# Exploring attentional deficits in multiple sclerosis. An investigation of sustained and divided attention in early stage relapsing remitting MS using novel computer based attentional paradigms

Research Portfolio

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# MSc in Clinical Neuropsychology

**University of Glasgow**

**MSc Research Project Proposal**

## Title of project:

Exploring attentional deficits in early stage multiple sclerosis.


**Supervisor:** Professor Jonathan Evans

**Postgraduate:** Dr Steven Meldrum


**Word Count:** 4126

## Summary of Project

This study is concerned with exploring possible attention deficits in a neurological population, namely participants with a diagnosis of multiple sclerosis. Specifically, we are interested in whether participants in the early stages of multiple sclerosis have difficulty with visual, auditory, and divided attention. Using computer based paradigms, attention abilities will be examined in unimodal visual and auditory conditions, and bimodal visual-auditory conditions. Results will be compared to a non-clinical, age and education matched control group. Results will be discussed within the cognitive theoretical framework of working memory, focusing on disruption within the central executive component.

## Introduction

Multiple sclerosis (MS) is a neurodegenerative inflammatory demyelinating condition of the central nervous system with a variable clinical course involving several disease subtypes. Multiple sclerosis means 'many scars' and disease progression follows four main subtypes, however the most common subtype is relapsing-remitting multiple sclerosis, characterised by acute attacks of neurological dysfunction, followed by partial or complete recovery (Bone et al. 2000). In addition, prevalence rates are calculated at 144 cases per 100,000 of the population in the West of Scotland. The pathology and ensuing disability is linked with the process of axonal demyelination, remyelination, and axonal and synaptic degeneration (Orhun, Kantarci, Brian, Weinshenker, 2005). The accumulating lesion profile in the brain is diffuse, affecting central nervous functioning, motor systems, and multiple brain regions. The clinical manifestation of the disease varies considerably between sufferers and is related to lesion site and subsequent effects on function.

In addition to the physical problems experienced, cognitive impairment in MS is well documented and estimates of cognitive deterioration in patients range from 45 – 65% (Rao, 1995). The nature and course of MS is heterogeneous and recognized cognitive deficits involve a range of domains including memory, attention, and speed of information processing (Zakzanis, 2000). Lezak, Howieson & Loring (2004) reports common circumscribed deficits in the cognitive domains of attention, memory, and executive function in relapsing-remitting patients.

Spilich, Mubrin, and Janculjak (2002) state that changes in cognitive processes may appear long before the physical manifestations of MS, suggesting that identifying patients earlier could be based on cognitive changes.

Even though the cognitive profile in MS is often heterogeneous, a consistent deficit found in multiple sclerosis is deficits of attention and the ability to attend to more than one thing at the same time, divided attention (Bobholz & Rao, 2003). In addition, an intact attentional system is vital for the efficient processing of other various cognitive systems, for example memory encoding. There is some suggestion that deficits in higher cognitive operations are actually secondary to primary attentional problems in MS. However the extant MS literature examining attentional dysfunction leaves unanswered questions as to the extent and nature of deficits (McCarthy, Beaumont, Thompson, Peacock, 2005).

When considering the concept of attention there are various theoretical cognitive models of attention and one of the most influential and frequently referenced theories is Baddeley's (1986) working memory model. He proposed a structural model involving multiple interactive components including a central executive controller that regulates and distributes the limited available attentional resources that a system possesses, and visuospatial and phonological slave systems (Baddeley, 2003).

The slave systems are responsible for storage of modality specific inputs and one of the principle roles of a central executive system would be to efficiently allocate and manage attentional resources when two or more tasks are being executed simultaneously or when attention is divided between the visual and auditory slave systems (Baddeley, 1986).

Dual tasking or divided attention paradigms have been used extensively to study this fundamental property of an executive control system in various patient populations (Baddeley, Della Sala, Papagno, Spinnler, 1997). Dual tasking designs involve performing two different tasks on their own and then concurrently, and comparing performance levels on one or more of the tasks. For example, established formats involve participants performing a verbal digit span task with a visual tracking task. In clinical populations, a dual task performance decrement is frequently observed and reported in the context of damage to an executive coordinator responsible for dividing and allocating attention; for example in Alzheimer's disease (Logie, Della Sala, Cocchini, Baddeley, 2004).

Further, Baddeley, Baddeley, Bucks, Wilcock (2001) found that Alzheimer's disease patients have a specific difficulty with dual task performance, even when controlling for the general overall cognitive demand, suggesting that available attentional resources is not the problem, but how they are allocated is. Also, in a frontal lobe lesion patient group Baddeley et al. (1997) found that patients with dysexecutive syndrome showed impaired capacity for dual tasking.

In multiple sclerosis, evidence indicates that the multifocal lesion profile may affect brain areas which form the working memory substrate, leading to working memory

impairment in the early stages of the disease (Pelosi, Geesken, Holly, Hayward, Blumhardt, 1997).

D'Esposito et al. (1996) investigated central executive functioning using dual tasking methodology comparing an MS group with a control group. In their study, the dual tasking paradigm involved performing a primary task concurrently with one of three secondary tasks. The primary task involved a line orientation judgment with the concurrent secondary tasks being finger tapping, alphabet recitation, and humming a melody. Results showed that the MS group performed less well during the more demanding dual task conditions (humming a melody and alphabet recitation) than the control group. The authors concluded that the dual task decrement found in the MS group, reflected an impaired central executive of working memory resulting in difficulty allocating sufficient attentional resources to support concurrent task execution.

Baddeley et al. (1997) states that paradigms exploring the central executive's coordination properties should involve simultaneous operation of the phonological loop and visuospatial sketchpad. A criticism of D'Esposito et al. (1996) study is that their paradigms utilise tasks that recruit higher cognitive functions of language, memory, and musical ability, and fail to isolate the basic properties of the working memory model.

Paul, Beatty, Schneider, Blanco, and Hames (1998) investigated several aspects of automatic and controlled attentional processing in MS using tests of focused and divided attention. They used the Posner spatial attention task (Posner, Cohen, Rafal, 1982), which involves visual stimuli presented with valid and invalid spatial cues, as a

test of automatic processing and found that the MS group performed as well as the control group. The Paced Auditory Serial Addition Task (PASAT) was used as a test of divided attention in this study and the MS group performed significantly worse than the controls. Whether the PASAT is truly a test of divided attention is worthy of thought as the nature of that task involves sustained attention over time with higher cognitive functions of calculation recruited. Often, the PASAT is used as an index of information processing speed and clearly, there is a large working memory involvement, but it is questionable whether this test fulfils the criteria that Baddeley (1997) suggests for divided attention methodology. Further to this the test has frequently been described as frustrating and is prone to practice effects (Tombaugh, 2006).

Reicker, Tombaugh, Walker & Freedman (2007) investigated the Computerised Tests of Information Processing's (CTIP) use in detecting cognitive functioning in those with multiple sclerosis (Reicker et al. 2007). They administered the CTIP to sixty multiple sclerosis patients and to sixty healthy controls. It was found that MS patients produced slower reaction times when completing the tests, with the difference in reaction times to the healthy controls increasing with rising processing difficulty. This study warrants the use of reaction times as a form of clinical assessment as opposed to the traditional PASAT (Reicker et al. 2007).

However as highlighted by the authors, the cognitive task must be sufficiently difficult to be used when considering cognitive decline in MS. Additional caution needs to be taken as only thirty trials were administered in the above study with stimuli presented for a long duration of 2.5 – 4 seconds. Further to this the trials were semantic in nature and may indicate problems with semantic memory and language as opposed to underlying cognitive deterioration.

McCarthy, Beaumont, Thompson, and Peacock (2005) considered the profile of attentional dysfunction in MS using divided and sustained attention methodology across unimodal and bimodal visual and auditory trials. The authors developed two new measures of sustained and divided attention as part of their study and recognised that their approach to investigating divided attention was in contrast with conventional dual tasking methodologies where primary task decrement is measured during concurrent secondary task execution. In the divided attention task, targets were digits that were consecutive pairs either ascending or descending with a temporal delay between digit presentation in a trial. Participants were required to divide their attention between retention of the first digit and presentation of the next digit. Thirty MS participants were compared with 30 controls across all six conditions (sustained vs divided task and auditory, visual, bimodal presentations). The results suggested that the MS group held slower reaction times and were less accurate than controls on both sustained and divided measures of attention. Of note, the MS group were disproportionately slower on the bimodal trials of the divided attention task, relative to unimodal trials. The authors concluded that their results were not related to motor slowing or information processing speed deficits, but linked with the task demands and the modality targeted.

When the MS group were performing the divided attention task in visuo-auditory bimodal trials, their performance suffered most and this could be explained within Baddeley's (2003) theoretical framework with a deficient central executive component, impaired in allocating attentional resources efficiently between visual and auditory modalities.

The general aspect of this present study is to further understand the nature of cognitive impairment in MS, and in particular to investigate further the attentional system in multiple sclerosis, in the early stages of the disease. Specifically, we are

interested in the participant's ability to divide their attention during concurrent modality demands. We will explore visual and auditory attention using unimodal tasks and divided attention using novel dual modality tasks. Our method is similar to McCarthy et al. (2005) insofar as our approach is a departure from established tests of divided attention and reflects our interest in establishing whether central executive attentional deficits are revealed by a novel dual modality test which measures accuracy and response times. This test utilises simpler perceptual stimuli (numbers) and restricts an over involvement of motor and associated cognitive processing demands on participants, combating the possible failings of the CTIP as mentioned earlier (Reicker et al. 2007). Participants must divide their attention between a visual (number) input and an auditory (number) input, which is combined into a choice response: is the sum of the two numbers greater than or less than the original threshold number? Our general hypothesis is that MS participants will show impairment in the central executive component of attention reflected by a decrement compared to controls: higher latency responses and increased error within the bimodal divided attention task.

The paradigms developed fit within the construct of working memory proposed by Baddeley (1986) and are in line with his suggestions for investigating the central executive component of working memory (Baddeley et al.1997). Further, Sarter & Turchi (2002) describe divided attention as the ability to divide resources between multiple and competing perceptual tasks. The tests in this study are designed to isolate the attentional system using multiple and competing perceptual tasks. Across the tasks cognitive load does not vary, with the same number of stimuli delivered within each trial. Therefore, the paradigms ensure that various attentional characteristics are examined, while maintaining a parity of cognitive load and information processing between tasks.

## Hypotheses

The specific hypotheses are:

1) MS participants will not differ from controls on modality specific single tests of attention.

2) MS participants will show poorer performance on bimodal divided attention tests, compared to controls.

## Plan of Investigation

*Participants:*

The study will aim to recruit participants with multiple sclerosis and a non-clinical, age and education matched control group. The *inclusion criteria* are as follows: the MS group will be in the early stages of the disease with mild impairment, as defined by their EDSS score (Kurtzke, 1983). Therefore, we are considering patients with a diagnosis of less than 5 years with an EDSS score of 3 or less (which reflects minimal motor disability). The EDSS is a 20-point rating scale, which is widely used in MS research samples, and rates the level of physical disability of a participant. The participants will be in the age range of 25-40 years, which is linked with the mean age of onset and early stages of the disease. Using a lower EDSS score and minimum time since diagnosis will enhance the clinical homogeneity of the clinical group and facilitate the research question of interest in investigating MS in the early stages. Other inclusion criteria will also specify that the MS group are of the same disease type (relapsing-remitting type) with a disease status in remission. To confirm, control participants will be recruited from asking patients if they have a friend or relative that would be willing to take part or recruiting via a local advert at the Southern General Hospital. The controls will be age and education matched to the patient group.

The *exclusion criteria* are: the participants will have no co-morbid neurological or psychiatric conditions, and no gross motor defects, or hearing or eyesight deficits. Brief neuropsychological assessment using the Wechsler Test of Adult Reading (Wechsler, 2001), and Addenbrooke's Cognitive Examination (Mathuranath, Nestor, Berrios et al. 2000) will be used, excluding participants with significant cognitive impairment. The mood and anxiety of the participants will be assessed using the Depression Anxiety Stress Scales (Lovibond & Lovibond, 1995).

*Recruitment:*

The MS group will be recruited from the department of Neurology, Southern General Hospital, Glasgow. The lead MS Consultant Neurologist will be liaised with and recruitment is expected to be facilitated by this consultant and the MS specialist nurses during routine clinic settings/appointments. Participants will initially receive a recruitment package, containing information on the research project. They will be offered the recruitment package either by the lead MS Consultant, Dr Colin O'Leary, Consultant Neurologist or the MS Specialist Nurses (Ms Lynn Cherry and Ms Carly Gillespie) during attendance at routine clinical appointments. From this participants can put themselves forward if they wish to participate. They can contact the lead researcher or the research assistant via telephone or email as outlined in recruitment package. These contact details will be NHS telephone lines and NHS email addresses.

Recruitment of the control group which will be an age matched friend or relative of each member of the clinical group will be invited to participate in the study. If this method fails to secure the required number of controls, then a recruitment advert will

be placed locally within the Southern General Hospital, Glasgow. The study is aiming to recruit a minimum of 34 participants (17 patients and 17 controls).

*Measures:*

Experimental measures will be quantitative behavioural data including error and latency data. Specifically, reaction time data to presented stimuli and accuracy rates to choice tasks will be collected. Reaction time will be measured from the presentation of the green response screen, until response is made. In addition, measures of current cognitive status and participant mood will be assessed.

*Design and Procedures:*

We are employing a between subjects design, comparing MS patients and non-clinical controls across three paradigms. The procedure will involve modality specific cognitive tasks and a bimodal attention task. It is envisaged that each participant will take approximately 1 - 2 hours to complete all aspects of the experiment. To minimise fatigue effects, experiments will be conducted in the morning/early afternoon. The project will be carried out at the one site, namely the Southern General Hospital and laboratory space within the Sackler Research Centre will be sourced. Three experiments will be delivered via a Windows PC using E-Prime experimental software.

An Honorary Assistant Psychologist alongside a Clinical Psychologist, trained in the procedures will chaperone participants and administer all tests. Experimental data will be computer based and calculated to guarantee inter-rater reliability.

Visual Sustained Attention Task:

In a trial the following will occur in a linear sequence:

A threshold number of between 5 and 20, will appear in the centre of screen, for 500 msecs to indicate the start of the trial. This will be followed by two numbers of between 0-20 flashing consecutively. The numbers appear on the screen in the centre for a duration of 150msecs with a gap between them of 250msecs. After both numbers appear the participant must decide whether the sum of both numbers is greater than or less than the initial threshold number and indicate their choice through a key press: button 'Z' for less than and 'M' for greater than. They have 1 second to make their choice before the next trial begins. A fixation cross will appear between trials for a duration of 500ms.

The experiment will have 2 blocks with 100 randomised trials per block. The keyboard will be used to collect participant responses, which will be key presses with the index finger of both hands. Experimental data will be stored anonymously for later combined analysis.

Auditory Sustained Attention Task:

This is analogous to the above except the stimuli are presented through headphones binaurally and there is no visual component. The exact same principles apply.

The participant will first hear a threshold number followed by two numbers consecutively with the same presentation parameters as above.

As before, performance is measured in response times and accuracy. The experiment will have 2 blocks with 100 randomised trials per block. A keyboard will be used to

collect participant responses, which will be key presses with the index finger of both hands. Experimental data will be stored anonymously for later combined analysis.

Divided Attention Task:

The same parameters incorporated as above, however one number is presented visually and one number presented binaurally during each trial. The interstimulus gap is 250 msecs for 100 trials, then 100 msecs for 100 trials, then simultaneous bimodal presentation for 200 trials. Software to choose at random which modality experiences stimulus first in the titrated trials.

*Settings and Equipment:*

The setting will be a laboratory room within the Sackler Research Centre at the Southern General Hospital, Glasgow, that is free from outside distraction. Equipment will include paper and pencil tests (WTAR, Addenbrooke's Cognitive Examination, and DASS), use of a Windows PC, monitor, stereo headphones, and E-Prime experimental software.

*Power Calculation:*

A recent study examining modality specific aspects of sustained and divided attention in MS recruited 30 MS participants and 30 neurologically intact healthy controls (McCarthy et al. 2005) and found a statistically significant difference between the MS group and control group. The effect size calculated from their reaction time data on the bimodal divided attention task was (Cohen's d = 1.18), with power calculated as 0.998. It is reasonable to assume that the present study will have a similar effect size with a significance level of alpha = 0.05. The sample sizes required are 17 participants from the MS group and 6 participants for the present study to have a power of 0.9. This power calculation was made using a software calculator, namely 'G-Power' at http://www.psycho.uniduesseldorf.de/aap/projects/gpower/ (Faul, Erdfelder, Lang & Buchner, 2007).

The present study will recruit an equal number from each group and recruit a minimum of 17 participants from the MS and control group, giving a total of 34 participants. Additional power calculations will be run to verify that the above is suffice.

*Data Analysis:*

Descriptive and inferential statistics will be employed to explore response time and response accuracy scores. Summary data including means and standard deviations will be tabulated and described for the participants' reaction times and accuracy rates across all three tasks. Further, Analysis of Variance (ANOVAs) will be calculated with group and tasks being the main factors. Performance between groups will be investigated for all three tasks and performance between tasks within groups will be investigated. Post-hoc analysis will be used to investigate where potential differences lie.

## Practical Applications

Results will add to the existing body of literature in this field and hopefully provide useful information for understanding the cognitive attentional profile in early multiple sclerosis. Also, the paradigms designed here may prove useful for researching aspects of attention in a neurological population and their validity and reliability as tools for investigating attention will be explored. Further, results may have practical implications for patients and may have the potential to inform some aspects of clinical practice. For example, if MS patients have difficulty with attending to more than one thing at a time, there are obvious implications for the practice of delivering complex information and daily living advice to patients within the clinic. A compromised attentional system may contribute to impaired memory and the ability to acquire and retrieve complex information. Therefore, investigations such as this one could inform future practice guidelines. Further, studies (Ling, 2002; Schultheis, Garay, DeLuca, 2001) have suggested that cognitive dysfunction in MS may contribute to a decrease in driving ability and higher rates of vehicle crashes. The present study may further elucidate where difficulties in attending to competing stimuli occur.

## Timescale

The project is aiming to work comfortably within the parameters of the published MSc research guidelines and deadlines. Demo versions of the experimental paradigms are currently being programmed. Submission to the ethics committee will be completed by December 2010. It is expected that recruitment packages will be sent to potential participants in February 2010 with experimental running commencing in April 2011 and completed by end of June 2012.

## Ethical Approval

This will be required and submission will be made to the local ethics committee before any potential participants are approached. No obvious ethical issues have been identified at this stage.

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# Chapter 2: Review of Literature

The neuropsychological aspects of multiple sclerosis

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## Abstract

The cognitive dysfunction associated with multiple sclerosis is now well recognised as being a cardinal feature of this degenerative disorder and the last few decades, with the advent of modern brain imaging and screening for cognitive changes in this population, have led to a greater understanding in the pathophysiological mechanisms underlying the cognitive disturbance and the relationship to the cognitive architecture of commonly involved domains. The cognitive abilities most affected by MS include episodic memory, working memory, and information processing speed. Further, the compound effect of disturbances in complex attention can affect fractionations of the executive processes. Less affected cognitive domains are in language, complex visual processing, praxis, and simple attention capacity. Aphasias, apraxias, alexias, agraphias, and agnosias are rarely reported. There is considerable interindividual variability in the extent of neuropsychological difficulties in MS and the pattern of impairments any one individual has will be associated with the lesion volume, brain atrophy, and microscopic changes in the normal appearing grey and white matter. Modern imaging protocols are further elucidating the extent of brain changes in this population.

The pattern of deficits has been most likened to a subcortical cognitive profile and psychometric tests that have been found to show sensitivity in detecting MS related cognitive changes include ones that focus on new learning, speed of processing, fluency, and divided attention/working memory tasks. This review will discuss the above factors and describe how brain pathology in this complex condition can lead to the cognitive changes related to this condition.

## Introduction

Multiple sclerosis is the most common neurological disease affecting young and middle aged adults and involves a process of chronic autoimmune attack on the central nervous system that leads to inflammation and destruction of myelin sheaths surrounding neuronal axons (Arnett, 2003). This destruction eventually leads to demyelination and subsequent axonal damage and loss. Characteristic changes in areas of the multiple sclerosis brain are lesions in the subcortical white matter fibres, particularly in the periventricular areas, corpus callosum, and infratentorial areas (Filippi and Rocca, 2007). These lesions represent areas of various pathology in the MS brain including inflammation and demyelination, and chronic axonal loss. Long term axonal and myelin loss can contribute, along with other tissue loss, such as grey matter, to atrophy within the MS brain (de Stefano, Battaglini, & Smith, 2007). The clinical manifestation of the disease varies considerably between sufferers and is related to lesion site, brain atrophy and subsequent effects on function.

Cognitive impairment is a well recognised and now accepted major symptom of multiple sclerosis with prevalence rates estimated to be anywhere between 45 – 65%, (Rao, 1995). However, it is only in the last few decades that this has become widely accepted and investigated (Bobholz and Rao, 2003). Due to predominately subcortical white matter aetiology in the MS brain, the cognitive domains or processes most affected are attention, speed of processing, and memory (DeSousa, Albert, Kalman, 2002). More cortical subserved functions such as language ability, and praxis are generally preserved with findings suggesting that widespread damage to white matter leads to a functional disconnection between different cortical areas and deep grey matter structures. Calabrese, and Penner (2007) suggest that cognitive

dysfunction in MS can be explained as a 'multiple disconnection syndrome' where a cognitive domain can be interrupted in its afferent or efferent loops producing a variety of cognitive deficits. Axonal fibre damage can also lead to a slowing in neuronal communication affecting the speed of cognitive processes (DeLuca et al. 2004). Due to the somewhat unpredictable and quasi-random distribution of lesions in the MS brain, presentation and progression of cognitive deficits vary enormously between sufferers (Gainotti, 2006). The anatomical distribution of inter-individual MS pathology, with respect to functionally eloquent neural areas and networks, determines the clinical phenotype (Guttmann, Meier, and Holland, 2006).

Multiple sclerosis does not typically lead to a dementia or global cognitive impairment and there are well documented areas of cognition which are vulnerable to change and domain areas that are relatively preserved. Rao, Leo, Bernardin, Unverzagy (1991) performed a study using a comprehensive neuropsychological battery to assess cognitive function in 100 community based MS patients and 100 matched healthy controls. They found that the cognitive domains most impaired involved memory, attention, processing speed, some aspects of executive functioning, and more complex visuospatial abilities. In their sample up to 65% of the patients experienced some cognitive dysfunction. There are mixed findings on the effects of disease characteristics on cognitive functioning and it is still unclear as to how strong the correlations are between MS related cognitive impairment and disease duration, physical disability, rate of progression, and disease subtype (Calabrese, 2006). Cognitive deficits can even be seen during early stages of the disease when there is little physical disability highlighting the difficulty in using disease related variables as predictors of cognition in MS.

**Brain Imaging in Multiple Sclerosis**

During the last 10 years MRI has been increasingly utilized in the study of MS and "the overall landscape has dramatically improved compared to that of the mid-1990s" (Filippi & Rocca 2007). The aetiology and relationship between MS brain changes and cognitive impairment have been of great interest in the last decade with many researchers seeking to establish a link between MRI detectable abnormalities and the association with physical and cognitive disability (Rovaris, Comi, and Filippi, 2006). In multiple sclerosis, conventional T2 weighted lesions appear hyperintense or very bright against the non-diseased tissue and are the most readily visible MS lesions reflecting different pathologies of various stages including inflammation, oedema, and demyelination. This imaging method can be used to measure the total visible lesion volume. In a conventional T1 weighted scan, MS lesions appear hypointense and within the white matter areas these are known as "black holes". This type of imaging finding is thought to reflect more destructive pathology and axonal loss (Rovaris et al. 2006). Brain atrophy is used as an index to monitor pathologic evolution of MS activity and several studies have shown that brain volume is significantly reduced in patients and that cognitive impairment in MS may be related to decreasing brain volume rather than just increasing lesion load (De Stefano, Battaglini, and Smith, 2007).

More contemporary, non-conventional imaging analysis techniques, such as Magnetisation Transfer Imaging and Diffusion Tensor Imaging allow assessment of tissue damage in what is known as Normal Appearing White and Grey Matter (NAWM, NAGM). Microscopic areas of damage are not readily detectable on T1 or T2 weighted images and these techniques can quantify more fully the extent of MS 'occult' pathology in the brain (Rovaris et al. 2006).

The magnetization transfer imaging provides a ratio with which to determine the integrity of grey and white matter tissue in normal appearing brain tissue (NABT) and has highlighted the global central nervous system involvement in MS pathology (Filippi and Agosta, 2007).

Diffusion tensor imaging is a technique that allows assessment of the integrity of white matter tracts in the brain. This non-conventional image analysis is of great interest in multiple sclerosis as white matter plaques and subsequent disconnectivity between brain regions has been reported as being significant in multiple sclerosis related cognitive deficits (Miller, Grossman, Reingold, and McFarland, 1998; Goldberg-Zimring and Warfield, 2006). DTI is based on the impeded movement of water within axonal bundles due to myelin sheaths which leads to water diffusion parallel to the fibres: anisotropic diffusion. Neuropathological processes, as in multiple sclerosis, that lead to microstructural changes in white matter and reduced axonal integrity are thought to interfere with normal anisotropy. MRI pulse sequences allow the assessment of white matter tracts and can show directionality and abnormal connectivity in white matter (Ge, 2006).

Benedict et al. (2002) sought to determine the association between total lesion area, 3$^{rd}$ ventricular width, and region specific ratings of cortical atrophy and neuropsychological impairment. Thirty five clinic and community based patients were recruited for this study and administered a battery of cognitive domain specific tests examining language, visuospatial, memory, attention, speed of processing and executive functioning.

The general MRI measures looking at total lesion area accounted for more variance in all cognitive measures apart from the PASAT which was correlated with 3$^{rd}$ ventricular width. In a second stage analysis examining the prediction of

neuropsychological impairment from cortical atrophy after controlling for total lesion area and 3rd ventricular width found that failures on tests of new learning, divided attention, and conceptual reasoning correlated strongly with superior frontal cortex atrophy. The main finding is an association between cognitive dysfunction and cortical atrophy in the frontal areas.

Benedict et al. (2004) looked at whether lesion burden or brain atrophy account for most of the variance in MS related cognitive decline. Thirty seven MS patients (clinic based) and 27 healthy controls participated in the study and underwent a battery of neuropsychological tests examining multiple cognitive domains and underwent MRI with four imaging analysis variables considered: T1 hypointense lesion volume, FLAIR lesion volume, bicaudate ratio, and 3rd ventricular width and a cortical atrophy measure using brain parenchymal fraction. Patients performed poorly compared to controls across a range of tests involving memory, attention, and speed of processing tasks. The authors found that 3rd ventricular width (3VW) and brain parenchymal fraction (BPF) accounted for more variance in MS cognitive performance than the total lesion burden. This finding may be explained by the anatomical significance of the thalamus which is close to the 3rd ventricular area and has widespread cortical and subcortical reciprocal connections. When 3WV was excluded from analysis, brain parenchymal fraction accounted for most variance indicating that central and whole brain atrophy account for more variance in MS cognition than lesion burden.

Morgen et al. (2006) recruited 19 relapsing remitting patients in the early stages of the disease to examine association between brain volume and cognitive performance with the view that grey matter pathology is a major contributor to MS related cognitive impairment. MRI measurements included global and regional white matter and grey matter volumes and white matter lesion load.

Cognitive tests used were the Digits forward and backwards, the Memo test, the PASAT, and the TAP computerised attentional test (Zimmermann & Fimm, 1992). The main findings were that grey matter volume decrease in the patients correlated with impaired cognitive performance. Poorer performance on the PASAT was linked with widespread cortical volume decrease in the frontal and temporal cortices. The authors suggest that cortical neuronal damage may be a result of retrograde axonal damage from fibre connections with periventricular white matter lesions. Surprisingly, in this group there was no correlation between white matter volume and cognitive impairment.

Zivadinov, Sepcic, et al. (2001) used a longitudinal study to assess whether cognitive changes in MS were dependent on the progression of the lesion burden, reduction in brain parenchyma, or both. Fifty three relapsing remitting patients underwent serial MRI scans and an extensive neuropsychological test battery at two time points with all patients being categorised into one of three groups at follow up: cognitively improved patients, cognitively stable patients, and cognitively worsened patients. At follow up 28 patients were judged as cognitively impaired and 15 worsened. At follow up the patients showed a significant increase in lesion load and decrease in brain parenchymal volume. The cognitively worsened group showed a significantly higher loss of brain parenchyma and this was significantly related to changes in cognitive performance. There was a significant change in patients' PASAT scores over the two years and the authors suggest that in the early phase of relapsing remitting MS cognitive deterioration depends more on the development of brain parenchymal atrophy rather than extent of lesion burden.

Zivadinov, De Masi, et al. (2001) explored which conventional or nonconventional MRI marker correlated best with cognitive impairment in early relapsing remitting

MS. Sixty three relapsing remitting patients were administered a battery of neuropsychological tests including the PASAT and MRI total lesion area, magnetisation transfer ratio, and brain parenchymal fraction were calculated. Fifteen of the patients in this sample were judged to be cognitively impaired (based on deficits in two or more cognitive domains) and no significant differences were found between cognitively unimpaired and impaired patients on total lesion load and average lesion MTR. In the 15 cognitively impaired patients there was a significant difference in brain parenchymal fraction and average normal appearing brain tissue MTR compared to cognitively intact patients.

The imaging literature has elucidated our understanding of the underlying pathology and its relationship with cognitive impairment and reveals quite clearly that the model of cognitive dysfunction is not due to one primary variable such as white matter lesions but a combination of many pathogenic variables affecting the global brain. Cortical and subcortical atrophy along with disconnection of interneuronal networks within the cortex and white matter play a role in the cognitive decline.

## Assessing Cognition in Multiple Sclerosis

The assessment of the cognitive dysfunction in MS has been evaluated with research highlighting optimal tests that should be used with this group to assess any potential cognitive impairment (Sartori and Edan, 2006). Recommendations have included test batteries with the following characteristics:

1) Tests independent of motor coordination and visuosopatial ability.
2) Focus on attention, working memory, and speed of processing.
3) Brief administration to minimise confound of fatigue.

Sartori and Edan (2006) recommend a brief 30-minute test battery that includes the Paced Auditory Serial Addition Test (PASAT), new learning with the California Verbal Learning Test, and digit span backwards. Importantly, the authors recognise the confounding factor of depression impacting on cognitive test results. The PASAT has remained as one of the most common neuropsychological test measures used in MS clinical evaluation and research studies and is a core measure of the Multiple Sclerosis Functional Composite. Deficits on the PASAT are one of the most robust findings in the neuropsychology of MS (Hoffmann, Tittgemeyer, and von Cramon, 2007).

The Brief Repeatable Battery of Neuropsychological Tests (BRBNT) (Rao, 1990) is a well-established and frequently referenced assessment battery of cognitive change in MS (Gainotti, 2006). This compound of tests includes:

| | |
|---|---|
| **PASAT** | *Measure of Attention* |
| **Symbol Digit Modalities Test** | *Processing Speed* |
| **Selective Reminding Test** | *Verbal Memory* |
| **10/36 Spatial Recall Test** | *Visuospatial Learning* |
| **Word List Generation** | *Verbal Fluency Task* |

These tests were decided upon by administering a comprehensive neuropsychological test battery of 31 test indexes to 100 patients with MS and 100 matched healthy controls and selecting the tests on which the MS group were most impaired. Rao (1990) found that the final test selection demonstrated a sensitivity value of 71% and a specificity value of 94% in discriminating between cognitively intact and cognitively impaired patients with MS.

In assessing the cognitive impairment in this group it is recommended that a brief battery be used to avoid confounding effects of fatigue and should minimise tests with a significant motor or visuospatial component. It is recommended that test batteries focus on the use of the PASAT, which is test that has been repeatedly validated for use with this population and is sensitive to the cognitive changes that take place in MS (Achiron et al. 2005).

In addition, Sartori et al. (2006) recommend the use of digit span backwards which further examines attention and working memory and a verbal learning test, the CVLT. Also, the SDMT has shown high rates of sensitivity (Parmenter, Weinstock-Guttman,

& Garg, 2007) in multiple sclerosis. The timing of the cognitive assessment is crucial and should be outwith relapse episodes and corticosteroid therapy which both reduce cognitive performance (Foong et al. 1998; Oliveri et al. 1998). In addition, assessment of mood is vital due to the significant association found between mood disturbance and cognitive impairment (Bobholz & Rao 2003).

A recent paper (Langdon et al. 2012) undertook the task of developing a clinical tool for neurologists and healthcare professionals to use as a brief monitoring tool for cognition in MS. A committee of seven neurologists and five neuropsychologists with expertise in MS convened to design a brief test battery. They recommended the Brief International Assessment of Cognition for MS (BICAMS) which is a 15 minute screen comprising the Symbol Digit Modalities Test, California Verbal Learning Test – II (first 5 recall trials), and the Brief Visuospatial Memory Test – Revised (first 3 recall trials).

## Attentional Problems in Multiple Sclerosis

Even though the cognitive profile in MS is often heterogeneous, a consistent deficit found in multiple sclerosis is deficits of attention and the ability to attend to more than one thing at the same time, divided attention (Bobholz & Rao, 2003). In addition, an intact attentional system is vital for the efficient processing of other various cognitive systems, for example memory encoding. There is some suggestion that deficits in higher cognitive operations are actually secondary to primary attentional problems in MS. However the extant MS literature examining attentional dysfunction leaves unanswered questions as to the extent and nature of deficits (McCarthy, Beaumont, Thompson, Peacock, 2005).

When considering the concept of attention there are various theoretical cognitive models of attention and one of the most influential and frequently referenced theories is Baddeley's (1986) working memory model. He proposed a structural model involving multiple interactive components including a central executive controller that regulates and distributes the limited available attentional resources that a system possesses, and visuospatial and phonological slave systems (Baddeley, 2003). The slave systems are responsible for storage of modality specific inputs and one of the principle roles of a central executive system would be to efficiently allocate and manage attentional resources when two or more tasks are being executed simultaneously or when attention is divided between the visual and auditory slave systems (Baddeley et al. 1997).

Dual tasking or divided attention paradigms have been used extensively to study this fundamental property of an executive control system in various patient populations (Baddeley, Della Sala, Papagno, Spinnler, 1997). Dual tasking designs involve performing two different tasks on their own and then concurrently, and comparing performance levels on one or more of the tasks. For example, established formats involve participants performing a verbal digit span task with a visual tracking task. In clinical populations, a dual task performance decrement is frequently observed and reported in the context of damage to an executive coordinator responsible for dividing and allocating attention; for example in Alzheimer's disease (Logie, Della Sala, Cocchini, Baddeley, 2004).

Further, Baddeley, Baddeley, Bucks, Wilcock (2001) found that Alzheimer's disease patients have a specific difficulty with dual task performance, even when controlling for the general overall cognitive demand, suggesting that available attentional resources is not the problem, but how they are allocated is. Also, in a frontal lobe lesion patient group Baddeley et al. (1997) found that patients with dysexecutive syndrome showed impaired capacity for dual tasking.

In multiple sclerosis, evidence indicates that the multifocal lesion profile may affect brain areas which form the working memory substrate, leading to working memory impairment in the early stages of the disease (Pelosi, Geesken, Holly, Hayward, Blumhardt, 1997). D'Esposito, Onishi, Thompson, Robinson, Armstrong, and Grossman (1996) investigated central executive functioning using dual tasking methodology comparing an MS group with a control group. In their study, the dual tasking paradigm involved performing a primary task concurrently with one of three secondary tasks.

The primary task involved a line orientation judgment with the concurrent secondary tasks being finger tapping, alphabet recitation, and humming a melody. Results showed that the MS group performed less well during the more demanding dual task conditions (humming a melody and alphabet recitation) than the control group. The authors concluded that the dual task decrement found in the MS group, reflected an impaired central executive of working memory resulting in difficulty allocating sufficient attentional resources to support concurrent task execution.

Paul, Beatty, Schneider, Blanco, and Hames (1998) investigated several aspects of automatic and controlled attentional processing in MS using tests of focused and divided attention. They used the Posner spatial attention task (Posner, Cohen, Rafal, 1982), which involves visual stimuli presented with valid and invalid spatial cues, as a test of automatic processing and found that the MS group performed as well as the control group. The Paced Auditory Serial Addition Task (PASAT) was used as a test of divided attention in this study and the MS group performed significantly worse than the controls.

McCarthy, Beaumont, Thompson, and Peacock (2005) considered the profile of attentional dysfunction in MS using divided and sustained attention methodology across unimodal and bimodal visual and auditory trials. The authors developed two new measures of sustained and divided attention as part of their study and recognised that their approach to investigating divided attention was in contrast with conventional dual tasking methodologies where primary task decrement is measured during concurrent secondary task execution. In the divided attention task, targets were digits that were consecutive pairs either ascending or descending with a temporal delay between digit presentation in a trial.

Participants were required to divide their attention between retention of the first digit and presentation of the next digit. Thirty MS participants were compared with 30 controls across all six conditions (sustained vs divided task and auditory, visual, bimodal presentations). The results suggested that the MS group had slower reaction times and were less accurate than controls on both sustained and divided measures of attention. Of note, the MS group were disproportionately slower on the bimodal trials of the divided attention task, relative to unimodal trials. The authors concluded that their results were not related to motor slowing or information processing speed deficits, but linked with the task demands and the modality targeted.When the MS group were performing the divided attention task in visuo-auditory bimodal trials, their performance suffered most and this could be explained within Baddeley's (2003) theoretical framework with a deficient central executive component, impaired in allocating attentional resources efficiently between visual and auditory modalities.

More recently, (Hamilton, Rochester, Paul, Rafferty, O'Leary, & Evans, 2009) examined cognitive – motor dual tasking in eighteen relapsing and remitting patients and eighteen age and gender matched controls. Participants took part in five conditions: walking alone, a fixed digit span task alone, a individually titrated digit task alone, walking with a fixed digit task, and walking with a titrated digit task; the latter two conditions representing the cognitive – motor dual tasking conditions. Compared to controls, the authors found that MS participants had greater decrements in dual task performance. These decrements were evident in walking speed, digit task, and swing time in fixed demand dual tasks and decrements in walking speed in titrated demand dual tasks. They concluded that the dual task decrement in the cognitive-motor paradigm could be due to a divided attention deficit or overloading of working memory as a result of walking requiring greater attention.

The implications of this are that people with MS may have everyday difficulty walking and talking and that this problem could be linked to an increased risk of falls. The authors highlight the need for a clinical tool to assess cognitive-motor dual tasking ability in MS.

Urbanek et al. (2010) examined attentional networks in the brains of 57 MS patients compared to 57 healthy controls. The authors employed the use of the 'Attention Network Test' which is a computer based paradigm that records participants' reaction times to presented visual stimuli. Participants had to press either one of two keys to indicate the direction of an arrow on screen. In the congruent condition the arrow would be accompanied by flankers in the same direction and incongruent condition with arrows in the opposite direction. The authors found that MS patients demonstrated a disease related breakdown in the alerting network of attention compared to controls evidenced by significantly longer mean reaction times.

Meyn, Kraemer, de Grieff, Diehl (2010) examined 13 patients in the early stages of relapsing remitting MS with very low EDSS scores on an attentional working memory task with fMRI analysis of brain activation patterns compared to 13 age and education matched healthy controls. The tasks used in their study were the PASAT, digit span forwards and backwards, and the Beck Depression Inventory. For the fMRI measurement an 'n-back' test involving two-back was used as the working memory paradigm. This paradigm is reported to assess the central executive component of working memory and participants had to monitor sequential presentation of random consonants and decide whether the current presented letter had been presented two sequences before. Interestingly the authors found no significant differences between patients and controls on the neuropsychological measures or in brain activation patterns thought to represent working memory activation such as the dorsolateral

prefrontal cortex and parietal cortex areas. This study highlights the inherent heterogeneity in this population in terms of the cognitive dysfunction with some patients clearly performing as well as healthy age matched controls.

**A neuropsychological model of cognitive decline in MS**

Cortical and subcortical atrophy along with disconnection of interneuronal networks within the cortex and white matter play a role in the cognitive decline seen in MS. This breakdown leads to reduced processing speed in the brain which then affects attentional resources and memory. The ability of brain areas to 'talk' to different brain areas in close proximity, and over longer distances, becomes compromised leading to a failure in synchronous neural firing. It is clear that damage to the brain takes place early in the disease process and involves volume reduction too, either through cell loss or axonal degradation. The pattern of cognitive impairment is linked with the subtype of the disease. Relapsing remitting MS involves a process of axon attack and reparation and the cognitive impairment is less severe and may follow a stepwise pattern.

In the progressive subtypes the cognitive impairment can follow a more steady and severe decline due to non remission of the disease process. Of note, there is a large amount of variability between individual patients and the individual pattern of brain damage dictates the cognitive outcome. For example, multiple lesions in the mid-brain limbic system will significantly impact on new learning while a preponderance of frontal subcortical lesions will affect working memory.

De Luca et al. (2004) proposed a useful model to consider when assimilating the evidence from working memory and attentional research in MS. They discuss findings in terms of the 'Relative Consequences Model' and 'Independent Consequences Model'. The former model states that breakdown in working memory and other higher order cognitive functions is a relative consequence of deficient processing speed. Therefore the by-product of slowed speed of processing is

inefficiencies within other cognitive domains. The latter model states that processing speed difficulties may be independent of breakdown in other cognitive functions in some patients with a particular pattern of lesions in the brain which may impact on specific higher order cognitive functions regardless of information processing speed.

## Conclusion

Cognitive impairments in multiple sclerosis are now a well recognized hallmark of the disease and research investigating the breakdown of attentional processes is of current interest. However what is less clear is the extent of the causal variables that contribute to this impairment. For example, it is accepted that white matter lesions can reduce speed of processing in the MS brain. These lesions damage the myelin sheathes leaving denuded axons that cannot efficiently execute saltatory conduction meaning neuronal signals have a decreased velocity and increased signal transit time. If the brain processes involved in cognition are assumed to operate within optimal synchronous firing patterns whose orchestration and timely arrival are the bedrock of efficient performance, then it is not surprising that this has a secondary effect on attentional systems. These systems are assumed to be subserved by a complex network of distant brain regions traveling between frontal, subcortical, and parietal cortices. Further, lesions in the cognitive-motor pathways can affect speed and automaticity of simple and complex movements, which are involved in many cognitive tasks. Also, the powerful effects of fatigue on cognition cannot be discounted and many patients testify to experiencing cognitive decline during times of fatigue. Perhaps then the attentional problem found in MS is actually multifactorial with different causal variables with different weightings depending on context rather than simply isolated damage to an attentional controller. It may be when under experimental conditions, deficits in attention will only be highlighted when cognitive tasks involve a motor component, having to work at speed, or most likely a combination of both. There are no definitive methods of isolating and testing divided attention processes in multiple sclerosis and consensus on optimal procedures is required for future research of divided attention to help elucidate this complex breakdown.

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# Chapter 3: Research Project Paper

Exploring attentional deficits in multiple sclerosis. An investigation of sustained and divided attention in early stage relapsing remitting MS using novel computer based attentional paradigms.

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## Abstract

The cognitive impairment profile in multiple sclerosis has been well documented, however less is known about the nature of cognitive changes in early stage relapsing remitting multiple sclerosis. The ability to sustain and divide attention is a complex and demanding cognitive process utilizing dedicated cortical areas requiring reciprocal short and long distance intact white matter connections. Such processes are vulnerable to disruption following axonal changes such as those in multiple sclerosis. Using novel computer based paradigms, 17 relapsing remitting multiple sclerosis patients and 15 healthy controls, participated in unimodal and bimodal visual and auditory attention paradigms. We computed a repeated-measures ANOVA with the 2-level between-factor Group (patients vs. controls) and the 5-level within-factor Modality (Audio, Visual, and three levels of Divided) for both reaction time (RT) and accuracy (AC) as dependent variables. For reaction time, we found significant main effects for both Group ($F(1,30) = 5.8234$, $p < .05$) and Modality ($F(4,27) = 31.7154$, $p < .01$), while the interaction Group x Modality was not significant. Patients were therefore generally slower than Controls. For accuracy, neither the main effects nor the interaction were significant with a parity of performance between patients and controls. Contrary to our hypotheses, the multiple sclerosis group were not impaired relative to controls across all variables as they were not disproportionatly poorer on divided attention tasks. These results indicate that divided attention, as assessed by this task, may remain intact in the very early stages of relapsing remitting multiple sclerosis. This suggests that detectable cognitive impairment, especially within the attentional network, is perhaps the result of protracted and sustained damage to multiple subcortical white matter tracts, which may not be evident in the disease pathology at this early stage.

## Introduction

Multiple sclerosis (MS) is a neurodegenerative inflammatory demyelinating condition of the central nervous system with a variable clinical course involving several disease subtypes. Multiple sclerosis means 'many scars' and disease progression follows four main subtypes, however the most common subtype is relapsing-remitting multiple sclerosis, characterised by acute attacks of neurological dysfunction, followed by partial or complete recovery (Bone et al. 2000). In addition, prevalence rates are calculated at 144 cases per 100,000 of the population in the West of Scotland. The pathology and ensuing disability is linked with the process of axonal demyelination, remyelination, and axonal and synaptic degeneration (Orhun, Kantarci, Brian, Weinshenker, 2005). The accumulating lesion profile in the brain is diffuse, affecting central nervous functioning, motor systems, and multiple brain regions. The clinical manifestation of the disease varies considerably between sufferers and is related to lesion site, lesion load, and subsequent effects on function.

In addition to the physical problems experienced, cognitive impairment in MS is well documented and estimates of cognitive deterioration in patients range from 45 – 65%, (Rao, 1995). The nature and course of MS is heterogeneous and recognized cognitive deficits involve a range of domains including memory, attention, and speed of information processing (Zakzanis, 2000). Lezak, Howieson & Loring (2004) reports common circumscribed deficits in the cognitive domains of attention, memory, and executive function in relapsing-remitting patients.

Spilich, Mubrin, and Janculjak (2002) state that changes in cognitive processes may appear long before the physical manifestations of MS, suggesting that identifying patients earlier could be based on cognitive changes. However, there are difficulties in identifying unique cognitive markers for any neurological condition, especially in the early stages due to overlap in presentation.

Even though the cognitive profile in MS is often heterogeneous, a consistent deficit found in multiple sclerosis is problems with attention and the ability to attend to more than one thing at the same time which is known as divided attention (Bobholz & Rao, 2003). In addition, an intact attentional system is vital for the efficient processing of other various cognitive systems, for example memory encoding. There is some suggestion that deficits in higher cognitive operations are actually secondary to primary attentional problems in MS. However the extant MS literature examining attentional dysfunction leaves unanswered questions as to the extent and nature of deficits (McCarthy, Beaumont, Thompson, Peacock, 2005).

When considering the concept of attention there are various theoretical cognitive models of attention and one of the most influential and frequently referenced theories is Baddeley's (1986) working memory model. He proposed a structural model involving multiple interactive components including a central executive controller that regulates and distributes the limited available attentional resources that a system possesses, and visuospatial and phonological slave systems (Baddeley, 2003). The slave systems are responsible for storage of modality specific inputs and one of the principle roles of a central executive system would be to efficiently allocate and manage attentional resources when two or more tasks are being executed

simultaneously or when attention is divided between the visual and auditory slave systems (Baddeley, 1996).

Dual tasking or divided attention paradigms have been used extensively to study this fundamental property of an executive control system in various patient populations (Baddeley, Della Sala, Papagno & Spinnler, 1997). Dual tasking designs involve performing two different tasks on their own and then concurrently, and comparing performance levels on one or more of the tasks. For example, established formats involve participants performing a verbal digit span task with a visual tracking task. In clinical populations, a dual task performance decrement is frequently observed and reported in the context of damage to an executive coordinator responsible for dividing and allocating attention; for example in Alzheimer's disease (Logie, Della Sala, Cocchini, Baddeley, 2004).

Further, Baddeley, Baddeley, Bucks, and Wilcock, (2001) found that Alzheimer's disease patients have a specific difficulty with dual task performance, even when controlling for the general overall cognitive demand, suggesting that available attentional resources is not the problem, but how they are allocated is. Also, in a frontal lobe lesion patient group Baddeley, Della Sala, Gray, Papagno & Spinnler, (1997) found that patients with dysexecutive syndrome showed impaired capacity for dual tasking.

In multiple sclerosis, evidence indicates that the multifocal lesion profile may affect brain areas which form the working memory substrate, leading to working memory impairment in the early stages of the disease (Pelosi et al. 1997) and thus difficulties with focusing and dividing attention during tasks.

D'Esposito et al. (1996) investigated central executive functioning using dual tasking methodology comparing an MS group with a control group. In their study, the dual tasking paradigm involved performing a primary task concurrently with one of three secondary tasks. The primary task involved a line orientation judgement with the concurrent secondary tasks being finger tapping, alphabet recitation, and humming a melody. Results showed that the MS group performed less well during the more demanding dual task conditions (humming a melody and alphabet recitation) than the control group. The authors concluded that the dual task decrement found in the MS group, reflected an impaired central executive of working memory resulting in difficulty allocating sufficient attentional resources to support concurrent task execution. Certainly under such dual task conditions there is a higher cognitive load and recruitment of more specialist cognitive systems such as memory, visuospatial ability, and even musical performance. However, the conclusion that it is attention that is breaking down has to be questioned as the task decrement could be explained by a breakdown in any one of the cognitive processes involved and not just attention. The fundamental properties of the central executive are attentional modification to task presence. Isolation of this fundamental should be aimed for when examining divided attention. Baddeley, Della Sala, Gray, Papagno & Spinnler (1997) states that paradigms exploring the central executive's coordination properties should involve simultaneous operation of the phonological loop and visuospatial sketchpad.

This doesn't equate to tasks such as those used by De'Esposito et al. (1996) that recruit higher cognitive functions of language, memory, and musical ability, and fail to isolate the basic properties of the working memory model.

Paul et al. (1998) investigated several aspects of automatic and controlled attentional processing in MS using tests of focused and divided attention. They used the Posner spatial attention task (Posner, Cohen, & Rafal, 1982), which involves visual stimuli presented with valid and invalid spatial cues, as a test of automatic processing and found that the MS group performed as well as the control group. The Paced Auditory Serial Addition Task (PASAT) was used as a test of divided attention in this study and the MS group performed significantly worse than the controls. Whether the PASAT is truly a test of divided attention is worthy of thought as the nature of that task involves sustained attention over time with higher cognitive functions of calculation recruited. Often, the PASAT is used as an index of information processing speed and clearly, there is a large working memory involvement, but it is questionable whether this test fulfils the criteria that Baddeley, Della Sala, Gray, Papagno & Spinnler, (1997) suggests for divided attention methodology.

Recently, McCarthy et al. (2005) considered the profile of attentional dysfunction in MS using divided and sustained attention methodology across unimodal and bimodal visual and auditory trials. The authors developed two new measures of sustained and divided attention as part of their study and recognised that their approach to investigating divided attention was in contrast with conventional dual tasking methodologies where primary task decrement is measured during concurrent secondary task execution. In the divided attention task, targets were digits that were consecutive pairs either ascending or descending with a temporal delay between digit presentations in a trial. Participants were required to divide their attention between

retention of the first digit and presentation of the next digit. Thirty MS participants were compared with 30 controls across all six conditions (sustained vs divided task and auditory, visual, bimodal presentations). The results suggested that the MS group performed slower and less accurately than controls on both sustained and divided measures of attention. Of note, the MS group were disproportionately slower on the bimodal trials of the divided attention task, relative to unimodal trials. The authors concluded that their results were not related to motor slowing or information processing speed deficits, but linked with the task demands and the modality targeted. When the MS group were performing the divided attention task in visuo-auditory bimodal trials, their performance suffered most and this could be explained within Baddeley's (2003) theoretical framework with a deficient central executive component, impaired in allocating attentional resources efficiently between visual and auditory modalities.

Hamilton et al. (2009) investigated the effects of performing a concurrent cognitive task when walking in people with RRMS. They investigated five conditions: walking, fixed digit task, titrated digit task, walking with fixed digit task, walking with titrated digit task. Compared to controls, MS participants had greater decrements in dual task performance with decrements in walking speed, digit task, and swing time in fixed demand dual tasks, decrements in walking speed in titrated demand dual tasks and dual task decrement in cognitive-motor paradigm could be due to divided attention deficit or overloading of working memory as a result of walking requiring greater attention. The authors highlighted the everyday and clinical implications: people with MS may have everyday difficulty walking and talking and dividing attention is a frequent part of everyday life. Therefore this problem could be linked to increased risk of falls.

The authors further address the need for a robust clinical tool to assess cognitive-motor dual tasking ability and divided attention.

The aim of this present study was to further understand the nature of cognitive impairment in multiple sclerosis, and in particular to investigate the attentional system in the early stages of the relapsing remitting disease type. Specifically, we were interested in the ability to divide attention during concurrent modality demands. We explored visual and auditory attention using unimodal tasks and divided attention using novel dual modality methodology. The method is similar to McCarthy et al. (2005) insofar as the approach was an attempt to depart from established tests of divided attention and reflects our aim of establishing whether central executive attentional deficits are revealed by a novel dual modality test. This test utilised simpler perceptual stimuli, numbers and counting, and restricts an over involvement of motor and associated cognitive processing demands on participants. Participants had to divide their attention between a visual number input and an auditory number input, which was combined into a choice response. Our general hypothesis was that MS participants would show an impairment in the central executive component of attentional control reflected by an experimental decrement compared to controls involving higher latency response times and increased error scores within the bimodal divided attention task. Further, it was hypothesized that during the 'divided attention' task there would be a stepwise performance decrement linked with the interstimulus interval (ISI) between auditory and visual stimuli. For example, performance would decrease as the (ISI) approached 0 msecs with the greatest performance decrement at simultaneous auditory – visual presentation (0 msecs ISI).

The paradigms developed fit within the construct of working memory proposed by Baddeley (1986) and are in line with his suggestions for investigating the central executive component of working memory (Baddeley, Della Sala, Gray, Papagno & Spinnler, 1997). Further, Sarter & Turchi (2002) describe divided attention as the ability to divide resources between multiple and competing perceptual tasks. The tests in this study were designed to isolate the attentional system using multiple and competing perceptual elements. Across the tasks, cognitive load did not vary, with the same number of stimuli delivered within each trial. Therefore, the paradigms ensured that various attentional characteristics were examined, while maintaining a parity of cognitive load and information processing between tasks.

## Methods

*Participants:*

Seventeen patients (5 males) diagnosed with relapsing remitting multiple sclerosis were recruited from a clinic-based sample of the West of Scotland Multiple Sclerosis Service. Fifteen (5 males) age matched healthy controls were recruited from the local area using spouses and friends of the clinical sample and advertising for participants. All patients had an expanded disability status score (EDSS) of less than 3 which reflects a minimal level of motor disability and sensory and physical disturbance (Kurtzke, 1983). The patients were in the early stages of the disease and all had a diagnosis of relapsing remitting multiple sclerosis of less than 3 years at the time of the study. There were no psychiatric or neurological comorbidities within the group and only patients without optic neuritis or hearing impairments were included. All had normal or corrected to normal vision and were in remission at the time of study. Although no formal record of individual pharmacotherapy use was detailed, some of the patient samples were on disease modifying treatment at the time of the study. No payment was offered to the participants. Ethical approval was obtained from the Local Research and Ethics Committee and informed consent was given by each participant. Characteristics of the sample are given in (Table 1).

The sample size was decided on from a recent study examining modality specific aspects of sustained and divided attention in MS where the authors recruited 30 MS participants and 30 neurologically intact healthy controls (McCarthy et al, 2005). They found a statistically significant difference between the MS group and control group. The effect size calculated from their reaction time data on the bimodal divided attention task was (Cohen's d = 1.18), with power calculated as 0.998. This power calculation was made using a software calculator, namely 'G-Power' at

http://www.psycho.uniduesseldorf.de/aap/projects/gpower/ (Faul, Erdfelder, Lang & Buchner, 2007).

Assuming a similar effect size and level of variance in each group, for the present study, with alpha = 0.05, a sample of 17 MS patients and 6 control participants would have power of 0.9 to detect significant effects. However, taking a more conservative approach we aimed to match numbers of patients and controls. In the timescale available for the project, it was possible to recruit 17 patients and 15 controls.

**Table 1: Sample Characteristics**

| | Sample | Age (mean) | Diagnosis duration | Education |
|---|---|---|---|---|
| Controls | **15** | **33.13 Range = 25 - 40** | **Not applicable** | **All attained higher grade education.** |
| Patients | **17** | **32.53 Range = 23 - 40** | **14.7 (13.5) months. Range = 2 - 36** | **Some attained higher grade education.** |

***Neuropsychological Measures:***

All participants completed a neuropsychological screening battery to assess any gross deficits. None of the participants had any significant vision or hearing problems. Premorbid intellectual functioning was assessed using the Wechsler Test of Adult Reading (Wechsler, 2001). The Addenbrooke's Cognitive Examination (Mathuranath, Nestor, Berrios, et al. 2000) was used as a multi domain cognitive screen and the mood and anxiety of the participants was assessed using the Depression Anxiety Stress Scales (DASS) and scores compared to established norms (Lovibond and Lovibond, 1995). Summary scores are given in (Table 2).

**Table 2: Summary neuropsychological results**

| | Predicted full scale IQ (mean) | ACE Screen Mean | DASS A Mean | DASS D Mean | DASS S Mean |
|---|---|---|---|---|---|
| Controls | **107.2 Range = 96 - 116** | **96.8 Range = 92 - 100** | **2.2 Range = 0 - 8** | **2.2 Range = 0 - 10** | **7.6 Range = 0 - 22** |
| Patients | **100.4 Range = 75 - 114** | **91.2 Range = 77 - 100** | **6.2 Range = 1 - 15** | **4.4 Range = 0 - 17** | **11.1 Range = 0 - 25** |

***Experimental Measures and Design:***

The experiments were delivered via a Windows PC using E-Prime experimental software. Reaction time data and error rates were calculated for each participant across five different paradigms consisting of 64 experimental trials in each paradigm apart from the three divided attention paradigms which had 64 trials in each sub task.

**Visual Sustained Attention Task:**

In a trial the following occured in a linear sequence: A threshold number always coloured red and between 5 and 20 appeared in the centre of screen, for 500 msecs to indicate the start of the trial. This was followed by two numbers (coloured black) of between 0-20 flashing consecutively. The numbers appeared on the screen in the centre area for a duration of 150msecs with a gap between them (interstimulus interval) of 250msecs. After both numbers appeared the participant had to decide whether the sum of both (black coloured) numbers was greater than or less than the initial threshold number (coloured red) and indicate their choice through a key press: button 'Z' for less than and 'M' for greater than. They had 1000 milliseconds to make their choice before the next trial began and the response screen was coloured green for 'Go!'. A 'READY' cue appeared between trials for a duration of 500ms. The experiment had 2 blocks with 32 randomised trials per block. The break in presentation allowed participants a short break if required. The keyboard was solely used to collect participant responses.

**Auditory Sustained Attention Task:**

This is analogous to the above process except the number stimuli were presented through headphones binaurally and there was no visual component apart from the threshold number (coloured red) appearing on the screen at the start of each trial. The exact same principles for responding applied. As before, performance was measured in response times and accuracy. The experiment had 2 blocks with 32 randomised trials per block.

**Divided Attention Task:**

The same parameters incorporated as above were used, however one number was presented visually and one number presented binaurally during each trial. The interstimulus gap was varied giving three divided attention conditions: 250 msecs (ISI) for 64 trials, then 100 msecs (ISI) for 64 trials, then simultaneous bimodal presentation (0 msecs ISI) for 64 trials. The experimental software was programmed to choose at random which sensory modality experienced the stimuli first in the trials (i.e, visual then verbal or verbal followed by visual) and randomised the ISI orders. It was hypothesized that during the 'divided attention' task there would be a stepwise performance decrement linked with the interstimulus interval (ISI) between auditory and visual stimuli. For example, performance would decrease as the (ISI) approached 0 msecs with the greatest performance decrement at simultaneous auditory – visual presentation (0 msecs ISI).

*Procedure*

All participants were assessed at the University of Glasgow, Sackler Institute, Southern General Hospital, Glasgow in a sound proof sleep laboratory which was climate controlled. Ambient lighting was minimal allowing maximum awareness of monitor emission. The author (SM) administered all the neuropsychological tests before giving standard instructions on the three computer based paradigms. These paradigms were delivered by a Toshiba Satellite Pro computer running E-Prime experimental software which had been programmed to produce the experimental paradigms (Psychology Software Tools, Pittsburgh, PA). For the auditory and divided attention tasks, participants wore a stereo headphone set. Participants sat approximately two feet from the monitor and instructions appeared on screen before each experiment commenced. This was followed by 10 practice trials and then each participant was given the opportunity to ask any further questions before beginning the experimental trials.

The participants were left in the room on their own while the experimental trials were running to ensure maximum concentration. Within each block the software would automatically create a forced rest break for the participants and the participants would choose how long they wished this to be by pressing the space bar to continue. There were also forced breaks between blocks as the experimenter had to re-enter the room to load the next software block. Participants were also asked if they needed extra rest breaks. The order of presentation of the computer based paradigms was manually counterbalanced for each participant. There were 6 possible configurations of the 3 conditions.

The experimenter viewed the participants via a remote video camera during the experiment and all participants were made aware of this. At the end of each paradigm the software automatically stopped, the participant raised their hand, and the experimenter returned to the laboratory and started the next experimental trial group. This ensured a standardized procedure for each participant.

## Results

We tested the significance of group differences between demographic variables with a percentile bootstrap of the experimental effect (H1) using the Harrell-Davis estimator. There was no significant difference between the groups with respect to age, DASS-Depression scores and DASS-Stress scores. However, the groups were significantly different in their premorbid intellectual abilities (WTAR, $diff_{HD}$=-7.6735 [-12.7002 -0.0961], p<.05), their overall cognitive abilities (ACE-R, $diff_{HD}$= -5.0971 [-8.1292 -2 .0120], p<.01), and their anxiety levels (DASS-A, $diff_{HD}$= 3.0412 [1.0969 6.3722], p<.01). This means that patients had generally lower premorbid intellectual abilities, lower global cognitive screen scores and higher anxiety levels than the control group.

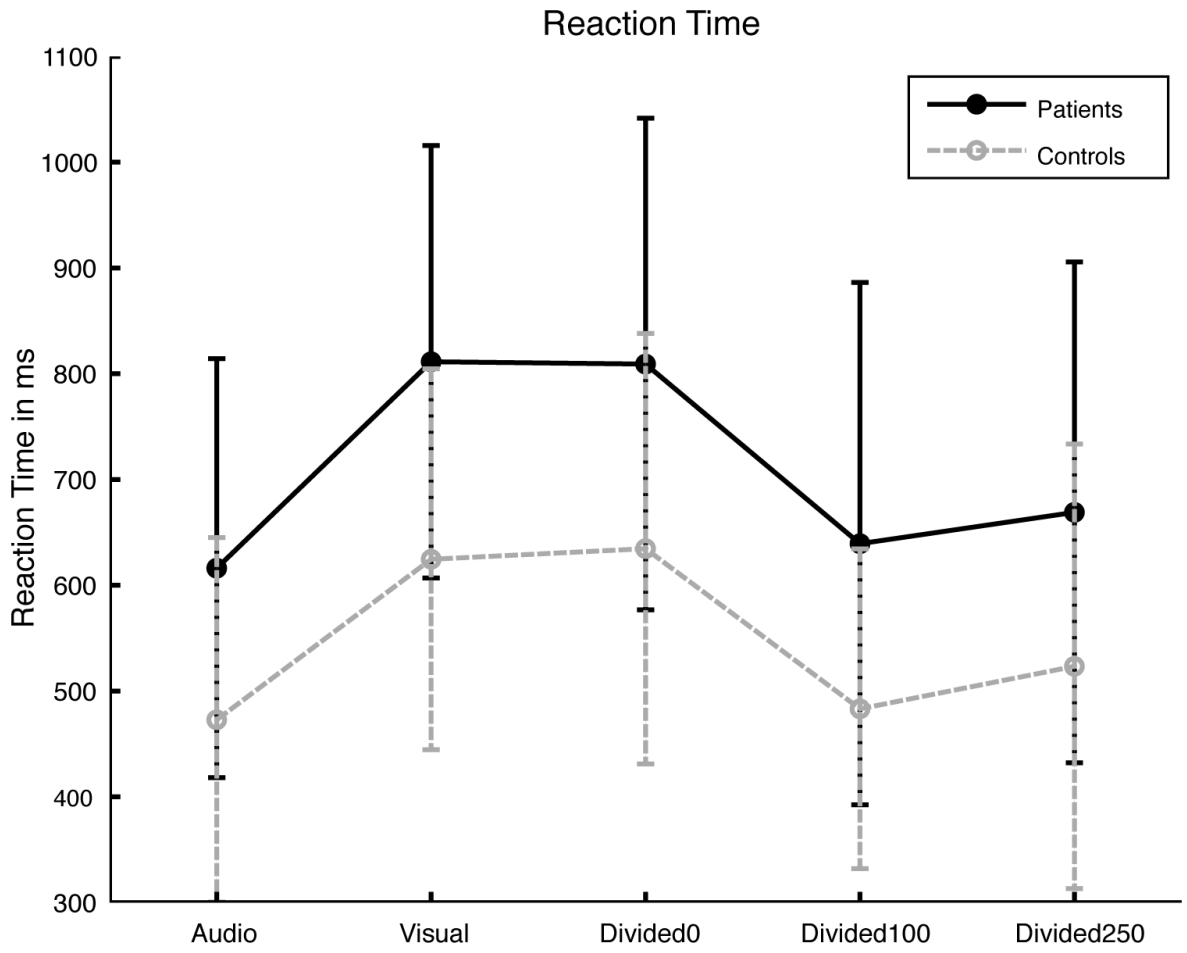
The reaction time mean data and accuracy mean data for both patients and controls across the five conditions is detailed in table 3.

Table 3. Latency and error data for patients and controls across each condition:

| **Reaction Times** | | | | | | |
|---|---|---|---|---|---|---|
| *Audio* | *Visual* | *Divided (0 ISI)* | *Divided (100 ISI)* | *Divided (250 ISI)* | *Divided overall* | |
| 616.17 | 811.36 | 809.16 | 639.34 | 668.96 | 653.58 | **Patients** |
| 472.82 | 624.59 | 634.62 | 483.18 | 523.37 | 606.26 | **Controls** |
| **Error Data** | | | | | | |
| *Audio* | *Visual* | *Divided (0 ISI)* | *Divided (100 ISI)* | *Divided (250 ISI)* | *Divided overall* | |
| 0.93 | 0.92 | 0.89 | 0.87 | 0.86 | 0.88 | **Patients** |
| 0.98 | 0.95 | 0.97 | 0.97 | 0.95 | 0.95 | **Controls** |

We plotted reaction time for both patients and controls across all five conditions as detailed in figure 1.

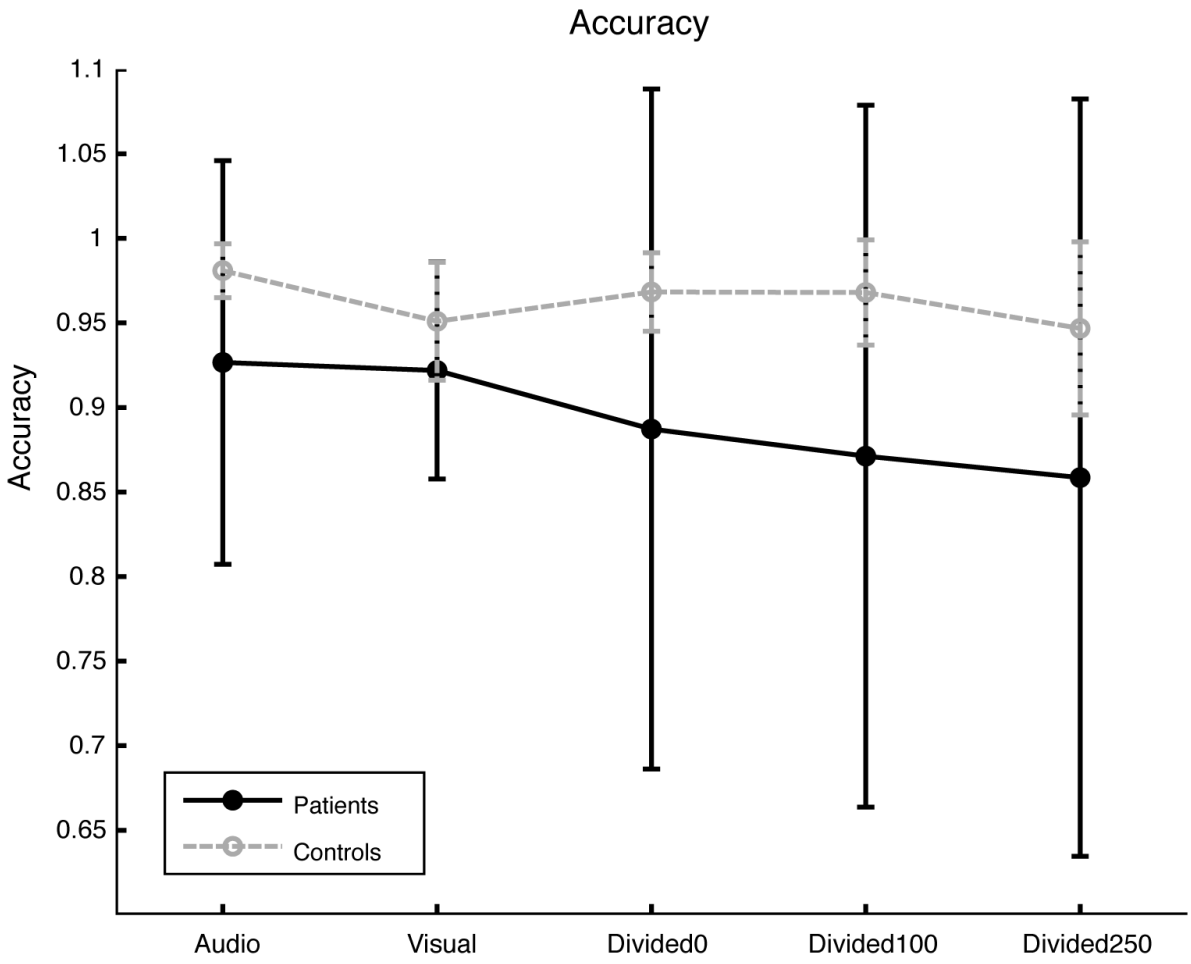
Figure 1: Latency data for both groups across five conditions. The error bars represent the standard deviation.




Subjectively, patients appeared generally to be slower than the control group across the five conditions.

We further plotted the error data for both patients and controls across all five conditions as detailed in figure 2.

Figure 2: Error data for both groups across five conditions. The error bars represent the standard deviation.




Subjective visual analysis of this reveals overall high rates of accuracy for both groups across all five conditions with an accuracy pattern concordance between the groups.

*Inferential Statistical analysis*

All reaction times were normally distributed allowing us to employ the use the ANOVA statistic. Accuracy was normally distributed in controls, but not in patients (apart from within the visual condition only). We did not need to transform the data, because the shift function analysis we performed doesn't assume normality (the Harrell-Davis estimator used is non-parametric).

Effect sizes were calculated to investigate the power of the current study:
-Cohen's d was .75 for the main group effect of reaction time in the ANOVA.
-Cohen's d was .56 for the main group effect of accuracy which was non-significant.
The effect size for reaction time was high which suggests the present study was not underpowered.

We computed a repeated-measures ANOVA with the 2-level between-factor Group (patients vs. controls) and the 5-level within-factor Modality (Audio, Visual, Divided ISI(0), Divided ISI (100), and Divided ISI (250) for both reactions time (RT) and accuracy (AC) as dependent variables. In order to determine robust confidence intervals (CI) for the *F*-value, we performed a percentile bootstrap under H0 with 1000 iterations, each time randomly sampling with replacement from the entire distribution of values. Only *p*-values from this bootstrap procedure are reported.
For RT, we found significant main effects for both Group ($F(1,30) = 5.8234$, $p < .05$) and Modality ($F(4,27) = 31.7154$, $p < .01$), while the interaction Group x Modality was not significant. Patients were generally slower than Controls, whereas RTs in the Visual and Divided ISI (0) conditions were longer than in the Audio and other Divided conditions (see Figure 1). For AC, neither the main effects nor the interaction were significant. These results are graphically displayed in Figure 2.

Instead of using post-hoc t-tests to compare individual groups, we decided to perform a shift function analysis (see for example Rousselet et al. 2011). While t-tests use measures of central tendency to measure the difference between two groups, the shift function compares two distributions quantile by quantile using the Harrell-Davis estimator (hd) of quantiles one to nine. Specifically, the shift function is a measure of how much each quantile needs to be shifted to be comparable to the data of the same quantile in the other group.

The Harrell-Davis estimator is an L-estimator, which performs particularly well with small sample sizes (Wilcox, 2005). A bootstrap procedure is then used to obtain a 95% confidence interval for the difference between the (hd) estimators of the groups. If this confidence interval excludes zero, the difference between quantiles is significant. For our purposes, the main advantage of this type of analysis is that we can see whether differences between groups are mainly driven by differences in the tails of distributions. If, for example, the patient group mainly consists of unimpaired individuals and only a few impaired individuals, then only one or two quantiles on one side of the distributions will be significantly different from each other between groups. Again, this analysis was performed for both RT and AC as dependent variables. While the distributions did not differ at all for AC, they did differ for RT in several conditions. In quantile 9 of the conditions Audio, Divided ISI (0) and Divided ISI (100), the CI for the difference between the two groups does not contain 0, which means that the RT of patients and controls at one end of the distribution was significantly different. Specifically, patients with the slowest RT were even slower than controls with the slowest RT. In the visual condition, only quantile 5 is significantly different between groups. This means that patients in the middle of the distribution are slightly slower than controls, shifting the peak of the RT distribution

of patients slightly to the right. However, it is important to note that with regard to RT, most patients did not differ from the control group at all.

In order to identify the patients with particularly slowed reaction times, it is possible to use a single subject approach as described by Crawford and colleagues (1998, 2002, 2010). Patients whose RTs differed significantly from the means of the control group in any of the conditions are listed in table 4. It became clear that patients 11, 14 and 15 are particularly slow in all conditions and are therefore probably driving the main effect of group in RT.

To determine whether this is the case, we recomputed the ANOVA without patients 11, 14 and 15. The main effect for Group then disappeared ($F(1,27) = 2.5187$, $p = .256$) and there was no significant difference.

**Table 4: Statistical analysis of subset of patient group.**

| Condition | Patient | mean | *t*-value | *p*-value | Effect Size Z-CC with CI |
|---|---|---|---|---|---|
| **Audio** | P11 | 881 | 2.297 | 0.019 | 2.372 (1.356 to 3.367) |
| group mean: 473 | P15 | 865 | 2.207 | 0.022 | 2.279 (1.292 to 3.245) |
| group std: 172 | P16 | 847 | 2.105 | 0.027 | 2.174 (1.219 to 3.107) |
| | P14 | 826 | 1.987 | 0.033 | 2.052 (1.134 to 2.947) |
| **Visual** | P11 | 1122 | 2.673 | 0.009 | 2.761 (1.620 to 3.882) |
| group mean: 625 | P2 | 1051 | 2.292 | 0.019 | 2.367 (1.352 to 3.360) |
| group std: 180 | P14 | 1000 | 2.017 | 0.032 | 2.083 (1.156 to 2.988) |
| | P16 | 1124 | 2.684 | 0.009 | 2.772 (1.628 to 3.897) |
| | P15 | 956 | 1.78 | 0.048 | 1.839 (0.984 to 2.670) |
| **Divided_ISI (0)** | P11 | 1267 | 3.019 | 0.005 | 3.118 (1.860 to 4.358) |
| group mean: 634 | P14 | 1006 | 1.774 | 0.049 | 1.833 (0.980 to 2.662) |
| group std: 203 | P15 | 1138 | 2.404 | 0.015 | 2.483 (1.431 to 3.513) |
| **Divided_ISI (100)** | P11 | 1049 | 3.629 | 0.001 | 3.748 (2.278 to 5.203) |
| group mean: 483 | P14 | 873 | 2.501 | 0.013 | 2.583 (1.500 to 3.646) |
| group std: 151 | P15 | 1093 | 3.911 | 0.001 | 4.040 (2.469 to 5.595) |
| | P2 | 884 | 2.571 | 0.011 | 2.656 (1.549 to 3.742) |
| | P16 | 901 | 2.68 | 0.009 | 2.768 (1.625 to 3.892) |
| **Divided_ISI (250)** | P11 | 1119 | 2.748 | 0.008 | 2.838 (1.672 to 3.985) |
| group mean: 523 | P15 | 1042 | 2.393 | 0.016 | 2.471 (1.424 to 3.498) |
| group std: 210 | P14 | 940 | 1.923 | 0.038 | 1.986 (1.088 to 2.861) |

## Discussion

The purpose of this study was to investigate cognitive changes in early stage relapsing remitting multiple sclerosis. In particular, ability to divide attention between multiple perceptual streams was explored. The specific hypotheses were that the MS group would attain a similar level of performance as the control group during unimodal visual and auditory tasks and show a disproportionate decrement in performance compared to controls on the test of divided attention involving bimodal attention. This performance decrement would be recorded as an increase in error rates and increased response latency. The attentional tasks used were in-house designed measures of visual attention, auditory attention, and visuo-auditory attention. These tasks were designed to minimize excessive motor demands that could confound reaction time data and focus as much as possible in isolating pure attentional processes and avoiding, as much as possible, other higher order cognitive processes. The target of interest was the central executive component of Baddeley's (1986) working memory model that is thought to be responsible for allocating and monitoring attentional resources.

Our first hypothesis that there would be no significant difference between patients and controls on unimodal attentional measures was not fully supported. In terms of the error data both groups were on average equally accurate in their performance across the tasks and conditions. However, when the reaction time data was examined patients were significantly slower than the control group even during unimodal attentional conditions. During divided attention conditions using the bimodal task, MS patients were on average slower than controls however this decrement in performance compared to controls was not statistically significant in terms of an interaction of group and condition.

The question of why no statistically significant difference for accuracy between groups was found has to be addressed and there are several possible explanations that may explain this lack of difference. Firstly the multiple sclerosis group studied here are unquestionably within the very mild spectrum of the disease. All patients were in the early stages of relapsing remitting disease and outwith relapse at time of study. Their global cognitive functioning was lower than that for the control group but relatively intact and some were on disease modifying therapy, which has a protective function with regards disease process including cognitive functioning (Fischer et al. 2000). MS is characterized by lesions within the cerebral hemispheres with a predilection for periventricular locations (Rovaris, Comi, & Filippi, 2006). However the lesion profile is not predictable and there is great variability between patients as to the location and number of lesions within the brain. In the early stages of MS it is likely that there will be fewer lesions within the brain and therefore the chances of a cognitive system being damaged is lower. Also, in some patients with a longer duration of illness, cognitive impairment has been found to be absent, again highlighting the variability within this complex disorder. It is likely that the patient group studied here had a minimal lesion load. Further, cognitive impairment in MS has been associated with cerebral atrophy and studies have found links between cognitive performance and neural volume decrease of the MS brain using the brain parenchymal fraction. Again, this type of atrophy is unlikely to be present in this patient group with such a short length of diagnosis as atrophy of neural structure takes time to occur.

Recent fMRI evidence during working memory tasks in MS suggests that there is compensatory recruitment of additional brain areas early on in the disease process and it is possible that this retaliative neural recruitment supports delay in cognitive demise

(Au Duong et al. 2005). Meyn, Kraemer, de Grieff, and Diehl (2010) looked at fMRI activation in 13 patients with early stages RRMS using the 'n-back' test. They proposed that this is a test of working memory assessing the central executive component of working memory and involves monitoring a series of presented random consonants and then deciding if the current letter had been presented 'n' number of letters back in the sequence (in this case 2 back), eg. B, G, B would be a positive response. They also used the PASAT and digit span forwards and backwards task. They found no differences between the controls and MS patients on any measures and no difference in the fMRI activation pattern of working memory which is purported to be a neural network involving the DLPFC the ventro lateral prefrontal cortex and frontal medial and frontal parietal areas. This was different to previous studies that have found additional activation patterns in MS thought to reflect brain compensation mechanisms during demanding tasks.

Therefore, any cognitive changes that are present within this group may be so mild that statistical significance cannot be found. Some of the MS group had been through higher education and attained degrees and some research (Pinn, 2001) suggests that higher levels of education act as a “buffer” effect in relapsing remitting MS particularly buffering against loss of executive functioning. This may partly explain the parity in accuracy performance within the patient group.

Previous research that has found divided attention deficits in MS and other neurological or dementing disorders has usually used dual tasking methodology, which involves tasks of greater complexity than those used in this study. More often, dual tasking methodology has a more significant motor component involved in the tasks and it may be this process that is largely responsible for the decrement in

performance found in these studies. In line with this observation it is likely that the paradigms designed here were perhaps not sufficient in terms of the cognitive load they exerted on the patients and therefore did not reveal cognitive changes that were present. While neither group hit a 'ceiling effect' in terms of accuracy performance, both groups did perform at a consistently high level of accuracy, which may reveal task simplicity.

The unimodal and divided attention tasks devised for this study were built with three integral points central: minimal motor demands across tasks, parity of cognitive load across tasks, and isolation of pure attention with minimal involvement of higher cognitive processes. Using tasks with a minimal motor component reduces the confounding variable of peripheral muscular slowness, which can by proxy affect cognitive measures giving an artificial assessment of cognitive functioning. A homogeneity of cognitive load was essential to ensure that, during the divided attention task, any decrement in performance was not just the result of increased task difficulty when doing two things at the same time, but a genuine breakdown when attention is split between bimodal perceptual streams. Therefore we could reliably interpret any performance decrement to a faulty attentional controller within working memory. This is a common complaint of existing dual tasking methodology, which purports to measure divided attention when cognitive load is not controlled for.

This methodology usually involves combining tasks with a motor component, for example walking, with a cognitive task like digit span or PASAT. These cognitive tasks arguably involve more cognitive processes than just attention. Perhaps in trying to focus on the attention system as purely as possible, the paradigms within this study may have tapped into perceptual processes much earlier in the stimulus to brain pathway and did not adequately tax the attention system itself. For example, perhaps

there is a difference between dividing perceptual attention and dividing working memory and attentional cognitive operations. The paradigms developed here require dividing of attention to perceptual streams but perhaps when the information reaches working memory space the necessity to divide attention is no longer required apart from holding in short term storage the threshold number presented at the start of each trial. The tasks used were built on basic and overlearned arithmetic ability. It may be that such stimuli can be recognized and computed at a relatively perceptual level within the ventral and dorsal stream visual pathways and requires little if any involvement of a central executive attentional controller which is assumed to be subserved by neural substrate including within the frontal cortices. Potentially, a divided attention deficit in early stage relapsing remitting MS may be present if the paradigms can be developed to tax more of the central executive within the cognitive attentional network.

In particular the tasks of this experiment involved the auditory and visual stimuli being presented on a trial by trial basis, therefore there was not continuous demand placed on the attentional network; there was a short break between trials. Perhaps this time period, albeit brief, was enough for the attentional system to 'reset' itself before the next trial. Future tasks could be explored that employ a continuous lag on one of the modality specific processing streams while dividing attention concurrently between another.

Despite the heterogeneity of MS a consistent finding within the literature is that 40-65% of patients will develop attentional problems of some kind. However what is less clear is the extent of the causal variables that contribute to this impairment. For example, it is accepted that white matter lesions can reduce speed of processing in the MS brain. These lesions damage the myelin sheathes leaving denuded axons that

cannot efficiently execute saltatory conduction meaning neuronal signals have a decreased velocity and increased signal transit time. If the brain processes involved in cognition are assumed to operate within synchronous firing patterns whose orchestration and timely arrival are the bedrock of efficient performance, then it is not surprising that this then has a secondary effect on attentional systems. These systems are assumed to be subserved by a complex network of distant brain regions traveling between frontal, subcortical, and parietal cortices. Further, lesions in the cognitive-motor pathways can affect speed and automaticity of simple and complex movements, which are involved in many cognitive tasks. Also, the powerful effects of fatigue on cognition cannot be discounted and many patients testify to experiencing cognitive decline during times of fatigue.

Perhaps then the attentional problem found in MS is actually multifactorial with different causal variables with different weightings depending on context rather than simply isolated damage to an attentional controller. It may be then that under experimental conditions, deficits in attention will only be highlighted when cognitive tasks involve a motor component, having to work at speed, or most likely a combination of both. If disconnection or slowing of connections between distant brain areas is the fundamental problem in the MS brain then perhaps simpler tasks will be less likely to create a 'bottleneck' in processing information.

The results found in this study will add to the existing body of literature in this field and provide useful information for understanding the cognitive attentional profile in early relapsing remitting multiple sclerosis and give pointers for future research.

In conclusion, there are no definitive methods of isolating and testing divided attention processes and consensus on optimal procedures is required for future research of divided attention. The tasks devised for this study deserve further development and perhaps investigation with MS patients with different subtypes of the illness and at different stages. For example, it is widely recognized that patients with the secondary progressive type of MS experience the greatest cognitive sequalae of the disease. Perhaps the tests used here may be sensitive in detecting this cognitive impairment in the early transition stages from relapsing remitting disease to secondary progressive and show utility in tracking progression. Further studies are therefore required to fully validate the paradigms, which may prove a useful addition when researching divided attention.

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