impact on a system that is already compromised.

A previous relationship between postural stability and anxiety has been shown in different clinical groups. For example, Matsuura and colleagues (2015) assessed postural instability in patients with schizophrenia and control subjects, finding that postural instability was exacerbated by anxiety in the patient group only. However, the precise nature of the relationship between anxiety and dual-task decrement is not clear.

Given that some of the conducted correlations were not statistically significant, it is important to consider the possibility of chance findings. Whilst a relatively conservative approach to significance level was adopted, nevertheless it is possible these were random errors.

Dual-tasking and disease severity

One may anticipate that dual-tasking performance may decrease as disability status increases. This effect has been found in previous studies [Boes et al., 2012]. However, the present study found no association between disease severity and dual-task decrement scores. This lack of association was also found in other studies such as Hamilton et al (2009). A recent systematic review by Wajda and Sosnoff (2015) further highlighted the discrepancy in results regarding the association between decrement and disability status. They postulated that divergent methodologies might explain the differences.

Everyday dual-tasking

PwRRMS reported significantly higher levels of everyday dual-tasking difficulties compared to control subjects. However, inconsistent with hypothesis two, no correlation was found between measures of dual-task decrement and scores on the DTQ Questionnaire. Seemingly a range of factors other than the impact of cognitively demanding tasks on balance are affecting functioning on the dual-tasks covered in this questionnaire. Alternatively, measures of dual-task decrement in this balance study and the gait related DTQ Questionnaire perhaps tap into different

motor abilities. Future research should explore the relationship between balance and gait parameters in RRMS.

Day-to-Day and Clinical Implications

Results suggest that PwRRMS will have difficulties maintaining balance and performing cognitive tasks, when attempted simultaneously. Furthermore, results suggest that dual-tasking performance may decrease when PwRRMS have heightened levels of anxiety/depression. These findings have consequences on everyday life where we commonly hold our balance while concurrently attending to cognitive tasks, for example, standing having a conversation. A review by Cameron and Lord (2010) highlighted that PwMS commonly fall, display a fear of falling, are at greater risk of sustaining fall-associated injuries, and have increased risk of fatal falls. They also found that impairments of balance are probable causes of falls in PwMS. Postural instability under day-to-day dual-tasking conditions may therefore increase the risk of falls in PwMS.

Explaining potential balance and cognitive dual-task difficulties and the associated impact of increased levels of anxiety/depression, may help to inform future clinical assessment and treatment planning. Present study findings propose that solely assessing balance may not translate to everyday balance ability, where additional tasks may need to be concurrently attended to. Assessing balance with and without a concurrent task may be a more reliable way of measuring dual-task abilities in clinical settings. The need to assess dual-task ability is further supported by the present study finding that dual-task decrement is not predicted by factors such as fatigue, disease severity, or general cognitive ability. Developing a clinical assessment that measures balance and cognitive performance under both single and dual-task conditions would be ideal but may not be practical for some clinical settings. Moreover, including measures of anxiety/ depression will be important in comprehensively assessing everyday dual-task difficulties in MS. Levels of anxiety/depression should also be considered when planning treatment of everyday dual-task difficulties - anxiety and mood management techniques could be applied and may improve dual-tasking, though this needs to be evaluated.

Limitations

The present study had several limitations. Firstly, multiple Spearman correlations were conducted to test hypothesis two and to assess the impact mood has on dual-task performance, and although the accepted level of significance was reduced to try and control for type I and II errors, multiple correlations still raise the possibility of chance findings. Secondly, RRMS was the only form of MS scrutinised in this study therefore, it is unknown if the same dual-tasking effects would be found in other types of MS. Thirdly, the methods do not allow for differentiation between potential explanations for the disproportionate dual-task decrement.

Future Research

This was the first dual-tasking study in an RRMS population to manipulate task demand by using backwards digit span, and so should be replicated. This methodology could also be applied to different types of MS. Future studies could also explore the impact of this more cognitively demanding task on gait. Despite reporting significantly higher levels of everyday dual-tasking difficulties (DTQ) the level of difficulty was not explained by the severity of dual-task difficulties on the balance/digit span tasks measured by degree of dual-task decrement. It will be important to determine whether the DTQ questionnaire is a valid measure of everyday dual-tasking difficulties and if so, what accounts for these difficulties. Furthermore, future work should also focus on developing a clinical tool to measure day-to-day balance and dual-tasking difficulties in MS.

Conclusions

RRMS causes difficulties with dual-tasking, impacting balance, particularly under challenging conditions, which may contribute to an increased risk of gait difficulties and falls. The striking relationship between anxiety/depression and dual-task decrement suggests that worry may be contributing to dual-task difficulties, and raises the possibility that therapeutic interventions aimed at managing worry may improve cognitive-motor dual-tasking.

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Appendix 1.1

JOURNAL OF THE INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY

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Scientific Article:
Giovannetti, T., Britnell, P., Brennan, l., Siderowf, A., Grossman, M., Libon, D.J., Seidel, G.A. (2012). Everyday action impairment in Parkinson's disease dementia. *Journal of the International Neuropsychological Society, 18,* 787–798.

Book:
Lezak, M.D., Howieson, D.B., Bigler, E.D., Tranel, D. (2012). *Neuropsychological Assessment.* New York: Oxford University Press.

Book Chapter:
Mahone, E.M. & Slomine, B.S. (2008). Neurodevelopmental disorders. In J.E. Morgan, & J.H. Ricker (Eds.), *Textbook of Clinical Neuropsychology* (pp. 105–127). New York: Taylor & Francis.

Report at a Scientific Meeting:
Weintraub, S. (2012, June). Profiles of dementia: Neuropsychological, neuroanatomical and neuropathologic phenotypes. International Neuropsychological Society, Oslo, Norway.

Manual, Diagnostic Scheme, etc.:
American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders (4th ed.).* Washington, DC: American Psychiatric Association Press.

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Appendix 1.2

Quality Rating Protocol

SECTION 1: INTERNAL VALIDITY

Study Question

Circle Response

1.1	The study addresses an appropriate and clearly focused question.	Yes No Can't Say

Selection of Subjects

1.2	The cases and controls are taken from populations that are comparable in all respects other than the factor under investigation e.g. age, gender, socio-economic status.	Yes No Can't Say
1.3	The same exclusion criteria are used for both cases and controls. *Controls will differ in one exclusion criteria with regards to disease status e.g. will not have diagnosis of Multiple Sclerosis.*	Yes No Can't Say
1.4	Comparison is made between participants (case and controls) and non-participants *(eligible but did not take part)* to establish their similarities and differences.	Yes No Can't Say
1.5	Cases are clearly defined and differentiated from controls.	Yes No Can't Say
1.6	It is clearly established that controls are non-cases.	Yes No Can't Say

Assessment

1.7	Exposure status is measured in a standard, valid and reliable way.	Yes No Can't Say

1.8	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes No Can't Say

Confounding

1.9	The main potential confounders are identified and taken into account in the design and analysis.	Yes No Can't Say

Statistical Analysis

1.10	Confidence intervals have been provided.	Yes No Can't Say

SECTION 2: OVERALL ASSESSMENT OF THE STUDY

Circle Response

2.1	How well was the study done to minimise the risk of bias or confounding? *High quality (++) = Majority of criteria met (7 or more yes responses). Little or no risk of bias. Results unlikely to be changed by further research.* *Acceptable (+) = Most of criteria met (5 or more yes responses). Some flaws in the study with an associated risk of bias. Conclusions may change in the light of other studies.* *Unacceptable (0) = Either most criteria not met or significant flaws relating to key aspects of study design. Conclusions likely to change in the light of further studies.*	High quality (++) Acceptable (+) Unacceptable (0)

2.2	Taking into account clinical considerations, your evaluation of the methodology used and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes No Can't Say
2.3	Are the results of this study directly applicable to the patient group targeted by this review?	Yes No

NOTES Add any comments on your own assessment of the study and the extent to which it answers your question. Mention any areas of uncertainty raised above.

Appendix 1.3

Quality Ratings of Included Studies

Question No: **Study:**	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**	**1.10**	**2.1**	**2.2**	**2.3**
Claros-Salinas et al, 2013	Y	Y	CS	N	Y	CS	Y	CS	N	Y	**+**	CS	Y
Devos et al, 2013	Y	Y	Y	N	Y	Y	Y	Y	N	N	**++**	Y	Y
McCarthy et al, 2005	Y	Y	CS	N	Y	CS	Y	CS	N	N	**0**	Y	Y
Patanella et al, 2010	Y	Y	Y	N	Y	CS	Y	N	N	N	**+**	Y	Y
Paul et al, 1998	Y	Y	Y	N	Y	Y	Y	N	N	N	**+**	Y	Y
Ruet et al, 2013	Y	Y	Y	N	Y	Y	Y	N	Y	N	**++**	Y	Y
De Sonneville et al, 2002	Y	Y	CS	N	Y	CS	Y	N	N	N	**0**	CS	Y
Stoquart-ElSankari et al, 2010	Y	Y	CS	N	Y	CS	Y	Y	Y	N	**+**	Y	Y

Note: Letter score criteria: Y = Yes; N = No; CS = Can't Say. Overall Quality Rating *(question 2.1)* Score Criteria: ++ = high quality; + = acceptable; 0 = low quality.

Appendix 1.4

Data Extraction Form

Study Characteristics

Study purpose or aims:

Study inclusion and exclusion criteria:

Inclusion:

Exclusion:

Participant Characteristics

Age Range MS Group:

Age Range Control Group:

Gender MS Group:

Gender Control Group:

Type of MS:

Disease stage / EDSS Score (MS only):

Recruitment

n MS:

n Control Group:

How were MS participants recruited:

How were Control participants recruited:

Measures

What were the measures of divided attention:

Results

Type of analysis used:

Conclusion:

Quality Rating (SIGN-MC4): _____

Appendix 2.1

JOURNAL OF THE INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY

Instructions for Contributors

Aims and Scope The *Journal of the International Neuropsychological Society* is the official journal of the International Neuropsychological Society, an organization of over 4,500 international members from a variety of disciplines. The *Journal of the International Neuropsychological Society* welcomes original, creative, high quality research papers covering all areas of neuropsychology. The focus of articles may be primarily experimental, applied, or clinical. Contributions will broadly reflect the interest of all areas of neuropsychology, including but not limited to: development of cognitive processes, brain-behavior relationships, adult and pediatric neuropsychology, neurobehavioral syndromes (such as aphasia or apraxia), and the interfaces of neuropsychology with related areas such as behavioral neurology, neuropsychiatry, genetics, and cognitive neuroscience. Papers that utilize behavioral, neuroimaging, and electrophysiological measures are appropriate.

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Regular Research Article: Maximum of 5,000 words (not including abstract, tables, figures, or references) and a 250 word abstract. Regular Research Articles are original, creative, high quality papers covering all areas of neuropsychology; focus may be experimental, applied or clinical.

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Critical Review: Maximum of 7,000 words (not including abstract, tables, figures, or references) and a 250 word abstract. Critical Reviews will be considered on any important topic in neuropsychology. Quantitative meta-analyses are encouraged. Critical Reviews must be preapproved by the Editor-in-Chief. For consideration, please e-mail your abstract to jins@cambridge.org.

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Page 2 should include an Abstract and a list of at least six keywords or mesh terms. Note: structured abstracts must be included with papers submitted after January 1, 2014. A structured abstract must include four header labels: *Objective*, *Method*, *Results*, and *Conclusions*. A total of six mesh terms (http://www.nlm.nih.gov/mesh/) or keywords should be provided and should not duplicate words in the title.

The full text of the manuscript should begin on *page 3*. For scientific articles, including *Regular Research Articles*, *Brief Communications*, *Rapid Communications*, and *Symposia*, the format should include a structured Abstract, Introduction, Method, Results, and Discussion. This should be followed by Acknowledgments, References, Tables, Figure Legends, Figures, and optional Appendices and Supplemental Material.

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Appendix 2.2

NHS
Health Research Authority

NRES Committee East Midlands - Nottingham 2
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839436

28 July 2015

Miss Emma-Louise Butchard
34 Culduthel Mains Circle
Inverness
IV2 6RH

Dear Miss Butchard

Study title:	**An Investigation of Balance and Cognitive-Motor Dual-Tasking in Multiple Sclerosis**
REC reference:	**15/EM/0356**
IRAS project ID:	**181030**

The Proportionate Review Sub-Committee of the NRES Committee East Midlands - Nottingham 2 reviewed the above application on 27 July 2015.

Provisional opinion

The Sub-Committee would be content to give a favourable ethical opinion of the research, subject to clarification of the following issues and/or the following changes being made to the documentation for study participants:

1. Clarify the reasoning for an upper age limit to the study.
2. Confirm that all members of the research team who will be interacting with patients have the ability and relevant training to assess capacity.
3. Clarify what will be used to construct the participant ID.
4. Clarify the minimum amount of time participants will be given to consider the study before consenting.
5. Updates to Participant Information Sheet;
   - Change the REC name to Nottingham 2.
   - Add a contact for raising complaints.
   - Add telephone number and/or email address for requesting further information.
6. Create two Consent Forms, one for patients and one for healthy controls. Note that the section regarding medical notes does not need to be included in the healthy controls.

When submitting a response to the Sub-Committee, the requested information should be electronically submitted from IRAS. A step-by-step guide on submitting your response to the REC provisional opinion is available on the HRA website using the following link: http://www.hra.nhs.uk/nhs-research-ethics-committee-rec-submitting-response-provisional-opinion/

Please submit revised documentation where appropriate underlining or otherwise highlighting the changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

Authority to consider your response and to confirm the final opinion on behalf of the Committee has been delegated to the Chair.

Please contact Joanne Unsworth, REC Assistant if you need any further clarification or would find it helpful to discuss the changes required with the lead reviewer.

The Committee will confirm the final ethical opinion within 7 days of receiving a full response. A response should be submitted by no later than 27 August 2015.

Summary of discussion at the meeting

The PR Sub-Committee confirmed the study raised no material ethical issues under the following headings: Recruitment arrangements and access to health information, and fair participant selection, favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future), care and protection of research participants; respect for potential and enrolled participants' welfare and dignity, independent review, suitability of supporting information, suitability of research summary.

Ethical issues raised and noted in discussion:

- **Social or scientific value; scientific design and conduct of the study**

  The Sub-Committee queried why there is an upper age limit to the study.

- **Informed consent process and the adequacy and completeness of participant information**

  The Sub-Committee queried what will be the minimum time participants will have to consider joining the study before consenting.

  The Sub-Committee noted that the REC name needed updating on the Participant Information Sheet.

  The Sub-Committee agreed a contact and information for raising complaints needed adding to the Participant Information Sheet.

  The Sub-Committee noted although there was a contact for requesting more information there was no telephone number or email address included and this should be added.

  The Sub-Committee agreed that two Consent Forms were needed, one for patients and one for healthy controls. They also noted that the section regarding medical notes would not be relevant to the healthy controls.

- **Suitability of the applicant and supporting staff**

  The Sub-Committee requested confirmation that all members of the research team interacting with participants would have the ability and relevant training to assess capacity.

- **Other general comments**

  The Sub-Committee queried what will be used to make up the participant ID.

Documents reviewed

The documents reviewed were:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Poster]	V2	06 July 2015
GP/consultant information sheets or letters [GP Letter Template]	V2	06 July 2015
Instructions for use of medical device [Biosway Portable Balance System Operation Manual]	Unknown	21 July 2015
IRAS Checklist XML [Checklist_21072015]		21 July 2015
IRAS Checklist XML [Checklist_22072015]		22 July 2015
Letters of invitation to participant [Invitation Letter Template]	V2	06 July 2015
Non-validated questionnaire [DivA]	Unknown	21 July 2015
Other [Demographic Information Sheet]	V1	22 July 2015
Other [TOPF]	V1	22 July 2015
Other [CORVIST 1]	1	22 July 2015
Other [CORVIST 2]	1	22 July 2015
Other [CORVIST 3]	1	22 July 2015
Other [CORVIST 4]	1	22 July 2015
Other [CORVIST 5]	1	22 July 2015
Other [CORVIST 6]	1	22 July 2015
Other [CORVIST 7]	1	22 July 2015
Other [CORVIST 8]	1	22 July 2015
Other [CORVIST 9]	1	22 July 2015
Other [CORVIST 10]	1	22 July 2015
Participant consent form [Consent Form]	V2	06 July 2015
Participant information sheet (PIS) [PIS - MS Participants]	V2	06 July 2015
Participant information sheet (PIS) [PIS - Controls]	V2	06 July 2015
REC Application Form [REC_Form_21072015]		21 July 2015
Research protocol or project proposal [Proposal]	V4	28 April 2015
Summary CV for Chief Investigator (CI) [CV]	V1	20 July 2015
Summary CV for supervisor (student research) [Academic Supervisor CV]	V1	21 July 2015
Validated questionnaire [MFIS]	Unknown	21 July 2015
Validated questionnaire [MSIS-29]	Unknown	21 July 2015
Validated questionnaire [HADS]	Unknown	21 July 2015
Validated questionnaire [ACE-III]	Unknown	22 July 2015

Membership of the Committee

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

Statement of compliance

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

15/EM/0356	Please quote this number on all correspondence

Yours sincerely

pp.

Dr Frances Game
Chair

Email: NRESCommittee.EastMidlands-Nottingham2@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Frances Hines, NHS Highland*

NRES Committee East Midlands - Nottingham 2

Attendance at PRS Sub-Committee of the REC meeting on 27 July 2015

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Frances Game	Consultant Physician	Yes	
Mrs Sally Ann Smith	Retired Audit Manager	Yes	
Dr Alison Thorpe	Research and Governance Facilitator	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Joanne Unsworth	REC Assistant

Appendix 2.3

Health Research Authority
NRES Committee East Midlands - Nottingham 2
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839309

03 August 2015

Miss Emma-Louise Butchard
34 Culduthel Mains Circle
Inverness
IV2 6RH

Dear Miss Butchard,

Study title:	**An Investigation of Balance and Cognitive-Motor Dual-Tasking in Multiple Sclerosis**
REC reference:	**15/EM/0356**
IRAS project ID:	**181030**

Thank you for your letter of 30th July 2015, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

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

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Miss Jessica Parfrement, NRESCommittee.EastMidlands-Nottingham2@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

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

Conditions of the favourable opinion

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

Management permission or approval must be obtained from each host organisation prior to the

start of the study at the site concerned.

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

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

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

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

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

Registration of Clinical Trials

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

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

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

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

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

Ethical review of research sites

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

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Poster]	V2	06 July 2015

Covering letter on headed paper [Cover Letter]	V1	30 July 2015
GP/consultant information sheets or letters [GP Letter Template]	V2	06 July 2015
Instructions for use of medical device [Biosway Portable Balance System Operation Manual]	Unknown	21 July 2015
IRAS Checklist XML [Checklist_21072015]		21 July 2015
IRAS Checklist XML [Checklist_22072015]		22 July 2015
Letters of invitation to participant [Invitation Letter Template]	V2	06 July 2015
Non-validated questionnaire [DivA]	Unknown	21 July 2015
Other [Demographic Information Sheet]	V1	22 July 2015
Other [TOPF]	V1	22 July 2015
Other [CORVIST 1]	1	22 July 2015
Other [CORVIST 2]	1	22 July 2015
Other [CORVIST 3]	1	22 July 2015
Other [CORVIST 4]	1	22 July 2015
Other [CORVIST 5]	1	22 July 2015
Other [CORVIST 6]	1	22 July 2015
Other [CORVIST 7]	1	22 July 2015
Other [CORVIST 8]	1	22 July 2015
Other [CORVIST 9]	1	22 July 2015
Other [CORVIST 10]	1	22 July 2015
Participant consent form [Consent Form]	V1	28 July 2015
Participant consent form [Consent Form - MS Participants]	V3	28 July 2015
Participant information sheet (PIS) [PIS - MS Participants]	V3	28 July 2015
Participant information sheet (PIS) [PIS - Controls]	V3	28 July 2015
REC Application Form [REC_Form_21072015]		21 July 2015
Research protocol or project proposal [Proposal]	V5	28 July 2015
Summary CV for Chief Investigator (CI) [CV]	V1	20 July 2015
Summary CV for supervisor (student research) [Academic Supervisor CV]	V1	21 July 2015
Validated questionnaire [MFIS]	Unknown	21 July 2015
Validated questionnaire [MSIS-29]	Unknown	21 July 2015
Validated questionnaire [HADS]	Unknown	21 July 2015
Validated questionnaire [ACE-III]	Unknown	22 July 2015

Statement of compliance

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

After ethical review

Reporting requirements

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

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

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

Feedback

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

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

15/EM/0356	**Please quote this number on all correspondence**

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

Yours sincerely

J. Parliament

pp
Chair
Dr Frances Game

Email: NRESCommittee.EastMidlands-Nottingham2@nhs.net

Enclosures: *"After ethical review – guidance for researchers" SL-AR2*

Copy to: *Sponsor/R&D Contact - Ms Frances Hines*

Appendix 2.4

Professor Angus Watson
Research & Development Director
NHS Highland Research & Development Office
Room S101
Centre for Health Science
Old Perth Road
Inverness
IV2 3JH

Tel: 01463 255822
Fax: 01463 255838
E-mail: angus.watson@nhs.net

NHS Highland

11 August 2015

NHS Highland R&D ID: **1121**
NRSPCC ID: **NA**

Miss Emma-Louise Butchard
Trainee Clinical Psychologist
34 Culduthel Mains Circle
Inverness
IV2 6RH

Dear Miss Butchard,

Management Approval for Non-Commercial Research

I am pleased to tell you that you now have Management Approval for the research project entitled: **'An Investigation of Balance and Cognitive-Motor Dual-Tasking in Multiple Sclerosis'. [Protocol V5 28 July 2015].** I acknowledge that:

- The project is sponsored by NHS Highland.
- The project does not require external funding.
- Research Ethics approval for the project has been obtained from the East Midlands – Nottingham 2, (Reference Number: 15/EM/0356).
- The project is Site-Specific Assessment exempt.

The following conditions apply:

- The responsibility for monitoring and auditing this project lies with the NHS Highland.
- This study will be subject to ongoing monitoring for Research Governance purposes and may be audited to ensure compliance with the Research Governance Framework for Health and Community Care in Scotland (2006, 2nd Edition), however prior written notice of audit will be given.

POSITIVE ABOUT DISABLED PEOPLE

- All amendments (minor or substantial) to the protocol or to the REC application should be copied to the NHS Highland Research and Development Office together with a copy of the corresponding approval letter.
- The paperwork concerning all incidents, adverse events and serious adverse events, thought to be attributable to participant's involvement in this project should be copied to the NHS Highland R&D Office.
- Monthly recruitment rates should be notified to the NHS Highland Research and Development Office, detailing date of recruitment and the participant trial ID number. This should be done by e-mail on the first week of the following month to Debbie McDonald, debbie.mcdonald@nhs.net.

Please report the information detailed above, or any other changes in resources used, or staff involved in the project, to the NHS Highland Research and Development Manager, Frances Hines (01463 255822, frances.hines@nhs.net).

Yours sincerely,

Frances Hines
Research, Development and Innovation Manager

cc Frances Hines, R&D Manager, NHS Highland Research & Development Office, Room S101, The Centre for Health Science, Old Perth Road, Inverness, IV2 3JH

Professor J Evans,
University of Glasgow
1st Floor, Admin Building,
Gartnaval Royal Hospital
1055 Great Western Road, Glasgow
G12 0XH

Jonathan.Evans@glasgow.ac.uk

Appendix 2.5

Centre Number:
Study Number:
Patient Identification Number for this trial:

CONSENT FORM

(For those with a diagnosis of Multiple Sclerosis)

Title of Project: "An Investigation of Balance and Dual-Tasking in Multiple Sclerosis"

Name of Researcher: Emma-Louise Butchard

Please initial box

1	I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3	I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4	I agree to my GP being informed of my participation in the study.	☐
5	I agree to take part in the above study.	☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Appendix 2.6

Centre Number:
Study Number:
Patient Identification Number for this trial:

CONSENT FORM

(For Healthy Volunteers)

Title of Project: "An Investigation of Balance and Dual-Tasking in Multiple Sclerosis"

Name of Researcher: Emma-Louise Butchard

Please initial box

1	I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3	I agree to my GP being informed of my participation in the study.	☐
4	I agree to take part in the above study.	☐

_____	_____	_____
Name of Patient	Date	Signature

_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Signature	Date

Appendix 2.7

"An Investigation of Balance and Dual-Tasking in Multiple Sclerosis"

Participant Information Sheet
(For those with a diagnosis of Multiple Sclerosis)

Invitation to take part in the research
You are invited to take part in a research project. We are looking for adults aged from 17 to 65 years old who have a diagnosis of Relapsing Remitting Multiple Sclerosis (RRMS), have had no previous neurological conditions (e.g. Traumatic Brain Injury; Stroke), do not have severe sensory deficits (e.g. partial or complete blindness), and do not have health conditions which significantly impact on their motor abilities (e.g. severe, uncontrolled diabetes).

Before deciding whether you want to participate or not it is important to understand why this research is being carried out and what taking part will involve. This information is outlined below. Please take the time to read this carefully and, if you wish, discuss it with others. If there is anything that is unclear or you would like more information on, please do not hesitate to ask. Take time to decide whether you would like to take part. Thank you for taking the time to read this information sheet.

Who is conducting the research?
The research project is being conducted by Emma-Louise Butchard (Trainee Clinical Psychologist), Dr Jim Law (Clinical Psychologist) and Professor Jonathan Evans from the Institute of Health and Well-being at the University of Glasgow. The study is being carried out to fulfil academic requirements for Glasgow University's Doctorate in Clinical Psychology degree course.

What is the purpose of the study?
(i) Background
Multiple sclerosis (MS) can cause a wide range of different difficulties, including physical (e.g. walking, balance), cognitive (e.g. memory and concentration) and emotional (e.g. low mood). Difficulties vary a lot between people with MS, and not everyone has difficulties in all these areas. In this project we are particularly interested in how different problems interact. Specifically, we are interested in balance and how it might be affected by engaging in mental activity. Previous work by our research group has shown that some people with MS have difficulties walking and talking at the same time. So doing two things at the same time (dual-tasking) is difficult. In this project we are investigating how balance is affected when people are engaged in mental activity at the same time. It is possible that difficulties with dual-tasking might be related to increased risk of trips and falls. If we find that balance is affected by engaging in other mental activities, this may therefore help us identify people who are

more vulnerable to falls and in the longer term we hope to develop rehabilitation strategies that help people with MS manage these dual-tasking difficulties. In this project we will measure balance under single-task (simple standing) and dual-task (standing whilst doing a simple mental activity). In addition we will investigate whether a short questionnaire that we have developed, called the Divided Attention (DivA) questionnaire is useful in examining difficulties with doing two things at the same time in everyday situations for people with MS.

(ii) Aims

To investigate: (1) Whether individuals with Multiple Sclerosis have greater difficulties with balance and cognitive-motor dual-tasking compared to people who do not have MS; and (2) If there is a relationship between dual-task performance and scores on a divided attention questionnaire namely DivA.

What does taking part involve?

If you would like to take part, we will arrange a time convenient to you to come along and meet our researcher at the Neuropsychology Department at Raigmore Hospital. Participation involves completing assessment and balance tasks which in total will take approximately 1 hour and 20 minutes. The assessment will include completing tasks such as a questionnaire about your mood, the DivA questionnaire mentioned above, and some short pen and paper tasks (e.g. puzzles and language tasks). The balance task involves standing on a machine called the BioSway which looks a bit like a scale. You will be given the opportunity to familiarise yourself and have a practice with the BioSway. You can take breaks during the testing. With your permission, we will also inform your GP that you are participating in this study.

What are the possible benefits of taking part?

Research gives us the opportunity to improve our knowledge about various difficulties people with MS may experience. Your participation in this study will help us increase our knowledge about balance and attention difficulties in individuals with MS and help us make improvements to assessment methods and treatment in the future.

What are the possible risks or disadvantages of taking part?

There are no significant risks or disadvantages of taking part in this study. As balance is being tested you may feel slightly unsteady on your feet. To minimise risk, you will be given the opportunity to familiarise yourself with the balance machine (BioSway) to decide if you want to take part in the study or not and the researcher will stand at your side to offer support if needed e.g. give you a hand to step off the BioSway.

Regular breaks will be taken during the study to avoid you feeling tired. Although we do not predict that participating in this study will cause you any distress, if this were to happen we would help you access appropriate support.

Do I have to take part?

It is up to you whether you decide to take part in this study. If you decide you want to take part, you will be given a copy of this information sheet to keep and be asked to sign a consent form. Although you will be signing the consent form, please be aware that you are free to withdraw from the study at any time. A decision to withdraw from the study or not take part at all will have absolutely no impact on the standard of care you receive.

Will my information be confidential?

All information collected about you during the study will be kept strictly confidential. If any information about you was required to leave the hospital, your name and address will be removed so that you cannot be recognised from it.

What happens to the information?
Your personal information and identity will be kept strictly confidential and known only by the researchers. Information will be stored within a locked filing cabinet in the locked Psychology Department. All information will be held in accordance to the Data Protection Act (1998), meaning that it be stored securely and not shared with other people without your permission. If any findings from this study are published, your identity will be anonymised so you are not identifiable.

What will happen to the results of the study?
At the end of the study, the finished report will be submitted to the University of Glasgow. We hope that the findings will be published in a medical journal and through other sources to make sure the general public know what the study found. Your identity and personal information will not be reported or published following this study.

Who is funding the research?
The research is funded by the Doctorate in Clinical Psychology course at the University of Glasgow.

Who has reviewed the study?
The study has been reviewed by Glasgow University to make sure that it meets standards outlined regarding scientific conduct. The Proportionate Review Sub-Committee of the NRES Committee East Midlands – Nottingham 2 has also reviewed this study to make sure that it meets standards outlined regarding ethical conduct.

Who can I contact for further information?
If you would like any additional information or have any questions, please do not hesitate to contact a member of the research team on the below contact details.

RESEARCH TEAM:		
Name	**Role**	**Contact**
Emma-Louise Butchard	Trainee Clinical Psychologist, NHS Highland	Drumossie Unit New Craigs Hospital Inverness, IV3 8NP Tel: 01463 253 632
Professor Jon Evans	Academic Supervisor, University of Glasgow	University of Glasgow 1st Floor, Administration Building, Gartnaval Royal Hospital, 1055 Great Western Road, Glasgow, G12 0XH Tel: 0141 211 0607
Dr Jim Law and Dr Louise Blackmore	Field Supervisors, NHS Highland	Drumossie Unit New Craigs Hospital Inverness, IV3 8NP Tel: 01463 253 632

Alternatively, if you would like to speak to someone independent to the study please use the below contact details. Please also use the independent contact information if you wish to raise a complaint.

INDEPENDENT CONTACT:		
Name	**Role**	**Contact**
Professor Thomas McMillan	Independent Contact, University of Glasgow	University of Glasgow 1st Floor, Administration Building, Gartnaval Royal Hospital, 1055 Great Western Road, Glasgow, G12 0XH Tel: 0141 211 0607

Appendix 2.8

"An Investigation of Balance and Dual-Tasking in Multiple Sclerosis"

Participant Information Sheet
(For Healthy Volunteers)

Invitation to take part in the research
You are invited to take part in a research project. The project is investigating dual-tasking in people with Multiple Sclerosis (MS), but in addition to people with MS, we need a group of healthy people with whom to compare the participants with MS. We are therefore looking for adults aged from 17 to 65 years old who are generally healthy, do not have a diagnosis of Multiple Sclerosis, have had no previous neurological conditions (e.g. Traumatic Brain Injury; Stroke), do not have severe sensory deficits (e.g. partial or complete blindness), and do not have health conditions which significantly impact on their motor abilities (e.g. severe, uncontrolled diabetes).

Before deciding whether you want to participate or not it is important to understand why this research is being carried out and what taking part will involve. This information is outlined below. Please take the time to read this carefully and, if you wish, discuss it with others. If there is anything that is unclear or you would like more information on please do not hesitate to ask. Take time to decide whether you would like to take part. Thank you for taking the time to read this information sheet.

Who is conducting the research?
The research project is being conducted by Emma-Louise Butchard (Trainee Clinical Psychologist), Dr Jim Law (Clinical Psychologist) and Professor Jonathan Evans from the Institute of Health and Well-being at the University of Glasgow. The study is being carried out to fulfil academic requirements for Glasgow University's Doctorate in Clinical Psychology degree course.

What is the purpose of the study?
(i) Background
Multiple sclerosis (MS) can cause a wide range of different difficulties, including physical (e.g. walking, balance), cognitive (e.g. memory and concentration) and emotional (e.g. low mood). Difficulties vary a lot between people with MS, and not everyone has difficulties in all these areas. In this project we are particularly interested in how different problems interact. Specifically, we are interested in balance and how it might be affected by engaging in mental activity. Previous work by our research group has shown that some people with MS have difficulties walking and talking at the same time. So doing two things at the same time (dual-tasking) is difficult. In this project we are investigating how balance is affected when people are engaged in mental activity at the same time. It is possible that difficulties with dual-

tasking might be related to increased risk of trips and falls. If we find that balance is affected by engaging in other mental activities, this may therefore help us identify people who are more vulnerable to falls and in the longer term we hope to develop rehabilitation strategies that help people with MS manage these dual-tasking difficulties. In this project we will measure balance under single-task (simple standing) and dual-task (standing whilst doing a simple mental activity). In addition we will investigate whether a short questionnaire that we have developed, called the Divided Attention (DivA) questionnaire is useful in examining difficulties with doing two things at the same time in everyday situations for people with MS.

(ii) Aims

To investigate: (1) Whether individuals with Multiple Sclerosis have greater difficulties with balance and cognitive-motor dual-tasking compared to healthy control subjects; and (2) If there is a relationship between dual-task performance and scores on a divided attention questionnaire namely DivA.

What does taking part involve?

If you would like to take part, we will arrange a time convenient to you to come along and meet our researcher at the Neuropsychology Department at Raigmore Hospital. Participation involves completing assessment and balance tasks which in total will take approximately 1 hour and 20 minutes. The assessment will include completing tasks such as a questionnaire about your mood, the DivA questionnaire mentioned above, and some short pen and paper tasks (e.g. puzzles and language tasks). The balance task involves standing on a machine called the BioSway which looks a bit like a scale. You will be given the opportunity to familiarise yourself and have a practice with the BioSway. You can take breaks during the testing. With your permission, we will also inform your GP that you are participating in this study.

What are the possible benefits of taking part?

Research gives us the opportunity to improve our knowledge about various difficulties people have. We are able to use this information in clinical settings to increase people's quality of life. Your participation in this study will help us increase our knowledge about balance and attention difficulties in individuals with Multiple Sclerosis and help us make improvements to assessment and treatment in the future.

What are the possible risks or disadvantages of taking part?

There are no significant risks or disadvantages of taking part in this study. As balance is being tested you may feel slightly unsteady on your feet. To minimise risk, you will be given the opportunity to familiarise yourself with the balance machine (BioSway) to decide if you want to take part in the study or not and the researcher will stand at your side to offer support if needed e.g. give you a hand to step off the BioSway. If you feel as if you will fall the task will be stopped immediately.

Regular breaks will be taken during the study to avoid you feeling tired. Although we do not predict that participating in this study will cause you any distress, if this were to happen we would help you access appropriate support. With your permission, we will notify your GP that you are taking part in the study.

Do I have to take part?

It is up to you whether you decide to take part in this study. If you decide you want to take part, you will be given a copy of this information sheet to keep and be asked to sign a consent form. Although you will be signing the consent form, please be aware that you are free to withdraw from the study at any time. A decision to withdraw from the study or not take part at all will have absolutely no impact on the standard of care you receive.

Will my information be confidential?
All information collected about you during the study will be kept strictly confidential. If any information about you was required to leave the hospital, your name and address will be removed so that you cannot be recognised from it.

What happens to the information?
Your personal information and identity will be kept strictly confidential and known only by the researchers. Information will be stored within a locked filing cabinet in the locked Psychology Department. All information will be held in accordance to the Data Protection Act (1998), meaning that it be stored securely and not shared with other people without your permission. If any findings from this study are published, your identity will be anonymised so you are not identifiable.

What will happen to the results of the study?
At the end of the study, the finished report will be submitted to the University of Glasgow. We hope that the findings will be published in a medical journal and through other sources to make sure the general public know what the study found. Your identity and personal information will not be reported or published following this study.

Who is funding the research?
The research is funded by the Doctorate in Clinical Psychology course at the University of Glasgow.

Who has reviewed the study?
The study has been reviewed by Glasgow University to make sure that it meets standards outlined regarding scientific conduct. The Proportionate Review Sub-Committee of the NRES Committee East Midlands – Nottingham 2 has also reviewed this study to make sure that it meets standards outlined regarding ethical conduct.

Who can I contact for further information?
If you would like any additional information or have any questions, please do not hesitate to contact a member of the research team on the below contact details.

RESEARCH TEAM:		
Name	**Role**	**Contact**
Emma-Louise Butchard	Trainee Clinical Psychologist, NHS Highland	Drumossie Unit New Craigs Hospital Inverness, IV3 8NP Tel: 01463 253 632
Professor Jon Evans	Academic Supervisor, University of Glasgow	University of Glasgow 1st Floor, Administration Building, Gartnaval Royal Hospital, 1055 Great Western Road, Glasgow, G12 0XH Tel: 0141 211 0607

Dr Jim Law and Dr Louise Blackmore	Field Supervisors, NHS Highland	Drumossie Unit New Craigs Hospital Inverness IV3 8NP Tel: 01463 253 632

Alternatively, if you would like to speak to someone independent to the study please use the below contact details. Please also use the independent contact information if you wish to raise a complaint.

INDEPENDENT CONTACT:		
Name	**Role**	**Contact**
Professor Thomas McMillan	Independent Contact, University of Glasgow	University of Glasgow 1st Floor, Administration Building, Gartnaval Royal Hospital, 1055 Great Western Road, Glasgow, G12 0XH Tel: 0141 211 0607

Appendix 2.9

DOCTORATE IN CLINICAL PSYCHOLOGY

SUBMISSION COVER SHEET

Trainee Name	Emma Butchard
Matriculation Number	2108995
Name of Assessment	MRP proposal
Submission Date	16th March 2015
Version number	4
Proposal Title	An Investigation of Balance and Cognitive-Motor Dual-Tasking in Multiple Sclerosis
Word count	3,615
Academic Supervisor (s)	Professor Jon Evans
Clinical Supervisor (s)	Dr Jim Law, Dr Louise Blackmore
Additional information	

Major Research Project Proposal

An Investigation of Balance and Cognitive-Motor Dual-Tasking in Multiple Sclerosis

Matriculation No: 2108995

Date of Submission: 16/03/2015

Version Number 4

Word Count: 3,615

An Investigation of Balance and Cognitive-Motor Dual-Tasking in Multiple Sclerosis

Background: Cognitive impairment is common in Multiple Sclerosis (MS), adding considerably to disease burden [41]. Dual-task designs, where participants perform cognitive and motor tasks concurrently, were used to investigate association between cognitive functioning and posture [2]. Studies show dual-task performance is impaired in people with MS (PwMS) compared to control subjects [5;18]. Evidence highlights deficits in attention and postural stability in MS but is scant regarding the association between these factors in PwMS. **Aims:** To investigate: (1) whether individuals with MS have increased difficulties with balance and cognitive-motor dual-tasking compared to healthy control subjects; (2) If there is a relationship between dual-task performance and scores on a self-report divided attention questionnaire namely DivA [15]. **Methods:** 34 participants with MS and 34 matched controls will provide demographic details, complete baseline assessment measures and DivA questionnaires. Subsequently, all will undertake three single tasks and two dual-tasks. Balance will be measured using the BioSway Portable Balance System [42], which measures neuromuscular control. The cognitive task is backwards digit-span [8]. Task order will be randomly assigned. **Applications:** Given the impact of disease burden, if PwMS have increased difficulty with balance and dual-tasking it will be pertinent to incorporate this knowledge clinically. For example, devising day-to-day management strategies will impact on symptom management and quality of life and inform treatment plans in various settings such as Rehabilitation and Psychology.

Introduction

Cognitive impairment is common in Multiple Sclerosis (MS), occurs at all disease stages and can be a primary source of social impairment, occupational disability and diminished quality of life [30;32;7]. Estimated prevalence of cognitive impairment in people with MS (PwMS) ranges between 43% and 65% [9]; typically involving difficulty with complex attention, memory, information processing speed and executive functions [20;13]. Whelan et al (2010) examined an event-related potential that indexes processing speed and attention allocation in PwMS and control subjects, and compared these findings to results of the paced auditory serial addition test (PASAT). Evidently both attention allocation and processing speed were impaired compared with control subjects.

Balance and gait difficulties and associated risk of falling in PwMS are well known [27;14;6;24]. Where balance/gait is impaired, greater attention allocation may be required to maintain effective balance/gait. Postural control has been defined as, “the control of the body’s position in space for the purposes of balance and orientation” [33]. Conventionally it has been considered a reflex or automatic controlled task, proposing that minimal attentional resource is used by postural control systems [38]. New research offers evidence contradicting this hypothesis, suggesting substantial attentional requirements for postural control [10;31;39].

Dual-task designs, where participants perform cognitive and motor tasks concurrently, have been used to investigate the possible association between cognitive functioning and posture [2]. Boes and associates (2012) investigated the effects of dual-tasking on postural control in PwMS with mild or moderate disability. Participants undertook posturography testing under a quiet single-task and cognitive dual-task condition. Results found postural control compromised by dual-task and declined with disability status. Moreover, a small amount of studies further suggest that PwMS display significant decrement in balance and gait under dual-task conditions when compared to control subjects [15;5;21;18]. Additionally, some research concludes that poor postural control contributes to increased risk of falling for PwMS [5;6;12]. However, other studies indicate no decrement to gait and

cognition under dual-task conditions [2;28;1]. Varying results within the evidence-base warrant further investigation of balance and gait decrement in PwMS; particularly towards understanding the impact of dual-tasking on the cognitive domain [35] and to explore further causal factors of dual-task cost [24].

Possible explanations for the development of dual-tasking decrements are currently few. One is that damage to motor functioning ultimately leads to greater demand of conscious attention while performing multiple tasks [21]. Another alternative is that in certain neurological disorders, working memory is overloaded by formerly normal loads of cognitive and motor content, resulting in reduced capacity [15;21] and poor balance or gait [24].

To determine if difficulties with dual-tasking are exclusive to divided attention process impairment, it is crucial to ensure level of demand is set according to individual ability based on performance under single-task conditions. For example, Hamilton et al (2009) examined the effects of performing a simultaneous cognitive task when walking in PwMS. Results found that, in comparison to control participants, MS subjects showed larger decrements in performance in dual-task conditions in cognitive task performance, suggesting impairment in divided attention. Consequently, by using individual ability as our titrated divided attention measure, we are able to determine any true association between attention and balance and resulting dual-task decrement.

Emerging evidence suggests that deficits in attention and balance/gait are present in MS. However, there is paucity in evidence regarding the association between these factors in PwMS. If true that for some PwMS balance/gait difficulties are either apparent or disproportionally impaired only under dual-task condition, then it may be prudent to measure this routinely in clinical practice. The twofold aim of this study is to investigate: (1) if individuals with MS have increased difficulties with balance and cognitive-motor dual-tasking compared to control subjects; (2) if there is a relationship between dual-task performance and scores on a self-report questionnaire, namely DivA [15], measuring divided attention in individuals with MS.

Hypotheses

1. Compared to healthy controls, individuals with MS will show a greater decrement under dual-task conditions compared to single task conditions on measures of balance, digit span, and a combined decrement score.
2. There will be a significant correlation between measures of dual-task decrement and scores on the Divided Attention Questionnaire.

Plan of Investigation

(i) Participants

Participants will be persons with a diagnosis of Relapsing Remitting MS (RRMS) (mild or moderate presentation) and control subjects matched for age and gender. The aim is to recruit 34 participants for each group. MS participants will be recruited through NHS Highland Neuropsychology service, Neurology, Physiotherapy, MS Nurses and the MS Therapy Centre. Control participants will include a convenience sample of friends/family/spouses of MS participants and others will be recruited through NHS email poster or NHS noticeboard advertisement and displayed in Inverness hospitals, MS Therapy Centre or community venues.

(ii) Inclusion and Exclusion Criteria

Inclusion

- Inclusion criteria for MS participants:
    - Age range 17-65
    - Diagnosis of RRMS. There are 4 subtypes of MS, however, to reduce variability in an already variable disease, only participants with RRMS will be included.
    - Free of relapse 30 days prior to task administration.
    - A Consultant Neurologist sub-specialising in MS will confirm diagnosis based on standardised investigation and in alignment with the revised McDonald [1] diagnostic criteria.
    - Expanded Disability Status Scale (EDSS) Score up to 6.5 [26].

Exclusion

- Exclusion criteria for MS and Control participants:
    - MS subtype other than RRMS.
    - Presence of major psychiatric disorders e.g. severe depression.
    - History of neurodegenerative disease (other than MS) or brain injury.
    - Significant sensory deficits e.g. visual impairment.
    - Severe co-morbid health condition which is affecting motor abilities e.g. diabetes.

(iii) Recruitment Procedures

The researcher will meet with potential participants. All will be given an information sheet and research methodology will be fully outlined so participants will know exactly what will be expected of them in each task. Potential balance instability will also be explained and participants given the opportunity to try the BioSway system. Questions about participation will be answered at the meeting and throughout the research process. Participants will know that they can withdraw from the study at any time and all related data anonymised to meet data protection legislation. Participants will be given all the time they need to consider if they wish to participate or not. If they wish to, written consent forms will be provided.

(iv) Measures

Baseline Assessment

- Demographic information: age, gender, education, disease type, onset and years of illness, mental health history.
- Test of Premorbid Function (TOPF) [37] – measure of premorbid functioning.
- Addenbrooke's Cognitive Examination (ACE-III) [17] – a short cognitive test (designed to screen for dementia) will be utilised to assess general cognition.
- Modified Fatigue Impact Scale (MFIS) [25] – self-report measure of fatigue.
- Multiple Sclerosis Impact Scale (MSIS-29) [16] – quality of life measure
- Hospital Anxiety and Depression Scale (HADS) [40] – screen for anxiety and depression.
- Cortical Vision Screening Test (CORVIST) [19] – assesses visuoperceptual ability.

- Individual digit span assessments will be completed based on a method developed by Cocchini et al (2004). The administration of this approach will be altered from forward span to backward span to increase task difficulty.

Divided Attention Questionnaire

- DivA – Questionnaire measuring self-reported divided attention [15]. To be administered after baseline assessment and prior to task commencement.

Balance Task

- Individuals will stand on the BioSway [42] during tasks 2, 3, 4 and 5. Participants will also stand on a firm or unstable surface and asked to focus on keeping as still as possible. The unstable surface is foam and should therefore alter balance only minimally compared to firm surface. The primary measure derived from the BioSway will be centre of pressure (CoP). Balance measure will be calculated under single and dual-task conditions and dual-task decrement score calculated in terms of percentage change from single to dual-task conditions.

Cognitive Task

- Backwards digit span using a method developed by Cocchini et al (2004).

(v) Design

A between-subjects design will be utilised to compare balance and dual-tasking performance amongst MS and control participants within single and dual-task conditions. A within-subjects design will be used to examine the association between self-reported DivA scores and dual-tasking performance. All assessments will take place in the Neuropsychology clinic room, Raigmore Hospital or a clinic room in the RNI Community Hospital.

(vi) Research Procedures

Informed consent will be obtained from each participant. Firstly, demographic information will be collected then, to characterise the sample in terms of cognitive ability, all participants will complete baseline assessment measures and the DivA

questionnaire. Subsequently, all participants will undertake three single tasks and two dual-tasks. Task 1 involves participants completing a backward digit span task [8]. Task 2 requires participants to stand on a device, namely BioSway Portable Balance System (BioSway) [42], which measures an individual's neuromuscular control and ability to balance on a firm or uneven surface. A firm surface will be used for task 2. Task 3 requires participants to stand on the BioSway device on an unstable surface. For task 4 participants will stand on the BioSway firm surface whilst completing the backwards-span task. Task 5 requires participants to stand on the BioSway unstable surface whilst completing the backwards-span task. To control for order effect, task order will be randomly assigned. There are many combinations task order could take; 5 have been selected for this study.

(vii) Data Analysis

Descriptive statistics will be produced to describe the data. Independent Samples T-tests, Mann-Whitney U and Chi-Square tests will be used as appropriate to compare MS and control groups on demographic information, baseline clinical features, and to compare groups on single-task versus dual-task performance. Using Independent Samples T-tests and Mann-Whitney U-Tests as appropriate, measures of dual-task decrement (for balance and digit-span tasks) and collective dual-task decrement scores (average for combined balance and digit span tasks) for both groups will be compared. Spearman correlations will be used to examine whether there is a relationship between DivA scores and pooled dual-task decrement scores. Pearson Correlation coefficients *(r)* will be used to explore relationships between pre-morbid ability, cognition, self-reported anxiety and depression, fatigue, and dual-task decrement scores. Additionally, Pearson Correlation coefficients (r) will be used to examine disease severity (EDSS Score) and dual-task decrement scores in the MS group only.

(viii) Justification of Sample Size

Few studies have examined dual-tasking with balance/postural measures as outcomes. Kalron et al (2011) considered the effect of a cognitive task on postural control in individuals with a clinically isolated syndrome (CIS) suggestive of MS and control subject. They found that controls showed greater decrement from single to

dual-task conditions than PwMS, but a limitation of this study was the very mild sample hence unrepresentative of PwMS. Jacobs and Kasser (2012) reported that PwMS showed significantly greater decrement compared to controls on a postural task but provided insufficient data to calculate an effect size. Wajda, Motl and Sosnoff (2014) investigated the demographic, cognitive and clinical correlates of dual-task-cost of balance in PwMS but had no control group.

In their study of gait under dual-task conditions, Hamilton et al (2009) found medium-large effect sizes for a number of dual-task decrement measures (ranging from d=0.7 to d=1.5). In the proposed study we have taken a number of approaches to try to maximise effect sizes, such as inclusion of a wider range of disability levels of MS participants and use of a backward digit span task which is more challenging than the previously used forward digit span tasks. However, given that the nature of the motor task is different from that used by Hamilton et al, we will take a conservative approach and power the proposed study on the basis of the lower of the effect sizes (d=0.7). So using G Power, with power set at 0.8, alpha at 0.05 (two-tailed), d=0.7, we find that a minimum of 34 participants per group are required. Following discussions with Consultant Neurologist colleagues, given the numbers of patients within the service, and taking into account the time needed to complete the research tasks we believe this number to be feasible.

(ix) Settings and Equipment

Setting

Participants will be tested in the Neuropsychology room, Raigmore Hospital or where they were recruited e.g. MS Nurse Clinic, Inverness.

Equipment

- BioSway – created by Biodex Medical Systems Inc. [42]. Measures an individual's neuromuscular control and ability to balance on firm and unstable surfaces.

Health and Safety Issues

Researcher Safety Issues

Researcher may need to physically support participants if feeling off balance. If at risk of falling the task will be stopped immediately. Participants will be given the opportunity to familiarise themselves with the BioSway prior to task administration and decide whether or not they would like to take part in the study.

Participant Safety Issues

As balance is being tested there is a possibility that participants may feel unsteady on their feet. The researcher will stand at their side and offer support if required. If participants are at risk of falling the task will be stopped immediately.

*Further details of Health and Safety issues can be found in Appendix A

Ethical Issues

Ethical approval for the study will be sought from the West of Scotland Research Ethics. The project will be submitted to NHS Highland Research and Development Department for approval.

Financial Issues

- Printing of the Consent Form, Information Sheet, Demographic Information sheet, Diva Questionnaire, Cocchini digit span materials, ACE-III and MFIS for each participant
- Contacting holder of copyright for copies of MSIS-29
- Purchase of TOPF, HADS, CORVIST

*Full details of expenses are outlined in Appendix B

Timetable

Ethical approval will, hopefully, be obtained by September 2015 with recruitment and the commencement of the study scheduled for October 2015.

*Full timetable is outlined in Appendix C

Practical Applications

If those with MS have increased difficulties with balance and dual-tasking it will be pertinent to incorporate this into clinical settings such as rehabilitation and Physiotherapy. Devising and implementing strategies around this area of difficulty to help individuals day-to-day will impact on symptom management and perhaps quality of life. Additionally, it is possible that DivA could be used across various clinical settings to support assessment of individuals with MS and inform aspects of treatment plans.

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Proposal - Appendix A

WEST OF SCOTLAND/ UNIVERSITY OF GLASGOW

DOCTORATE IN CLINICAL PSYCHOLOGY

HEALTH AND SAFETY FOR RESEARCHERS

1. Title of Project	An Investigation of Balance and Cognitive-Motor Dual-Tasking in Multiple Sclerosis
2. Trainee	Emma Butchard
3. University Supervisor	Prof. Jon Evans
4. Other Supervisor(s)	N.A.
5. Local Lead Clinician	Dr Jim Law and Dr Louise Blackmore
6. Participants: (age, group or sub-group, pre- or post-treatment, etc)	Participants will be persons with a diagnosis of Relapsing Remitting MS (RRMS) (mild or moderate presentation) and control subjects matched for age and gender. It is estimated that 34 participants will be recruited for each group.
7. Procedures to be applied (eg, questionnaire, interview, etc)	Informed consent will be obtained from each participant. Firstly, demographic information will be collected then, to establish a sense of cognitive ability, all participants will complete baseline assessment measures and the DivA questionnaire. Subsequently, all participants will undertake three single tasks and two dual-tasks. Task 1 involves participants completing a backward digit span task (based on Cocchini et al, 2004). Task 2 requires participants to stand on a device, namely BioSway Portable Balance System (BioSway) (Biodex 2015), which measures an individual's neuromuscular control and ability to balance on a firm or unstable surface. A firm surface will be used for task 2. Task 3 requires participants to stand on the BioSway device on an unstable surface. Task 4 necessitates

	participants to stand on the BioSway firm surface whilst completing the backwards-span task. Task 5 requires participants to stand on the BioSway unstable surface whilst completing the backwards-span task. To control for order effect, task order will be randomly assigned. There are a multitude of combinations task order could take however, 5 have been selected for the purposes of this study.
8. Setting (where will procedures be carried out?) i) General	NHS Highland Neuropsychology Room, Raigmore Hospital or where the participant was recruited e.g. MS Nurse clinic in RNI hospital, Inverness.
ii) Are home visits involved	No

9. Potential Risk Factors Identified	As balance is being tested there is a possibility that participants may feel unsteady on their feet.
. 10. Actions to minimise risk (refer to 9)	1) Participants will be given the opportunity to familiarise themselves with the BioSway system prior to task administration and subsequently decide whether they are comfortable continuing to participate in this study or not. 2) The researcher will stand at their side and offer support e.g. hand to help them step off BioSway, if required. 3) If participants are at risk of falling the task will be stopped immediately

Trainee signature: Date:

University supervisor signature: Date:

Proposal - Appendix B

RESEARCH EQUIPMENT, CONSUMABLES AND EXPENSES

Trainee: Emma Butchard

Year of Course: 2nd year

Intake Year: 2013

Please complete the list below to the best of your ability

Item	Details and Amount Required	Cost or Specify if to Request to Borrow from Department
Stationary	None	**Sub total: £0**
Postage	None	**Sub total: £0**

Photocopying and Laser Printing (**includes cost of white paper**)	Consent form - 1 page x68	£3.40
	Information sheet - 2 pages (double-sided) x68	£3.40
	Demographic information sheet - 1 page x68	£3.40
	DivA Questionnaire – 1 page x68	£3.40
	Printing Cocchini Digit Span Material – 1 page x68	Not copyright. £3.40
	Addenbrooke's Cognitive Examination-III (ACE-III) – 3 pages x68	Copyright held by John Hodges who is happy for the test to be used clinically and for research projects [Hsieh, 2012]. Print cost £10.20
	Modified Fatigue Impact Scale (MFIS) – 3 pages x68	Not copyright. £10.20
	Hospital Anxiety and Depression Scale (HADS): 1 page x68	£3.40
		Subtotal: £40.80
Equipment and Software	BioSway	Borrow from Glasgow University **Subtotal: £0**
Measures	The Multiple Sclerosis Impact Scale (MSIS-29) – 2 pages x68	Copyright. Publically available on MS Trust website. Printing cost: £6.80
	Test of Pre-morbid Functioning (TOPF): 68 record forms	Copyright. Test provided by NHS Highland. Purchase cost: £0

	Hospital Anxiety and Depression Scale (HADS): 68 record forms Cortical Vision Screening Test (CORVIST): 68 record forms	Copyright. License held by Professor Jon Evans to photocopy HADS. Purchase cost: £0 Copyright. Borrowing manual and stimulus book from Glasgow University. Record forms sold in packs of 25 @ £18.50. Purchase cost: £55.50 **Subtotal: £62.30**
Miscellaneous	None	**Subtotal: £0**
Total		**£103.10**

For any request over £200, please provide further justification for all items that contribute to a high total cost estimate:

N/A

Trainee Signature…… …

Date……

Supervisor's Signature ……..

Date ……

Proposal - Appendix C

MRP Research Timetable

Date	**Task/Progress**
March 2015	Submit MRP proposal Submit cost form Submit Health & Safety Form
April – September 2015	Research and Development approval Ethics approval Complete MRP supervision agreement Begin research logbook Recruit once approval gained
October 2015	Commence study
October 2015 – January 2016	Start data collection
January – April 2016	Complete data collection
May – July 2016	Draft MRP to supervisor May and finalised July
July 2016	Loose bind and submit
August 2016	Viva Preparation
September 2016	Viva
September – November 2016	Submit corrections (if required)

Appendix 2.10

Divided Attention Questionnaire

The following questions are about problems which everyone experiences from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the last few weeks. There are 5 options, ranging from *very often* to *never, or not applicable*. Please tick the appropriate box.

	Do you have any of these difficulties ..…	Very often	Quite often	Occasionally	Very rarely	Never	N/A D/K
1	P**aying attention to more than one thing at once**?						
2	**Needing to stop an activity to talk**?						
3	Being unaware of **others speaking** to you when doing another activity?						
4	Following or taking part in a **conversation where several people are speaking** at once?						
5	**Walking** deteriorating when you are talking or listening to someone?						
6	Busy **thinking your own thoughts**, so not noticing what is going on around you?						
7	**Spilling a drink** when carrying it.						
8	S**pilling more** if talking at the same time.						
9.	B**umping into people or dropping things** if doing something else as well?						
10.	Difficulty **eating and watching television or listening to the radio** at the same time.						

	Total in each category:	x4	x3	x2	x1	x0	-
	Subtotals:						

Sum of 4 subtotals = ; Divided by no. answered =
Mean per question answered =

REF: Evans, J.J., Greenfield, E., Wilson, B.A., & Bateman, A. (2009). Walking and talking therapy: Improving cognitive–motor dual-tasking in neurological illness. *Journal of the International Neuropsychological Society, 15*, 112-120.

Appendix 2.11

Lists for Digit Span Determination (Baseline)

After each of the following lists, in the space provided, enter a tick (√) if the list is correctly recalled and a cross (×) if it is not. At the bottom of the page, in the space provided, enter the subject's Digit Span as the maximum length of the lists of which the subject recalled 5/6 correctly. Present only 6 lists to the subject.

List	Result (√ or ×)	List	Result (√ or ×)	List	Result (√ or ×)
For Span = 2					
83		54		27	
28		37		91	
68		96		87	
For Span = 3					
829		687		871	
132		356		251	
152		637		915	
For Span = 4					
6241		1372		5316	
2359		7392		4815	
7132		6539		1872	
For Span = 5					
84132		85293		79514	
62143		91635		82691	
97438		16592		75468	
For Span = 6					
587261		492617		148239	
261384		247681		423896	
632147		429735		641357	
For Span = 7					
2941378		6297865		1897562	
1285394		8243167		3185624	
8693735		3945782		2473961	
For Span = 8					
65148279		28653197		85729136	
18472913		65792381		76591243	
42785921		74529638		76921358	
For Span = 9					
679174382		239874615		539748216	
746231958		867934612		513985267	
398724615		794831265		231986734	
For Span = 10					
4982176453		2853967624		2914984357	
5731298426		9781734826		6983285149	
8182397465		8491287637		6391727362	

Subject's Digit Span =

Appendix 2.12

List memory (Single Task)

Digit Span =

Note to experimenter. The table contains only lists of ten digits. The lists actually given must be equal in length to the subject's digit span. Starting from the left of each list below, read out lists of length equal to the subject's digit span. Since the lists are presented for only 1.5 minutes, the number actually read out will depend upon the subject's digit span. As the subject tries to reproduce the list, enter each item below the item that was actually in the same ordinal position when the list was read out. The raw score is the number of digits in each list that were correctly recalled in their correct serial positions. These raw scores can be converted to proportions by using the conversion table, or simply dividing by the number of lists. The subject's final List Memory score is the mean proportion, that is the total of the proportions in the rightmost column, divided by the number of lists dictated.

List	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Score	Score/n
1.	1	5	8	7	3	6	2	9	5	4		
Response												
2	3	7	9	8	1	4	6	1	2	5		
Response												
3	6	9	3	1	4	7	5	9	8	2		
Response												
4	2	4	3	8	7	1	9	4	2	3		
Response												
5	2	1	5	3	8	6	4	7	9	6		
Response												
6	7	9	6	3	1	4	2	8	3	5		
Response												
7	8	1	6	3	9	5	7	4	2	1		
Response												
8	1	7	3	2	9	3	6	4	8	5		
Response												
9	9	6	1	2	5	3	8	2	7	4		
Response												
10	8	7	1	3	9	4	6	5	7	2		
Response												
11	3	2	1	9	5	4	3	6	8	7		
Response												
12	4	7	2	4	5	8	1	9	3	6		
Response												
13	8	4	5	1	6	2	3	4	9	7		
Response												
14	6	2	7	1	3	8	5	2	9	4		
Response												
15	8	3	9	1	6	2	7	6	5	4		
Response												

List Memory Score (Single Task) =

Appendix 2.13

List memory (Dual Task 1)

Digit Span =

Note to experimenter. The table contains only lists of ten digits. The lists actually given must be equal in length to the subject's digit span. Starting from the left of each list, read out lists of length equal to the subject's digit span. Since the lists are presented for only 1.5 minutes, the number actually read out will depend upon the subject's digit span. As the subject tries to reproduce the list, enter each item below the item that was actually in the same ordinal position when the list was read out. The raw score is the number of digits in each list that were correctly recalled in their correct serial positions. These raw scores can be converted to proportions by using the conversion table (see List Memory – Single Task), or simply dividing by the number of lists. The subject's final List Memory score is the mean proportion, that is the total of the proportions in the rightmost column, divided by the number of lists dictated.

List	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Score	Score/n
1.	9	5	6	1	3	6	1	9	8	2		
Response												
2	7	2	9	1	5	4	8	1	6	3		
Response												
3	5	8	9	7	2	4	5	3	1	4		
Response												
4	9	6	3	8	2	5	4	7	1	8		
Response												
5	2	4	6	3	1	8	7	2	5	4		
Response												
6	5	7	8	7	2	9	4	3	5	2		
Response												
7	1	3	4	8	3	1	2	6	2	9		
Response												
8	8	2	7	5	4	6	1	3	8	9		
Response												
9	1	9	4	2	7	4	8	3	6	2		
Response												
10	3	1	2	6	9	4	8	3	5	2		
Response												
11	2	5	4	9	6	1	9	4	8	2		
Response												
12	3	8	6	4	5	7	5	2	9	6		
Response												
13	7	5	6	3	2	8	5	1	9	1		
Response												
14	9	3	5	9	6	8	2	1	3	7		
Response												
15	5	4	3	6	5	7	3	8	7	3		
Response												

List Memory Score (Dual Task) =

Appendix 2.14

List memory (Dual Task 2)

Digit Span =

Note to experimenter. The table contains only lists of ten digits. The lists actually given must be equal in length to the subject's digit span. Starting from the left of each list, read out lists of length equal to the subject's digit span. Since the lists are presented for only 1.5 minutes, the number actually read out will depend upon the subject's digit span. As the subject tries to reproduce the list, enter each item below the item that was actually in the same ordinal position when the list was read out. The raw score is the number of digits in each list that were correctly recalled in their correct serial positions. These raw scores can be converted to proportions by using the conversion table (see List Memory – Single Task), or simply dividing by the number of lists. The subject's final List Memory score is the mean proportion, that is the total of the proportions in the rightmost column, divided by the number of lists dictated.

List	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Score	Score/n
1.	2	8	9	1	6	3	1	6	5	9		
Response												
2	3	6	1	8	4	5	1	9	2	7		
Response												
3	4	1	3	5	4	2	7	9	8	5		
Response												
4	8	1	7	4	5	2	8	3	6	9		
Response												
5	4	5	2	7	8	1	3	6	4	2		
Response												
6	2	5	3	4	9	2	7	8	7	5		
Response												
7	9	2	6	2	1	3	8	4	3	1		
Response												
8	9	8	3	1	6	4	5	7	2	8		
Response												
9	2	6	3	8	4	7	2	4	9	1		
Response												
10	2	5	3	8	4	9	6	2	1	3		
Response												
11	2	8	4	9	1	6	9	4	5	2		
Response												
12	6	9	2	5	7	5	4	6	8	3		
Response												
13	1	9	1	5	8	2	3	6	5	7		
Response												
14	7	3	1	2	8	6	9	5	3	9		
Response												
15	3	7	8	3	7	5	6	3	4	5		
Response												

List Memory Score (Dual Task) =