MONASH University

An Ocular Motor Investigation of Attention in Multiple Sclerosis

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Abstract

Multiple Sclerosis (MS) is a chronic neurological disease characterised by widespread inflammation and neurodegeneration involving both white and grey matter. In MS, clinical presentation and disease course are highly heterogeneous, reflecting differences in subdomains and severity of pathology. Given this heterogeneity, a complete understanding of MS symptom characteristics remains elusive. Cognitive deficits, in particular, are still relatively poorly characterised. Although deficits across multiple cognitive domains have been reported in MS, one of the domains most commonly affected is attention, the process that prioritises information through active selection of relevant information for further processing, and prevents irrelevant information from disrupting this process. However, attention is a multifaceted process, comprising several subdomains. Whether attentional failure in MS represents a global attentional failure or a failure of specific subdomains is still unclear. This thesis therefore aimed to further our understanding of attentional deficits in MS, by characterising performance using a range of tasks that assess specific attentional subdomains. Three attentional subdomains were explored (attentional orienting, selective attention and divided attention) and deficits characterised as a function of overall disability as measured by the Expanded Disability Severity Scale (EDSS).

For the attentional orienting task, a delayed inhibition of return (IOR) was revealed, suggesting deficits at the most basic or subconscious level of attention (Chapters 3 and 6). However, this inhibitory failure was found only with more advanced disease (high disability group), consistent with failure across a more extensive network. An increased proportion of errors on this task was also revealed, again only for the high EDSS disability group. Greater disability, likely equated to greater disease burden, with greater potential for network dysfunction. The finding of a larger proportion of selection errors on the selective attention task (Chapters 4 and 6)

similarly suggested inhibitory failure. This task required both a greater level of top down inhibitory control (inhibiting an overt response while covertly orienting towards the target for informational content), and unlike the attentional orienting task, both MS sub-groups performed more poorly on this task. This was arguably a consequence of greater attentional demands, and the implication of a more extensive inhibitory network. Finally, although results revealed no dual task decrement for MS patients on the divided attention task (Chapters 4 and 6), the proportionately larger error rate for antisaccades, with or without a secondary task, was again consistent with poor inhibitory control. Like the selective attention task, this task required both top down inhibitory control (inhibiting an overt response while covertly orienting towards the target for informational content) and the generation of a separate response to a target stimulus. Again, both high and low disability groups generated significantly more errors, however, for the low disability group, only in the context of the secondary task.

Collectively, these results demonstrated that MS patients with relatively less disability (low EDSS scores) only performed more poorly on more complex attentional tasks, or those governed by executive processes requiring the resolution of conflict between competing processes (e.g. inhibit a response AND instead generate a volitional response). In MS, the disease process initially implicates relatively isolated, often distributed neural regions. Compensatory mechanisms ensure relative preservation of function, although it is more likely that complex processes implicating a more extensive cortical network may be compromised with lower levels of overall disability. As the disease process progresses, compensation is less effective, resulting in a broader range, and greater degree, of deficit. It is anticipated that this nuanced understanding of attentional deficits in MS may potentially assist symptom management and inform future research on the development of cognitive rehabilitation strategies for patients.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

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Date: 1st October, 2019

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Abbreviations

ACC	Anterior Cingulate Cortex
ANT	Attention Network Test
BDI	Beck Depression Inventory
BG	Basal Ganglia
CIS	Clinically Isolated Syndrome
cMRF	Central Mesencephalic Reticular Formation
cFN	Caudal Fastigial Nucleus
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DAN	Dorsal Attention Network
DLPFC	Dorsal Lateral Prefrontal Cortex
EBN	Excitatory Burst Neurons
EDSS	Expanded Disability Standard Scale
FEF	Frontal Eye Field
IBN	Inhibitory Burst Neurons
IgG	Immunogloblin
IOR	Inhibition of Return
IPS	Information Processing Speed
MS	Multiple Sclerosis
MRI	Magnetic Resonance Imaging
NART	National Adult Reading Test
nRIP	Nucleus Raphe Interpositus

NRTP	Nucleus Reticularis Tegmenti Pontis
OCB	Oligoclonal Bands
OM	Ocular Motor
OMV	Ocular Motor Vermis
OPN	Omnipause neuron
PASAT	Paced Auditory Serial Addition Task
PICF	Participants Information and Consent Form
PPC	Posterior Parietal Cortex
PPMS	Primary Progressive Multiple Sclerosis
PPRF	Paramedian Pontine Reticular Formation
PreSMA	Pre-supplementary area
riMLF	Medial Longitudinal Fasciculus
RRMS	Relapse-Remitting Multiple Sclerosis
SEF	Supplementary Eye Field
SDMT	Serial Digit Symbol Task
SNr	Substantia Nigra
SOA	Stimulus Onset Asynchrony
SPMS	Secondary Progressive Multiple Sclerosis
STN	Subthalamus Nucleus
SC	Superior Colliculus
TPJ	Temporoparietal Junction
VEN	Ventral Attention Network
VFC	Ventral Frontal Gyrus

V1 Primary Visual Cortex

Chapter 1: Literature review

1.1. Introduction

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disease of the central nervous system (CNS), and is the most common cause of non-traumatic neurological disability in young adults (Feigin et al., 2017). Pathologically, MS is a complex disease, epitomised by heterogeneous pathological processes that mediate a variable disease course and symptom presentation (Murray, 2005). Of the range of symptoms that can occur, changes to cognitive functioning have emerged as a devastating component of the disease, affecting an individual's capacity to function both socially and vocationally (Ruet et al., 2013).

Cognitive changes have been reported to affect between 40 and 70% of patients (Chiaravalloti & DeLuca, 2008), manifesting at any stage of the disease, including at first presentation (Amato, Ponziani, Siracusa, & Sorbi, 2001; Potagas et al., 2008). Although the disseminated nature of the pathology throughout the brain means that any cognitive domain may be affected, changes to information processing speed, memory, and attention are frequently and consistently reported (Amato et al., 2010; Chiaravalloti & DeLuca, 2008). Of these, attentional changes appear to be particularly important, with deficits shown to be associated with changes in other cognitive domains (Chiaravalloti & DeLuca, 2008; Kujala, Portin, Revonsuo, & Ruutiainen, 1995) and related to poorer patient quality of life (Amato et al., 1995; Bobholz & Rao, 2003). However, attention is not a unitary construct. It comprised a set of sub processes or sub-domains that function to facilitate the processing of relevant information and the inhibition or filtering of irrelevant information under different conditions.

Currently there is little understanding about how MS affects these attentional sub-domains, whether deficits occur in isolation of each other or in combination. The purpose of this thesis is to

begin to address this lack of understanding, by assessing and comparing performance across a number of different attentional sub-domains in patients with MS.

1.2. Multiple Sclerosis

1.2.1. Aetiology

There is no known cause of MS, with current theories suggesting that MS occurs because of a complex interplay between genetic and environmental factors. A genetic contribution to MS is evident from family and twin studies. For example, individuals with an affected first-degree relative have a 2 to 4% risk of developing MS, compared to a 0.1% risk in the general population. Concordance in monozygotic twins is between 30 and 50%, compared to 5% in dizygotic twins (Leray, Moreau, Fromont, & Edan, 2016). Over 200 gene variants have been identified as associated with an increased risk of developing MS, with variations in the genes encoding human leukocyte antigens found to be particularly important. Specifically, these genes are known to encode the major histocompatilibity complex, which regulates the immune system by enabling it to differentiate the body's own proteins from proteins from foreign agents (Hollenbach & Oksenberg, 2015). However, the validity of a genetic explanation as the single mitigating factor determining MS appears unlikely, with monozygotic discordance approximately 70%, and higher with environmental separation (Bergkvist & Sandberg-Wollheim, 2001). This strongly suggests that environmental factors appearing to influence expression of MS in genetically susceptible individuals.

Epidemiological studies have revealed latitudinal differences in MS prevalence, where low MS prevalence is observed in regions closer to the equator, with decreasing prevalence observed as distance from the equator increases (Hirst et al., 2009; Wallin, Page, & Kurtzke, 2004). It is thought that this gradient effect might be related to varying amounts of sunlight

exposure, as well as vitamin D, which has been shown to mediate such effect, with both sharing inverse relationship with MS susceptibility. Viral infection, through infectious agents such as measles, mumps, rubella and the Epstein-Barr virus has also been proposed as potential triggers (Nielsen et al., 2007; Ramagopalan et al., 2009). Other environmental factors implicated include smoking, stress, toxins exposure, anaesthesia and physical trauma (O'Connor & Canadian Multiple Sclerosis Working, 2002). Interestingly, the timing of exposure to environmental risk factors has been shown to mediate the risk of developing MS, with risk heightened after exposure in early adolescence (Ramagopalan, Dobson, Meier, & Giovannoni, 2010).

1.2.2. Pathology and pathophysiology

MS has a complex pathology, characterised by immune-mediated inflammation predominantly within the white matter regions, resulting in demyelination and axonal loss. During the early stages of the disease, tissue injury is largely driven by the inflammatory process, where inflammatory perivascular infiltrates (e.g. T-cells, B-cells, Plasma cells) attack myelin and oligodendrocytes, causing chronic demyelination at the site of attack but relative preservation of axons (Lassmann, 2008, 2013). Active inflammatory lesions are formed as a consequence of these attacks, with predilection sites including the peri-ventricular and peri- aqueductal areas, corpus callosum, chiasm and the brainstem (Markus Kipp, Paul van der Valk, & Sandra Amor, 2012). Presenting neurological deficits depend upon the areas of pathological change, resulting in heterogeneity. Presenting deficits may initially recover due to early neurocompensatory mechanisms or when inflammation resolves (Helekar et al., 2010), however, deficits may worsen and become irreversible with accumulative axonal loss that characterises disease progression.

Although a poorly understood process, neurodegenerative changes also appear to occur from disease onset. As the disease progresses, these changes become increasingly prominent, and predominantly drive tissue damage at the later stage of MS. Evidence supporting neurodegeneration as a separate process in MS stems from the fact that anti-inflammatory and immunomodulatory treatments are partially effective in treating clinical disability in the early stages of disease, but have modest or no effect during the more progressive stages (Kawachi & Lassmann, 2017). Diffuse axonal loss is evident within normal appearing white matter and grey matter regions, especially in later disease stages, which appear to develop independently from white matter lesions (Bö, Geurts, van der Valk, Polman, & Barkhof, 2007; Kutzelnigg et al., 2005).

Cortical pathology also becomes increasingly evident, with diffuse demyelination occurring in the absence of inflammatory infiltration (Bo, Vedeler, Nyland, Trapp, & Mork, 2003). Although inflammation occurs during later stages of MS, it becomes less pronounced, as evident by the rare appearance of active inflammatory lesions and conversion of existing lesions to inactive or slowly expanding lesions (Kipp, van der Valk, & Amor, 2012). Despite our current understanding of the pathological profile of MS, it remains unclear whether inflammation or neurodegeneration is the driving mechanism of the disease, and more importantly, whether they are concomitant or independent processes (Trapp & Nave, 2008). As a consequence of the large heterogeneity in pathological processes and pathological targets, neurological deficits are equally as diverse resulting in a wide variety of symptoms.

1.2.3. Symptomology

Symptoms may manifest in isolation, or combination, as part of distinct MS ‘attacks’, or as a consequence of degenerative processes (Selchen et al., 2012). Attacks or relapses represent the emergence of new or the worsening of current neurological symptoms. Symptoms may have a sudden and intense onset, or emerge gradually developing over a period of days or weeks. An acute attack may last from 24 hours to 2 weeks, however, more chronic attacks also occur, lasting for a period of a month (Selchen et al., 2012).

Although many different symptoms can occur throughout the course of the disease, some symptoms occur with more frequency. The characteristic symptoms seen in MS include sensory symptoms, motor symptoms, spasticity, bladder and sexual dysfunction, visual disturbances and cognitive deficits. In particular, sensory changes, fatigue and cognitive deficits are reported to occur in 80-90% of patients, and have been associated with poorer quality of life (Bishop & Rumrill, 2015). A list of common symptoms is provided in Table 1. Cognitive deficits will be discussed in more detail in the following section.

Table 1. *Common symptoms reported in multiple sclerosis*

Category	Symptom
Motor	Incoordination
	Balance difficulties
	Tremor
	Impaired speech
	Impaired swallowing
	Weakness
	Spasms
	Gait impairment
Sensory	Paresthesias
	Dysesthesias
	Neuropathic pain
	Increased sensitivity to temperature
Visual	Optic neuritis
	Nystagmus
	Internuclear opthalmoplegia
	Diplopia
Cognition	Mood disorders
	Personality changes
	Cognitive deficits
Other	Urinary symptoms
	Bowel symptoms
	Sexual dysfunction
	Fatigue

Table adapted from Compston & Coles (2008)

1.2.4. Diagnosis

Currently, no single clinical feature or diagnostic test is sufficient for diagnosing MS. Rather, the diagnosis of MS is based upon careful evaluation of a mixture of clinical and radiological evidence. To aid in the diagnosis of MS, a set of diagnostic criteria was first developed in 2001 by an international expert panel (McDonald et al., 2001). Since this time, the criteria has undergone several revisions to accommodate new data, emerging technologies and updated consensus, with the latest revision released in 2017 (Thompson et al., 2018). Consistent

across each revision, is the requirement for clear evidence of disease dissemination in both time and space for a diagnosis to be made. Dissemination in time refers to the presence of a new T-2 lesion(s) on a follow up magnetic resonance imaging (MRI) scan or a second neurological attack. The revised criteria also allow the presence of both gadolinium-enhancing and non-enhancing lesions, evidence of prior disease activity, to constitute dissemination in time. Dissemination in space, on the other hand, requires at least two lesions in separate areas of the CNS (e.g. Periventricular, Juxtacortical, Infratentorial, Spinal Cord) or neurological symptoms that are suggestive of impairment in at least two areas.

In the case of atypical presentation, para-clinical tests may be used to compliment a diagnosis, although cannot be used as a substitute for diagnosis. In particular, the presence of an elevated immunoglobulin G index and multiple oligoclonal bands in cerebral fluid analysis may signify inflammation and therefore, possible MS. However, care must be taken upon interpreting positive cerebral fluid analysis findings as they are not consistently observed in early MS (Karussis, 2014) and may be present in other inflammatory conditions (e.g. acute disseminated encephalomyelitis). Evaluation of visual evoke responses may also assist in identifying MS, where abnormal or delayed potentials may indicate the presence of lesions in the optic nerve which are not detectable by MRI or clinical presentation.

Whilst not MS specific, the analysis of cerebrospinal fluid (CSF) remains a clinically informative tool in MS diagnosis. CSF abnormality, exemplified by the presence of oligoclonal bands (OCB) and/or elevated IgG index, signifies inflammatory activities within the CNS, potentially reflecting MS pathology. Specifically, the presence of two or more OCBs in the CSF without mirrored bands present in the serum are indicative of intrathecal immunoglobulin (IgG) synthesis, an autoimmune response mediated by local b-cells, is considered important participants in MS inflammatory

attacks. Indeed, using the gold standard isoelectric focusing, CSF-unique OCBs are detectable in 95% of MS patients and the presence of OCBs in CIS patients predicts higher MS conversion rate (Puccioni-Sohler, 2012). However, positive OCBs findings alone cannot confirm a MS diagnosis as many neurological or viral conditions, such as acute disseminated encephalitis, may share this pathology. Perhaps one discernible difference in MS-specific OCBs is their mode of presentation, which tends to persist throughout the course of MS, compared to that of other neurological conditions where presentations are often transient. Conversely, the absence of OCB does not rule out a possible MS diagnosis, although a confirmed diagnosis is only possible with the available clinical or neurological data suggesting disease dissemination in time and space.

Table 2. *2017 McDonald criteria for diagnosis of MS*

Clinical attacks	**Number of lesions with objective clinical evidence**	**Additional data needed for a diagnosis of MS**
≥2 clinical attacks	≥2	None
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)	None
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site **or** by MRI
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack **or** by MRI **or** by demonstration of CSF-specific oligoclonal bands.
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site **or** by MRI AND Dissemination in time demonstrated by an additional clinical attack **or** by MRI **or** by demonstration of CSF-specific oligoclonal bands.

Table adapted from Thompson et al. (2018).

1.2.5. Clinical course

Approximately 85% of MS patients initially present with a clinically isolated syndrome (CIS); an episode of acute neurological disturbance corresponding to a lesion location within the CNS (Çinar & Özakbaş, 2018). A CIS is always isolated in time and is usually isolated in space with clinical signs reflecting the lesion site. CIS lesions commonly appear in the optic nerve, spinal cord or brainstem (Miller, Chard, & Ciccarelli, 2012)

Following a diagnosis of MS classification into one of three disease sub-types usually occurs, with each sub-type having a different temporal profile of disease. For 85% of patients diagnosed with MS, their clinical profile typically follows a relapse-remitting course known as relapsing-remitting MS (RRMS). RRMS is characterised by recurrent inflammatory attacks followed by periods of complete or partial recovery and a lack of disease progression between these attacks (Bitsch & Bruck, 2002; Lublin et al., 2014). As the disease progresses, 80% of RRMS patients will go on to develop secondary progressive MS (SPMS), which is characterised by a gradual decline in neurological functioning with or without distinct neurological attacks. Considerably fewer patients (~15%) exhibit a primary progressive (PPMS) course from the onset of the disease. Unlike RRMS or SPMS, PPMS is marked by progressive and continuous decline in function from disease onset. MS subtyping has important ramifications for treatment. For example, larger emphasis is placed upon anti-inflammatory treatments in RRMS as opposed to the slowing of neurodegeneration in SPMS (Bitsch & Bruck, 2002; Lublin et al., 2014).

1.2.6. Measures of progression and status

Given the heterogeneity of the symptoms seen in MS, no single measure can capture the full spectrum of disease changes. At present, there are three types of assessment that are used to assess the status of the patient, their progression and response to therapy: relapse rate, physical disability, and biological markers.

Relapse rate is quantified as the number of clinically evident attacks that occurred within a defined period; usually the number that occurred between clinical visits. Relapse rate represent fluctuations in disease activity and is often used as an indicator of the efficacy of current medication.

The Expanded Disability Severity Scale (EDSS) is the most widely used measure to assess level of physical disability and progression, and routinely forms part of standard clinical care. The EDSS measures disability on a 20 point scale, with 1 representing a normal neurologic exam, and 6 representing death due to MS (Kurtzke, 1983). The EDSS measures impairment or limitations in activity, based on the examination of eight functional systems and ambulation. Despite the widespread clinical reliance on the EDSS, it has significant limitations due in part it its bias towards motor function and its relative exclusion of cognitive assessment (Chiaravalloti & DeLuca, 2008; Wybrecht et al., 2017).

Currently MRI represents the gold standard assessment tool for not only diagnosing MS, but also monitoring disease progression. Acute T2-hyperintense MRI lesions are used to assess disease activity, with increasing number indicating active disease. Gadolinium enhanced T1-weighted MRI images allow ramification of lesions associated with inflammation, a consequence of recent disease activity, whilst chronic or persistent T1-hypointense lesions appear as ‘black holes’ and represent chronic changes associated with axonal loss and neuronal atrophy. Although

not widely used clinically, more advanced MRI techniques such as magnetisation transfer imaging, diffusion tensor imaging and magnetic resonance spectroscopy provide additional information about the pathological processes not seen on standard clinical MRI measures. However, analyses of these measures are costly and time consuming, limiting their frequency of use in clinical settings.

While all of the above assessments provide a good measure of specific areas of disease symptomology, none provides a means for assessing cognitive function. Over the past 20 years changes in cognitive function have become recognised as a primary deficit of MS, appearing at all disease stages and evolving with disease progression (Amato et al., 2001; Potagas et al., 2008). However, routine assessment of cognitive function still does not constitute part of standard clinical management. While the reason for this is multifaceted, it centres on access to personnel with the expertise to administer and interpret cognitive tests coupled with the long administration time necessary to conduct the range of tests required to capture the full spectrum of deficits. Consequently, there is a necessity to develop clinically appropriate tools that allow the assessment of cognitive function in a timely and sensitive manner. Fundamental to this is the need to understand the exact nature of cognitive changes in MS. This necessarily requires the directed and thorough interrogation of the specific cognitive domains most frequently affected in MS. The following section discusses cognition in MS generally leading to a discussion of attention, an important and multidimensional cognitive function that is frequently impaired in MS.

1.2.7. Cognition in MS

Cognitive changes are thought to affect 40-70% of MS patients (Chiaravalloti & DeLuca, 2008), and are present at all disease stages, including onset, and in all subtypes (Amato et al., 2001; Potagas et al., 2008). Although the heterogeneity of MS pathology throughout the brain means that a range of cognitive domains can be affected, changes to information processing speed (IPS), attention and memory (particularly episodic) are most prominent, with executive deficits and verbal fluency less frequently reported; basic language abilities usually remain intact, even at more advanced stages of the disease (Amato et al., 2010; Chiaravalloti & DeLuca, 2008). Cognitive deficits appear to worsen with advancing disease, with the number of domains implicated usually extending (Amato et al., 2001). However, dementia as seen in other progressive neurological disorders (e.g., Alzheimer's disease) is rare (Defer & Branger, 2015), with the more common presentation remaining domain specific and comparatively subtle. Despite this, cognitive deficits can have a huge impact on a patient's quality of life, with those affected engaging in fewer vocational and social activities, and reporting higher levels of depressive symptomology (Ruet et al., 2013).

1.2.7.1. Information processing speed

Although there is no consensus on the definition of IPS, generally it can be viewed as the efficiency with which information is processed and integrated with other cognitive processes, resulting in the formulation of a behavioural response. In MS, slowed IPS is prominent and has been shown to predict future cognitive decline (Bergendal, Fredrikson, & Almkvist, 2007; Costa, Genova, DeLuca, & Chiaravalloti, 2017; J. DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004). IPS deficits rarely appear in isolation and are usually related to deficits in

other cognitive domains, namely, executive function, memory and attention (Covey, Zivadinov, Shucard, & Shucard, 2011; Drew, Starkey, & Isler, 2009; Owens, Denney, & Lynch, 2013; Roth, Denney, & Lynch, 2015). This has led to the suggestion that slowed information processing speed underlies deficits in other cognitive domains: relative consequence model (DeLuca et al., 2004). Indeed, several studies have shown that, once time is removed as a task constraint, MS patients do not perform differently from healthy controls on measures of working memory, attention and executive function (Covey et al., 2011; DeLuca et al., 2004; Genova, DeLuca, Chiaravalloti, & Wylie, 2013; Leavitt et al., 2014; Owens et al., 2013). Information processing speed and other cognitive domains are also highly correlated in healthy individuals. This makes conclusions about a direct link between decline in IPS and other cognitive domain performance in MS, independent of premorbid ability or pathological measures of disease, dubious at present.

1.2.7.2. Memory

While a range of deficits in memory have been reported, evidence suggests that MS patients have a primary deficit in the initial learning or consolidation of information, not retrieval as was initially thought (Benedict et al., 2006; DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998; Thornton & Raz, 1997). Memory deficits often manifest as requiring increased repetition of new information to achieve memory consolidation; however, once consolidation has occurred, recall and recognition is no different to healthy individuals (DeLuca, Barbieri-Berger, & Johnson, 1994; DeLuca et al., 1998). In patients with very early disease, deficits are more commonly associated with working memory, a limited capacity, temporary storage system that enables the active maintenance and integration of information (Fuso, Callegaro, Pompeia, & Bueno, 2010; Panou, Mastorodemos, Papadaki, Simos, & Plaitakis, 2012; Pelosi, Geesken, Holly, Hayward, & Blumhardt, 1997).

1.2.7.3. Attention

Attention deficits are frequently reported in MS, present even at the earliest stages of the disease, and are reportedly some of the most detrimental to normal functioning (Amato et al., 1995; Bobholz & Rao, 2003). Attention is a central cognitive process that facilitates the processing of relevant information and the inhibition or filtering of irrelevant information. In MS, deficits purportedly affect functions associated with sustaining, selecting, dividing and alternating between attentional sets, with simpler functions largely preserved (Amato et al., 2010; Beatty, Paul, Blanco, Hames, & Wilbanks, 1995; McCarthy, Beaumont, Thompson, & Peacock, 2005; Paul, Beatty, Schneider, Blanco, & Hames, 1998). Deficits in attentional processes are often associated with memory (maintenance and consolidation) and IPS changes in MS (Chiaravalloti & DeLuca, 2008; Kujala et al., 1995). Potentially, attentional changes may represent a central cognitive deficit in MS, which precipitates changes in other cognitive domains. This makes attention an ideal domain to target for the creation of screening tools.

However, currently little is known about the exact nature of the attentional changes that occur in MS, with deficits largely inferred from performance on neuropsychological assessments that measure multiple cognitive domains. These include the Symbol Digit Modalities Test (SDMT) , Paced Serial Addition Test (PASAT), Stroop (Clough, Millist, Lizak, Beh, et al., 2015; Clough et al., 2015; Dujardin, Donze, & Hautecoeur, 1998; Fielding, Kilpatrick, Millist, & White, 2009a, 2009b, 2009c; Ishigami, Fisk, Wojtowicz, & Klein, 2013; Llufriu et al., 2017; Paul, Beatty, Schneider, Blanco, & Hames, 1998; Urbanek et al., 2010; Vázquez-Marrufo et al., 2014). Attention comprises a number of sub-domains including attentional orienting, or shifting attention between locations; selective attention, concerning visuospatial selectivity of stimuli; dividing attention, the ability to concurrently perform two or more tasks. Consequently, determining the nature of

attentional deficits present in MS requires a targeted approach and the explicit interrogation of sub-domains.

A few studies have attempted to do this, using the attention network test (ANT). The ANT was designed to simultaneously measure three broad categories of attention: alerting, a measure of basic sustained attention; orienting, a measure of shifting attention; executive control, a measure of conflict resolution introduced when disagreement between an automatic response and a goal response occurs. In one study by Roth et al. (2015), they found that MS patients had deficits in alerting and executive attention; however, other studies have only reported changes in alerting, a likely consequence of the different MS populations used (Crivelli et al., 2012; Urbanek et al., 2010). While results from the ANT do suggest that attentional deficits in MS might be sub-domain specific, caution needs to be taken from inferring results from calculations derived from a test that simultaneously measures sub-domains and generates scores through subtraction. Indeed, studies have demonstrated that scores on the ANT are highly correlated, with sub-domain scores having little to no unique variation (Macleod et al., 2010; McConnell & Shore, 2011). This calls for a more tailored and targeted approach towards attentional assessment in MS, supporting the use of individually designed tests that assess specific subdomains of attention. The following section will discuss attention in more detail, overviewing current theories and methods of assessment.

1.3. Attention

1.3.1. Overview of attention

At any one time, we are exposed to far more sensory information than the brain can process. Attention allows us to actively selects and enhance elements of this information that are important to us, and determine the subset of information in the visual scene that needs to be selected for further processing from that which is irrelevant and can be filtered out (Carrasco, 2011; Gilbert & Li, 2013).

Attention can be oriented towards certain stimuli in both a 'bottom-up' and 'top-down' manner. Bottom-up or exogenous orienting occurs when a change in the environment draws attention towards a visually salient stimuli, such as a flashing light or the appearance of a predator. Top-down or endogenous orienting occurs when attention is drawn towards certain stimuli based on a pre-existing goal such as finding a particular person in a crowd (Chica, Bartolomeo, & Lupianez, 2013). Top-down attentional orienting requires more conscious cognitive control than bottom-up attentional orienting, that is more or less reflexive.

1.3.2. Theoretical models of attention

A number of theoretical models of attention have been proposed. The most well-known are the Posner and Corbetta theories. A thorough review of these theories is beyond the scope of this thesis; readers are directed to Posner and Rothbart (2007) and Corbetta and Shulman (2011) for a more comprehensive review.

1.3.2.1. Posner model

In brief, the Posner theory characterises attention as comprising three components, each with their own distinct underlying networks: alerting, orienting and executive attention. Alerting allows a person to achieve and maintain a high degree of sensitivity to incoming information. Orienting allows the selection of salient information from sensory input. Executive attention allows the control of attention enabling functions such as conflict resolution and response inhibition. Neuroimaging studies support the existence of three bilaterally represented networks for each of these attention functions: an alerting network incorporating the thalamus, parietal lobe and areas of the frontal cortex; an orienting network, incorporating the superior colliculus (SC), pulvinar, temporoparietal junction, superior parietal lobe, and frontal eye fields (FEF), and the executive attention network, incorporating the anterior cingulate gyrus and the prefrontal cortex (Petersen & Posner, 2012; Posner, 2012; Posner & Rothbart, 2007).

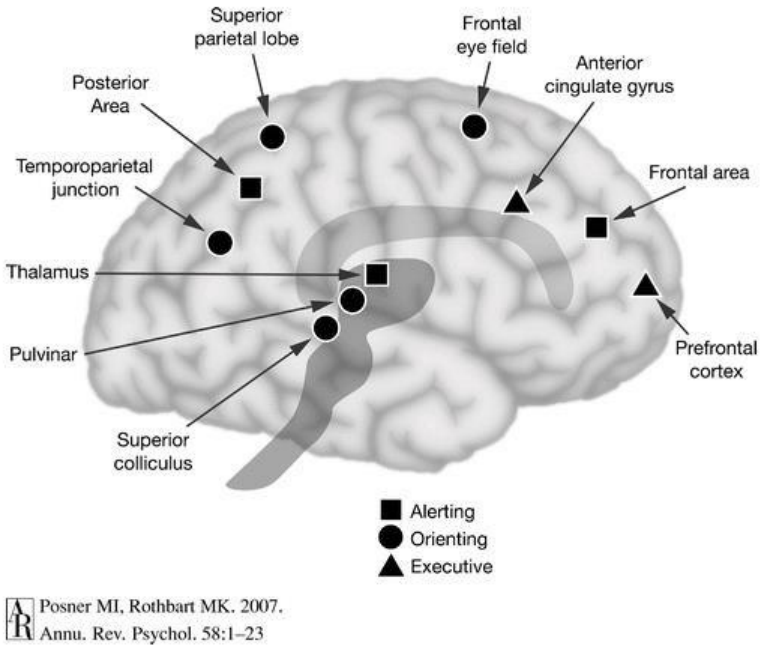

Figure 1. Posner model of attention**.**

1.3.2.2. Corbetta model

The Corbetta model of attention characterises attention as comprising two components, each with their own distinct underlying networks: the dorsal attention network (DAN) and the ventral attention network (VAN). The DAN purportedly processes the spatial aspects of attention and modulates the selection and shifting of attention towards salient stimuli. This network also exerts top-down cognitive control by assessing the salience of stimuli based on pre-existing goals. The VAN allows the reorienting of attention from one stimulus to another. It also enables attentional vigilance by maintaining arousal. The DAN comprises the intraparietal sulcus, superior parietal lobe, precuneus, and the supplementary and FEF. The VAN comprises the inferior parietal lobe, superior temporal gyrus, inferior and medial frontal gyri, and the insula. While The DAN is bilaterally represented, the VAN is localised to the right hemisphere (Chica et al., 2013; Corbetta & Shulman, 2011).

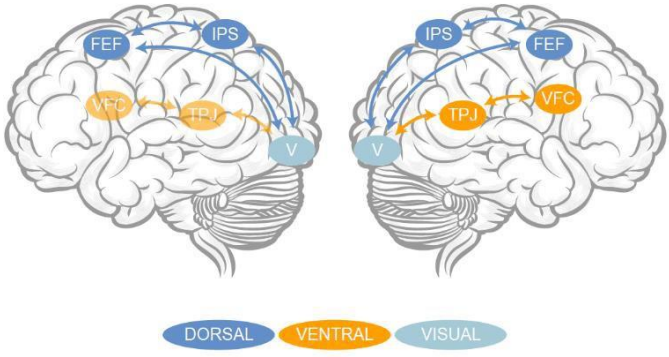

Figure 2. Corbetta model of attention. DAN: IPS: intraparietal sulcus (superior parietal lobe); FEF: frontal eye fields; VAN: TPJ: temporoparietal junction (inferior parietal lobe, superior temporal gyrus); VFC: ventral frontal gyrus (inferior frontal gyrus, medial frontal gyrus)

1.3.2.3. Integration of models: a central neural model of attention

Despite some differences, there are a number of similarities between these models. Each recognises the same basic attentional processes including arousal/vigilance, selection, shifting and goal-directed attention. Both also emphasise the roll of bottom-up and top-down control of attention. In both models the more posterior and inferior structures (including subcortical nuclei) modulate bottom-up attentional processes such as arousal and vigilance. More anterior structures exert top-down control such as response inhibition and the orienting of attention based on pre-existing goals. As such, Corbetta's DAN is analogous to Posner's orienting and executive components of attention, while VAN is analogous to the alerting component. While the precise structures implicated in attention control vary between the models, both models acknowledge the importance of subcortical structures in the maintenance of arousal and the role of fronto-parietal networks in both bottom-up and top-down control of attention.

The synthesis of attentional research allows the formulation of an overall neural model of attention. Cohen (2014) has proposed a 'general attention model' that proposes an overall flow of information from sensory cortex, to subcortical nuclei, to posterior cortex, to anterior cortex, to the brainstem. The majority of attention research has been performed in terms of visual sensory information and so the model will be explained in reference to this modality, though research demonstrates that beyond the primary sensory cortex the neural underpinnings of attention are largely the same across sensory modalities (Cohen, 2014). In the context of vision, visual information is projected to the lateral geniculate nucleus in the thalamus as well as the SC. Visual stimuli also activates the midbrain reticular system which facilitates arousal of the organism in order to attend to the stimuli. The visual information then reaches the primary visual cortex (V1) in the occipital lobe. Projections from V1 extend to the parietal cortex and superior temporal cortex

and then on to frontal and limbic areas including the prefrontal cortex and the anterior cingulate cortex. These frontal areas provide top-down control of attention by controlling behavioural responses based on higher-order cognitive information such as goals and motivation.

Consistent with the models by Posner and Corbetta, in this general model there is an anterior/posterior dichotomy such that more subcortical and posterior structures facilitate bottom-up processing of attention, for example arousal and vigilance, and anterior areas modulate top-down control of attention, for example response inhibition and goal-oriented behaviour (Cohen, 2014). Behavioural and neuroimaging research has supported a dichotomy between top-down/endogenous control of attention in more anterior and dorsal networks and bottom-up/exogenous control of attention in more posterior and ventral networks (Chica et al., 2013). However there is not a complete dichotomy between these networks and there is often interplay between them (Chica et al., 2013).

1.3.3. Attention and eye movements

Vision is not a purely stimulus-driven, hard-wired response to visual input. Neural responses depend intimately upon the viewer's state of attention. With respect to vision, the capacity to orient overtly towards a source of information by generating an eye movement towards its location, is supplemented by covert processes which enhance neural processing without a concurrent shift in gaze, controlling the potentially overwhelming flow of visual information (Yantis, 2003). More rapid response of cortical neurons to attended stimuli improves detection and discrimination, shortening reaction times relative to other locations (Posner, 1980). Whether summoned by an external, or exogenous visual event, or by an endogenous or goal-directed process, evidence suggests that this mechanism plays an important role in guiding overt behaviour, and is increasingly considered a critical component of the programming and

execution of eye movements (Hoffman, 1998). However, how they are linked has been, and still is, the subject of much debate.

The most extreme view of this connection was proposed by Rizzolatti et al. in the premotor theory of attention (Rizzolatti, Riggio, Dascola, & Umilta, 1987; Rizzolatti, Rigolet, & Sheliga, 1994; Sheliga, Riggio, & Rizzolatti, 1994). Premotor theory proposes that there are many different representations of space (or maps), and that each is responsible for a particular motor action, whether an eye movement or some other behaviour. Here, attention essentially equates to the activation of motor programs in regions responsible for the system being employed, therefore visuospatial attention is related to activity in those brain mechanisms directly involved in eye movements. The assumption is, therefore, that the act of attending to a particular spatial location is simply the act of preparing to execute some sort of response to that location, motor plan *set*, but not executed.

Support for a functional relationship between attention and eye movement stems historically from various neurophysiological studies in monkeys and humans which have revealed parietal and frontal regions, containing systems relating to spatial representations, and motor control, and attention (Bon & Lucchetti, 1997; Colby, Duhamel, & Goldberg, 1993, 1996; Kodaka, Mikami, & Kubota, 1997; Rizzolatti et al., 1994). Ablation of these regions has been shown to result in neglect or inattention to a particular space vector, accompanied by motor deficits concerning effectors represented in those areas, as well as deficits in movements directed towards space represented in it (Rizzolatti, Matelli, & Pravesi, 1983). Further, a number of imaging studies investigating covert shifts of attention in the absence of eye movement (overt attentional shift) have historically demonstrated activation in the same network of structures involved in volitional eye movements, including a host of frontal, parietal, and cingulate regions (Beauchamp, Petit, Ellmore, Ingeholm,

& Haxby, 2001; Corbetta et al., 1998; Nobre, Gitelman, Dias, & Mesulam, 2000; Nobre et al., 1997; Perry & Zeki, 2000).

1.4. The Ocular Motor Network

Mechanisms subserving the control of eye movements are well understood due to decades of human and primate research (Leigh & Zee, 2015). Specifically, the generation of eye movement relies on the integration of sensory information and higher order processes; this is underpinned by a large network of cortical and subcortical structures. Disruption within any part of this network may result in abnormal, although characteristic, eye movements.

1.4.1. Saccadic eye movements

Considered one of the quickest and most dynamic response, a saccade is a rapid eye movement generated to align an object of interest with the fovea, so that it is perceived with the highest visual acuity. These shifts are performed in a conjugate and ballistic-like manner, capable of reaching up to 700deg/s in speed and spanning a brief duration between 20 – 100ms (Leigh & Zee, 2015). A latent period of around 150 – 300 ms is thought to reflect saccadic planning process as well as computation of a saccade's metrics (Enderle, 1995; Kipp et al., 2012; Leigh & Zee, 2015). Such rapid and complex response promotes an open-loop system, whereby saccade accuracy depends on the comparison between an efferent copy of the desired shift and the current position of the eyes during saccades (motor error) (Enderle, 2002). This is complimented by a closed loop system after a saccade is performed, which utilises feedback to correct eye position or determine the next saccade endpoint (Enderle, 2002).

Visual exploration of the environment involves the constant interchange between reflexive and volitional saccades (Hutton, 2008). Reflexive or visually-guided saccades are elicited upon a sudden change in the visual periphery. Voluntary or volitional saccades, on the other hand, are generated based on intention or goal, requiring relatively complex cognitive processing such as determining 'when' and 'where' to look, or inhibiting a response.

1.4.2. Saccadic network

Experimental work with both humans and animals has provided a wealth of data describing the various brain regions involved in saccadic eye movement. These regions span almost the entire neuraxis, the critical nodes in the network including parietal and frontal cortices, as well as the SC, cerebellum, basal ganglia (BG), and brainstem reticular formation.

The ocular motor plant, being the most fundamental part of saccadic physiology, is directly responsible for the physical movement of the eye, comprising a pair of eye balls and three pairs of extraocular muscles attached to each eye (Leigh & Zee, 2015). These antagonistic, extraocular muscles contract and extend in pairs to propel eye balls in the horizontal, vertical or oblique directions (Leigh & Zee, 2015). Signals instigating contraction are drawn from innervated motor neuron discharge, controlled by the saccadic burst generator to signal the direction and amplitude of a saccade (Scudder, Kaneko, & Fuchs, 2002). Saccade metrics are encoded and monitored by the SC and cerebellum respectively (Blázquez & Pastor, 2013; Wurtz, 2009).

Higher order regions subserving saccadic eye movements comprise a fronto-parietal network, encompassing the FEF, dorsal lateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC) and supplementary eye fields (SEF) (McDowell, Dyckman, Austin, & Clementz, 2008). These reciprocally connected regions participate in a range of sensorimotor transformations and

decision-making processes (e.g. target selection or inhibition), conveying convergent saccadic commands downstream to the SC (McDowell et al., 2008). The pathway connecting PPC to SC in particular, is considered critical to generating reflexive saccades. Alternatively, direct and indirection projection to the SC (via the BG) from frontal regions are thought to principally drive voluntary saccades, both suppressing reflexive saccades (DLPFC/FEF) or memory-based saccades (Van der Stigchel, van Koningsbruggen, Nijboer, List, & Rafal, 2012).

1.4.3. Brainstem

The saccadic burst generator can be conceptualised as a central processing unit, converting commands from the SC, cerebellum and other cortical regions (e.g. PPC, FEF, SEF) into pre-motor output. Saccadic burst generator nuclei are located within the paramedian pontine reticular formation (PPRF), rostral interstitial nucleus of medial longitudinal fasciculus (riMLF) and nucleus raphe interpositus (nRIP) (Leigh & Zee, 2015).

Neurons critical to saccadic control in the saccadic burst generator are burst neurons, whose burst firing provides motoneurons with the required force to generate a saccade (Fuchs, Kaneko, & Scudder, 1985; Scudder et al., 2002; Sparks, 2002). Burst neurons discharge during all saccades, but cease firing when approaching, or during, fixation (Fuchs et al., 1985). The characteristics of these bursts dictate the nature of a saccade, with burst duration and a peak level corresponding with the duration and size of saccade, respectively (Scudder et al., 2002). The anatomical site of burst reflects saccade direction, the caudal group of burst neurons modulating horizontal saccades, and the rostral group modulating vertical saccades (Fuchs et al., 1985; Scudder et al., 2002).

Comprising functionally distinct subgroups, burst neurons can be subdivided into excitatory burst neurons (EBNs) and inhibitory burst neurons (IBNs). EBNs are found primarily

within the PPRF and riMLF, with both regions sharing monosynaptic excitatory projection to ipsilateral motoneurons in the abducens nuclei (Leigh & Zee, 2015). The excitatory 'burst' signal from EBNs stimulates motoneurons that innervate agonist ocular muscles, causing subsequent muscle contraction and generating the muscle force needed to propel the eyeballs to foveate (Scudder et al., 2002). IBNs in the medullary reticular formation and riMLF project inhibitory outputs towards contralateral motor neurons in the abducens nuclei during ipsilateral saccades (Leigh & Zee, 2015). The inhibitory output silences motoneurons innervating antagonistic muscles, thereby relaxing antagonistic muscles and allowing the eyes to move (Leigh & Zee, 2015).

Another important contributor to saccade generation in the saccadic burst generator is the omnipause neuron group (OPNs) located in the nucleus raphe interpositus, midline of pons (Leigh & Zee, 2015). Acting primarily as an on-off switch for a saccade, OPNs govern saccade initiation as well as fixation maintenance, based on signals received from the SC, SEF, FEF and central mesencephalic reticular formation (cMRF) (Girard & Berthoz, 2005; Leigh & Zee, 2015). During fixation, OPNs tonically discharge at a constant rate and project strong inhibitory output to EBNs and IBNs, suppressing burst neuron activity associated with a saccade (Girard & Berthoz, 2005; Shinoda, Sugiuchi, Izawa, & Takahashi, 2008). In order for a saccade to take place, the saccadic burst generator circuitry must undergo disinhibition, whereby OPN discharge is suppressed by a 'trigger' signal originating from the rostal pole of the SC, resulting in the disinhibition of EBNs and IBNs. OPNs are inhibited for the duration of saccade, sustained by a 'latch' signal (Girard & Berthoz, 2005; Shinoda et al., 2008).

1.4.4. Superior Colliculus

The key function of SC is the programming of saccade metrics, as well as fixational control (Leigh & Zee, 2015; White & Munoz, 2011a). Stationed at the dorsal midbrain, the SC is strategically placed to enable the convergence of sensory and cortical afferents, integrating them to generate the appropriate pre-motor command downstream (White & Munoz, 2011a). Such complex interplay involves multiple layers with distinct properties within the SC. More superficial layers are considered 'sensory', receiving input directly from the retina and visual cortex (White & Munoz, 2011a), containing well defined visual receptive fields that jointly form a retinotopic map of the contralateral visual space (Quaia, Lefèvre, & Optican, 1999; White & Munoz, 2011a; Wurtz, 2009). Intermediate layers comprise both sensory and motor regions, and feature motor maps that encode saccade metrics in the contralateral visual space (R. Wurtz, 2009). Saccade amplitude and direction are topographically represented on the motor map, with activation (White & Munoz, 2011a; R. Wurtz, 2009).

Important projections to the SC include those from the striate, extrastriate, PPC, SEF, FEF, and the DLPFC, either directly or indirectly through the BG (Leigh & Zee, 2015). These excitatory projections, along with inhibitory input from the BG guide the neuronal activity within the motor map, effectively creating the schematics for motor movement via local inhibitory interneurons (Munoz, 2002; Munoz & Fecteau, 2002).

The dynamic interaction within the motor map is governed by two classes of neurons; fixation neurons, located in the rostro-lateral pole, and saccadic neurons, extending throughout the rest of the motor map (Munoz & Schall, 2004). Fixation neurons exhibit tonic discharge during fixation and pause during a saccade.

An independent motor plan is generated through a competitive coding process, whereby plans for fixation and saccadic movement compete for expression, with the winner dictating when and where the impending movement will occur (Munoz & Fecteau, 2002). On a neural level, the point of maximal neuronal discharge on the motor map determines where the saccade should be directed (Munoz & Fecteau, 2002; Munoz & Schall, 2004).

1.4.5. Basal Ganglia

The BG play an important role in controlling volitional eye movements, both in terms of initiating and suppressing saccades (Wurtz & Hikosaka, 1985). A modulatory channel, the BG does not drive saccadic action independently, but mediates the signal selection process underpinning saccade execution or inhibition (Mink, 1996). This is accomplished by multiple nuclei, aggregated to form functionally distinct pathways. Importantly, the BG receives projections from major cortical sites, including the FEF, SEF and PEF, with the caudate nucleus and putamen serving as the primary point of input (Utter & Basso, 2008). After selecting the appropriate signals, command outputs are channelled through the substantia nigra (SNr), travelling downstream to the SC (Utter & Basso, 2008).

Two opposing mechanisms appear to mediate the saccade initiation and fixation through the BG. The first mechanism entails disinhibition of a pathway connecting the SNr to the SC, the overall effect, facilitative (Leigh & Zee, 2015). The SNr by default projects tonic inhibition to the SC to prevent converging excitatory signals from triggering unwanted saccades (Hikosaka, 2009). Saccade initiation is only possible with the removal of this ‘default’ inhibition, engaged by the direct pathway from the caudate nucleus to the SNr (Wurtz & Hikosaka, 1985). The second mechanism concerns strengthening inhibitory outflow toward the SC, a process modulated by indirect pathways connecting the subthalamus nucleus (STN) and globus pallidus to the SNr

(Leigh & Zee, 2015; Watanabe & Munoz, 2011). Input from both pathways enhances activation of the SNr neurons, resulting in further suppression of SC activity and the inhibition of unnecessary eye movements (Utter & Basso, 2008; M. Watanabe & Munoz, 2011).

1.4.6. Cerebellum

The cerebellum does not appear to play a critical role in saccade initiation, but instead exerts a modulatory influence over saccadic movements (Glickstein & Doron, 2008), implicated in the control of accuracy (both amplitude and direction) (Blázquez & Pastor, 2013; Liem, Frens, Smits, & van der Geest, 2013). Two subregions subserve this process; the ocular motor vermis (OMV) and caudal fastigial nucleus (cFN), receive important saccade information from fronto-parietal regions (e.g. FEF, EF) and the SC via the pontine nucleus and the nucleus reticularis tegmenti pontis (NRTP), and projects efferent copies downstream to the same brainstem structures (e.g. NRTP), establishing a closed loop circuit appropriate for modifying a saccade (Leigh & Zee, 2015).

OMV activation pervades across all types of saccades (Robinson & Fuchs, 2001). Local discharge of Purkinje cells typically taken place prior to a saccade, corresponding to a change in eye position, but not presentation of a visual target, suggesting a role in monitoring or correcting saccade performance (Thier, Dicke, Haas, Thielert, & Catz, 2002). The cFN, through its heavy projection to the brainstem, modulates saccade metrics based on the ‘modified’ command of the OMV (Glickstein & Doron, 2008). cFN discharge prior to saccade onset and at the end of a saccade, may facilitate saccades via two mechanisms, assisting the initiation or acceleration of a saccade through disinhibiting IBN, and terminating a saccades by producing a timely brake signal through activating IBN (Leigh & Zee, 2015).

1.4.7. Anterior cingulate cortex

The anterior cingulate cortex (ACC) participates in orchestrating a range of intentional eye movements, with PET scan studies revealing pre-saccadic activation during performance of volitional saccades (Robinson & Fuchs, 2001). ACC activation prior to a response likely reflects preparation of ocular motor areas and motivation for engaging upcoming eye movements. It been proposed that it achieves this through facilitating neural transmission and enhancing activity within motor areas requisite in making a saccade, owing largely to its strong connection to frontal (e.g. FEF, SEF) and brainstem structures (Prsa & Thier, 2013). The ACC is also thought to be involved in monitoring saccade performance, with activation observed following errors and reinforcement during inhibitory tasks (Quaia et al., 1999).

1.4.8. Frontal eye fields

The FEF are thought to have direct influence over all saccade production. Electrical stimulation of this region invariably elicits saccades to the contralateral space, with saccade direction and amplitude varied depending on site stimulated (Paus, 1996). The capacity to elicit saccade directly stems from FEF build-up neurons discharging prior to or during eye movements. These topographically-organised neurons likely convey information regarding timing and location of the impending saccade to SC-brainstem saccade circuitry (Jantz, Watanabe, Everling, & Munoz, 2013; Schall, 2009). A portion of the FEF is also populated by fixation neurons, whose discharge during fixation strengthens tonic inhibition of the push-pull mechanism (Schall, 2009), thus confirming a secondary role in suppressing reflexive saccades or maintaining fixation (Jantz et al., 2013). Importantly, activation of this region is stronger for voluntary than reflexive saccades,

reflecting the FEF's significant involvement in planning and triggering a saccade (Munoz & Schall, 2004; Van der Stigchel et al., 2012).

1.4.9. Dorsal lateral prefrontal cortex

The DLPFC is housed within the middle frontal gyrus, just anterior to the FEF corresponding to Brodmann's area 46 (Petrides, 2005; Pierrot-Deseilligny, Müri, Ploner, Gaymard, & Rivaud-Pechoux, 2003). The area has reciprocal connections with major fronto-parietal regions including the FEF, SEF, PPC and the cingulate cortex, and sends efferent projections to the SC and brainstem (Petrides, 2005). Although not exclusively an ocular motor (OM) region, current views on the DLPFC emphasise its important involvement in executive control over saccades. Neuroimaging and electrophysiological evidence suggest that it plays a key role in suppressing unwanted reflexive saccades (Müri et al., 1998; Nyffeler et al., 2007). Disruption by electrically stimulation during the 'preparation' stage, for example, result in increased errors directed to a distractor stimulus (Nyffeler et al., 2007). The DLPFC also participates in the short-term maintenance of visual/spatial information, a step crucial in delayed or memory-guided saccades (Curtis & D'Esposito, 2003). Damage to this region results in prolonged latency and hypometric saccades in delayed saccade. Activity during the delay period potentially reflects encoding of spatial coordinates of a 'to-be memorised' target (e.g. amplitude, direction) by spatially selective neurons. Alternative accounts suggests a more facilitative role, with the DLPFC, favouring 'refreshing' or directing attention to internally stored representations over simple maintenance and attributing maintenance of information to PPC and other OM regions during delayed saccade.

1.4.10. Supplementary eye fields

The SEF are assumed to play a supervisory role, indirectly influencing saccades by means of executive control over a range of complex saccadic responses (Schall, Stuphorn, & Brown, 2002; Stuphorn, 2015). Anatomically, the SEF are located in the dorsal medial frontal cortex, on the medial surface of the superior frontal gyrus and the upper portion of the paracentral sulcus corresponding to Brodman's area 6 or F7 (Sommer, 2009). This region has similar structural connectivity with the FEF, receiving afferents from fronto-parietal regions, and projecting to the SC and saccadic burst generator (Parton et al., 2007). Importantly, the SEF do not appear to drive saccade production independently, with ablation studies reporting mild to no impairment on producing saccades after damage to the area (Parton et al., 2007). One proposed function concerns error monitoring or signalling conflict during a saccadic response (Stuphorn, Taylor, & Schall, 2000). Electrophysiology studies reveal strong activation of the SEF during tasks involving two competing task rules, with activation greatest during or failure to cancel of a pre-potent response (Stuphorn et al., 2000). This has been attributed to the strong reciprocal connection between SEF and the ACC, a structure important to error monitoring.

1.4.11. Parietal eye fields

The parietal eye fields (PEF) lie within the lateral intraparietal area in monkeys, just adjacent to area 7a, while the human equivalent occupies the medial space of the same region (Andersen, Brotchie, & Mazzoni, 1992). Local discharge, mainly prior to saccades, has been implicated in preparatory or motor planning activity, concerning programming of metrics and motor error for an intended saccade (Leigh & Zee, 2015). Regional activity correlates with memory-guided saccades and sequential saccades, pointing toward a likely role in maintaining or

updating representation of a target (Duhamel, Colby, & Goldberg, 1992). PEF activity also correlates with the allocation and maintenance of visuospatial attention, with enhancement observed during the competitive selection of target (Donner et al., 2000).

1.4.12. Posterior parietal eye fields

The PPC serves primarily as a sensorimotor interface within the saccade network, with regions known to perform visuospatial coding of the environment and the programming of saccadic motor plan (Corbetta, 1998; Maurizio Corbetta et al., 1998). Area 7a, a subregion located in the caudal-medial PPC, is critical to the former, utilising eye-head position combined with visual signals to represent object in space (Goldberg, Bisley, Powell, & Gottlieb, 2006). Representation of target location, through heavy connection to the prefrontal cortex, likely influences the shaping of a premotor plan or target selection for impending saccades (Egly, Driver, & Rafal, 1994).

1.4.13. Ocular motor research in MS

A range of ocular motor abnormalities are commonly seen in MS, including dysmetria, internuclear ophthalmoparesis, gaze-evoked nystagmus, and disorders of pursuit and vestibular–ocular reflexes (Derwenskus et al., 2005; Downey et al., 2002; Frohman, Frohman, Zee, McColl, & Galetta, 2005). These primarily reflect the integrity of lower-level brainstem or cerebellar structures. However, a number of studies have demonstrated the capacity for ocular motor paradigms to characterise attentional deficits in MS (Clough et al., 2018; Clough, Millist, Lizak, Frohman, et al., 2015; Clough, Mitchel, et al., 2015; Fielding, Kilpatrick, Millist, Clough, & White, 2012b; Fielding, Kilpatrick, Millist, & White, 2009a, 2009b).

The earliest of these studies revealed inhibitory control deficits in MS. Failure to inhibit a reflexive saccade to a visual stimulus was revealed while employing the antisaccade paradigm (Fielding et al., 2009a), which required subjects to refrain from looking at a suddenly appearing visual stimulus and instead look to its mirror opposite location. This study demonstrated increased error rates (Prosaccade towards a visual-nontarget), and prolonged latencies, which was thought to be indicative of psychomotor slowing. In a 2-year longitudinal study investigating the utility of the antisaccade task in measuring disease-related changes in MS, the same researchers found increased interindividual and intraindividual variation in both error rate and latency (Fielding et al., 2012b).

Using a memory-guided saccade task, whereby saccades are generated to a remembered location, MS patients exhibited a higher proportion of erroneous response (saccades failed to land on target) directly to the target. This was associated with a failure of inhibitory control. Further, patients exhibited prolonged latencies and poorer visuospatial abilities, characterised by inaccurate eye movements toward remembered locations (Fielding, Kilpatrick, Millist, & White, 2009). Using an endogenous cueing paradigm, where a directionally informative central cue preceded a peripheral target, MS patients demonstrated significant inhibitory control deficits (Fielding et al., 2009b), with higher error rates generated directly as a function of the cue, and not the target.

A later study demonstrated that these inhibitory control deficits covaried temporally with disease duration (Clough, Millist, Lizak, Frohman, et al., 2015; Clough, Mitchel, et al., 2015). All patients, including those with CIS, generated a significantly greater number of errors across all of the above paradigms, and latencies for each were shown to increase linearly as a function of disease duration. Importantly, it must be remembered that the capacity to inhibit a response to an irrelevant visual stimulus is a key component of attentional control.

Essential to maintaining inhibitory control is the ability to retain mentally represented information and to use it to form and sustain appropriate stimulus–response relationships, a key function of working memory (Stuyven, Van der Goten, Vandierendonck, Claeys, & Crevits, 2000). Working memory has also been investigated in MS using an ocular motor *n-back* task. Here, a patient is presented with a series of visual stimuli, and asked to generate a saccade to a location a specified number of places (*n*) back in the series. Increasing *n* increases working memory load. Again, testing across all stages of the disease including CIS, the study revealed a significantly greater proportion of working memory errors for all patients. The proportion of errors and impact of the load increased linearly, as a function of disease duration (Clough, Mitchel, et al., 2015).

1.5. Rationale for Thesis

From the above discussion, it is evident that MS is a highly variable disease with little conclusive understanding of the aetiological and pathological processes that underlie it. This extends to the symptomology of MS, with cognitive symptoms particularly difficult to characterise. Of the range of cognitive deficits that may occur in MS, attention deficits appear to be particularly prevalent and impactful to patients. However, the fact that attention is not a unitary construct, instead consisting of multiple sub-domains, makes it difficult to characterise using standard assessment techniques. Consequently, in order to properly characterise attentional deficit(s) in MS, a targeted approach is required that explicitly interrogates attentional sub-domains. Further, given the often-subtle nature of the changes that occur in MS, a highly sensitive methodology is needed to fully elucidate and meaningfully quantify the deficits if present. Ultimately, this will allow the development of therapies and treatment strategies that specifically target and modify the exact deficit(s) present.

1.5.1. Aim

The aim of this thesis was to characterise the types of attentional deficits in patients with MS. Specifically this involved the development/application of a battery of OM tasks, with each task designed to specifically assess a sub-domain of attention; orienting, selective and dividing attention. As this study represents a pilot study, these sub-domains of attention were chosen as they represent differing levels of attentional load, from basic attentional orienting to more challenging selecting and dividing attention. The findings of this thesis will inform a larger more comprehensive study of attention in MS that more specifically targets the domain(s) affected.

Chapter 2: General Methods

Chapter 2 GENERAL METHODS

This chapter outlines the general methodology of the research study, providing a broad overview of its design and assessment methods. The study entailed a cross-sectional investigation of attentional control in MS, using ocular motor tasks aimed at capturing and profiling selected attentional sub-domains. These tasks were completed by both patients clinically diagnosed with MS and a healthy control group, and performance was compared across groups for each sub-domain.

2.1. Ethics

Ethics approval for the study was granted by the Melbourne Health Human Ethics Research Committee and the Monash University Human Ethics Research Committee. All research procedures were in compliance with the Helsinki Declaration and criteria outlined by each of the ethics committees. Informed consent was given by all participants at the time of testing, authenticated by an independent witness. All participants were physically and mentally competent to give informed consent at the time of testing.

2.2. Participant Recruitment

MS patients were recruited through Malvern Neurology or the Royal Melbourne Hospital in Melbourne, Australian, while controls were recruited though online advertisements posted on the Melbourne University staff forum. Participants who responded to the study were given a copy of the participation information and consent form (PICF) and a general description of the research study. Participants who expressed interests were followed up with a series of screening questions assessing their study eligibility. To be eligible, participants had to 1) be aged between 25 and 65 years, 2) have no history of any other neurological or psychiatric condition, and 3) have

not currently taking any drug or medication that would affect attentional performance. 4) have healthy eye sight (astigmatism with corrective eye sight acceptable, with no reported visual defects or impaired vision). For MS patients, they would also need to be diagnosed by a neurologist with MS and with an EDSS of 6 or below. Participants were required to attend one single two hour testing session, with all testing conducted at the Royal Melbourne Hospital. All sociodemographic information including gender, age, educational level and disease profile for MS (e.g. time of diagnosis, disease duration, disease type, medication) were collected at the time of testing. There were no incentives given for study participation. However, patients who lived in remote areas or had difficulty accessing transportation were provided with a return trip taxi voucher for travelling to and from the hospital.

2.3. Participant Characteristics

2.3.1. MS patients

As patient cohorts differed slightly between experimental tasks, these data will appear in the individual chapters.

2.3.2. Controls

The control group comprised 29 neurologically healthy individuals (M = 11; F = 20), aged between 25 to 48 years (*M* = 36, *SD* = 6.14). Control and MS groups were comparable for IQ on the National Adult Reading Test (NART) (Controls *M* =11, *SD* = 6.1, MS patients *M* = 14.83, *SD* = 4.45) and depressive state on the Beck Depression Inventory (BDI) (Controls *M* = 5.9, *SD* = 4.5, MS patients *M* = 8.5, *SD* = 9.97). Although two controls exhibited moderate symptoms of depression, scores were not significantly different from other control participants.

2.4. Testing Methods and Procedures

All participants completed testing within a single two-hour session. Participants were given brief breaks between tasks to minims fatigue.

2.4.1. Neuropsychological assessment

Neuropsychological measures selected for this study were the PASAT and the SDMT, which derive from the commonly used Multiple Sclerosis Composite Function Scale. A set of screening measures (e.g. NART, BDI) were also included to demonstrate comparable intellectual and emotional functioning across MS and control groups. The MS modified fatigue impact scale was used to demonstrate patients' fatigue level were comparable.

2.4.2. Beck Depression Inventory

The BDI was administered as a measure of depressive state. Here, this measure presents 21 multiple choice questions assessing symptoms and attitudes distinct to depression. Each question comprised at least four possible responses, ranging in intensity from 0 to 3; for example, from 'I do not feel sad' to 'I am so sad or 'so unhappy that I can't stand it'. Participants were required to respond to these questions according to how they felt, generally, over the past week. The BDI was scored by adding the assigned values (0, 1, 2, or 3) from each response, with a possible total score between 0 – 63. Final scores determined severity of depressive state, ranging from minimal (0-9), mild (10- 18), moderate (19-29) and severe (30-63).

2.4.3. National Adult Reading Test

The NART was used to assess participants' premorbid intellectual functioning. Participants read aloud a list of 50 words with atypical phonemic pronunciations. Words gradually increased in complexity. Participants were encouraged to guess the correct pronunciation where they found words unfamiliar or difficult to pronounce. The number of correctly pronounced words was used as final score to derive a premorbid IQ estimate.

2.4.4. Modified Fatigue Impact scale.

The MFIS was used to administered as a measure of fatigue level. The measure presents 21 items that assess symptoms of fatigue spanning across three areas, physical, cognitive and psychosocial. Participants were required to respond to rate each item, ranging in intensity from 0 to 4, based on how they felt generally over the past 4 weeks. The MSIF was scored by adding the assigned values (0, 1, 2 or 3) from each response based on their assigned subscale. The scale

comprised three subscales, the physical subscale (0 – 36), the cognitive subscale (0 – 40), psychosocial subscale (0 – 8), with the total of the three subscales taken as the total MFIS score. The total score determined participants' general level of fatigue, ranging from 0 - 84, with a cut-off score of 38 or above presented as significantly fatigue.

2.4.5. Symbol Digit Modality Test

The SDMT was administered as a measure of general cognitive functioning, assessing various domains including attention, visuospatial processing and psychomotor speed (Parmenter, Weinstock-Guttman, Garg, Munschauer, & Benedict, 2007). Participants were presented with a reference key containing 9 abstract symbols, each correspondingly matched with a number. Beneath the reference key were symbols randomly presented in 8 rows of 15, with each row sitting directly above a row of empty spaces. Participants were required to match the row of symbols with the corresponding number listed in the reference key and record a response in the empty space below. Participants were given ten practice trials to familiarise themselves with the task. After completing the practice trials, participants were given 90 seconds to complete the rest of the task. Scores represented the number of correct responses produced within the given time frame. The SDMT is considered a gold-standard measure of attention in MS,

2.4.6. Paced Auditory Serial Addition Test

The PASAT assessed a range of cognitive functions, including information processing speed and sustained as well as divided attention. Participants listened to a sequence of single digit numbers. Each time a new number was presented, participants added the new number to the number immediately prior and verbally gave the correct response. Responses must have been given

prior to the next digit in order to be counted as correct. The PASAT comprised a total of 60 trials, with the final score taken as the total number of correct responses. Participants were given ten practice trials prior to task commencement. Each participant was required to complete at least eight trials correctly.

The PASAT utilised in the study was extracted from the Multiple Sclerosis Functional Composite (PASAT-3), which was based on the original version of the task by Gronwall (Gronwall, 1977). This modified version of the PASAT differed in the rate at which numbers were presented, with numbers presented at rate of 3 seconds per number, rather than 2 seconds in the original task. The PASAT is considered a gold-standard measure of general cognitive functioning in MS.

2.5. Ocular Motor Assessment

2.5.1. Ocular Motor Recording

Participants were seated in a dark room with their heads stabilised on a head and chin rest, situated 840mm directly in front of a 22-inch LCD monitor. Horizontal eye displacement was recorded using an Eyelink II dark pupil, video-oculography system (SR-Research Ltd, Mississauga, Canada). This is a high resolution (noise limited at <.01), high acquisition rate (500 Hz) system.

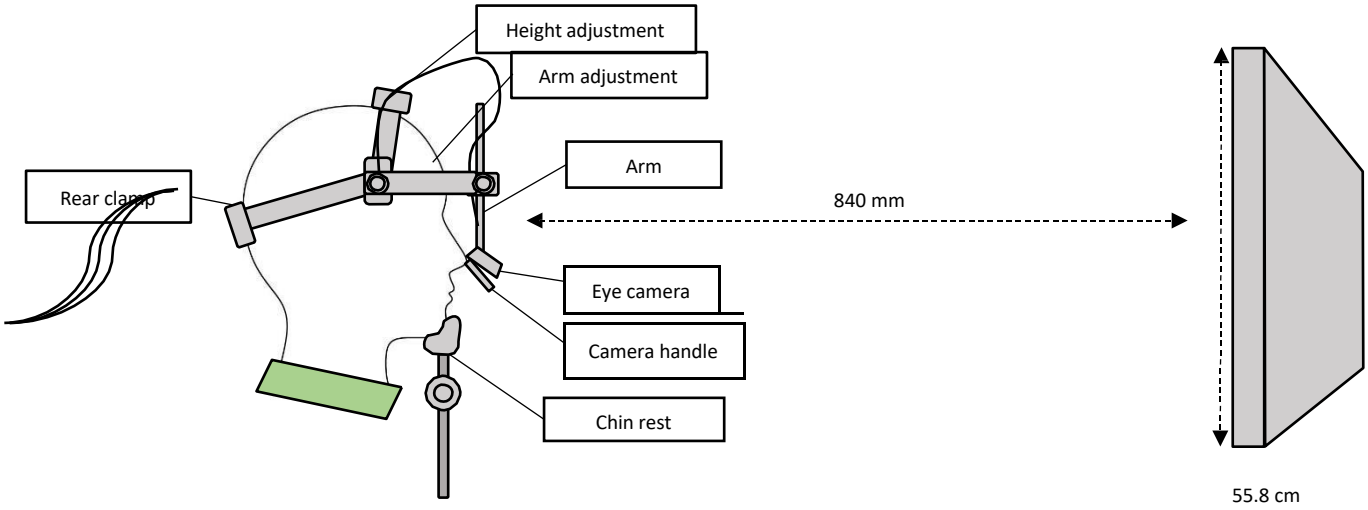

Figure 3. Ocular motor recording setup

Figure 4. Eyelink II dark pupil, video-oculography system

2.5.2. Ocular Motor Paradigms

This battery was created to assess the attentional sub-domains attentional orienting, selective attention, and divided attention.

2.5.2.1. Attentional Orienting Paradigm

This paradigm was based upon the original exogenous cue design by Posner (Posner, 1980). In this task, participants were required to perform saccades toward a cross target after presentation of a non-informative peripheral cue on screen (brightening of a peripheral box). The task was modified to examine attentional orienting at different stimulus onset asynchronies (SOAs; 67, 150, 300, 500ms). Both error (saccade made toward the cue) and latency were primary measures of the task. A full description of the task is available in Chapter 3.

2.5.2.2. Selective Attention Paradigm

The selective attention task was designed and created by the author of this thesis. The task involved two stimuli, both a target and a non-target, which simultaneously appeared on screen. Participants were required to generate a saccade to the target while inhibiting a responses to the non-target. In the current version, the target would either appear alone or accompanied by a non-target in the mirror opposite location, with both trial types presented with equalled probability. Target location varied between 4 and 8 degrees from centre. Error (saccades directed toward the non-target) and latency were primary measures. A full description of the task is available in Chapter 4.

2.5.2.3. Divided Attention Paradigm

The divided attention task was designed and created by the author of this thesis. Participants performed a series of antisaccades, and engaged in manual rhythmic tapping on a controller, simultaneously. It was emphasised that participants treated both tasks with equal importance. Both the antisaccades and rhythmic tapping were performed independently (single task condition) prior to task commencement to obtain baseline performance for each task.

Single task condition

- For the antisaccade task, participants were required to perform eye movements in the mirror opposite location of a peripherally presented blue cross. The blue cross was presently in either horizontal direction, always 10 degrees from central fixation.
- For the rhythmic tapping task, participants were required to engage in manual rhythmic tapping on a game controller for one minute after listening to a set of sample tones. The intervals between each tone was set at 1000ms. Participants were instructed to mimic the rhythm of the sample tone.

Dual task condition

The task commenced with participants listening to eight tones that were set 1000ms apart. Participants were instructed to tap along on the controller as soon as they heard the first tone to familiarise with the rhythm, and continue tapping in the same rhythm after the set of tones had extinguished. A blue on-screen cross served as cue to commencing the antisaccade task and immediately after the last tone had played.

The performance difference between dual and single task conditions was dubbed a dual task decrement, and computed for each measuring variable, including errors, latency and tap time discrepancy (the amount of time taps were out of synch with the original rhythm). A full description of the task is available in Chapter 5.

2.6. Data Analysis

2.6.1. Neuropsychological Measures

Where possible, scores derived from neuropsychological measures were correlated against ocular motor performance.

2.6.2. Ocular Motor Measures

Raw eye movement data were analysed using a custom built Zoomtool program written in Matlab. Data were then analysed using SPSS.

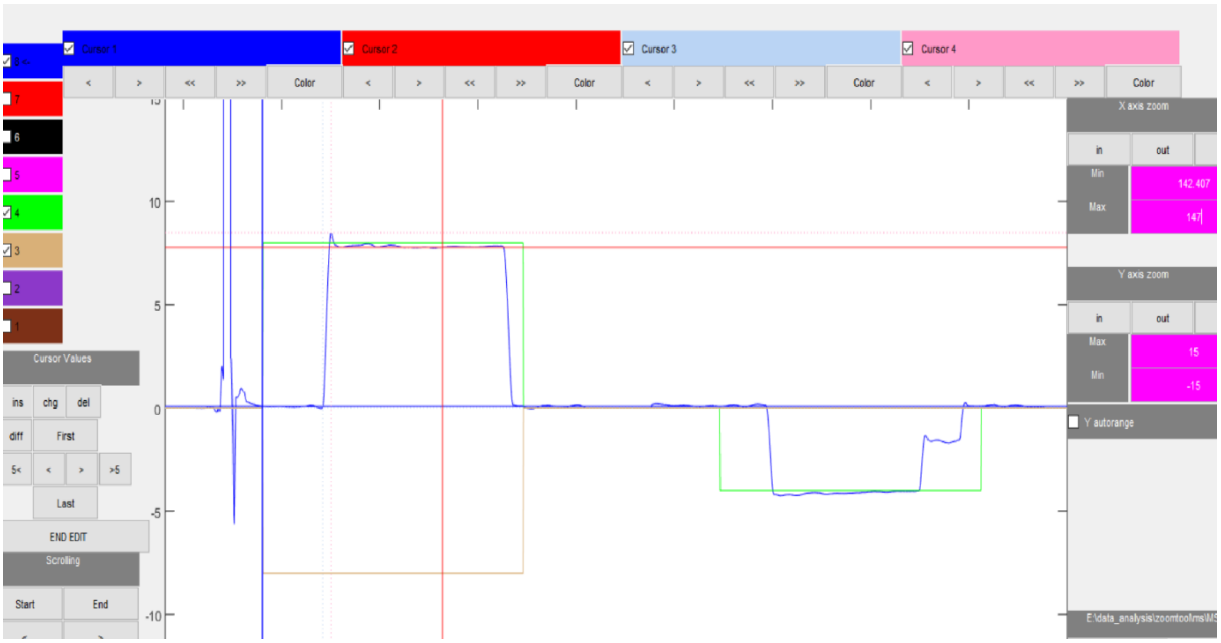

Figure 5. Saccadic movement depicted using Zoomtool

*Saccadic movements represented graphically by blue lines, and targets represented by green line. Upward movement represents a rightward saccade (blue line) while downward movement represents a leftward saccade (blue line).

2.6.3. Errors

Error was defined according to task, with each task encompassing its own parameters and sets of task requirements. The various error types are described in more details in the following chapters.

2.6.4. Latency

Latency was defined as the time period between target onset and saccade onset, and calculated using a velocity criterion of 30º per second.

2.6.5. Unstable fixation

Unstable fixation referred to any micro-movement falling outside of 1.5 degrees from central fixation.

Chapter 3: Attentional Orienting

3.1. Introduction

Attention prioritises the processing of information according to its relevance to behavioural needs. Specifically, it facilitates the processing of relevant information and inhibits or filters unwanted information, determining which information we ultimately perceive and act upon (Desimone & Duncan, 1995; McDowd, 2007; Ungerleider & G, 2000). Behaviourally, the orientating of attention represents the outcome of the competitive interaction of stimulus-driven processes, based on the distinct properties of an external event, and goal directed processes, represented by internal expectations or goals (Desimone & Duncan, 1995). Further, a shift of attention can occur either overtly, accompanied by eye movements or covertly, in the absence of eye movement (Singh, Upadhyay, & Singh, 2016; Spence, 2014). Both modes of orienting share a close relationship neurologically and anatomically, with an attentional shift often viewed as a precursor to an eye movement (MacLean, Klein, & Hilchey, 2015; Giacomo Rizzolatti & Craighero, 2010; Zhao, Gersch, Schnitzer, Dosher, & Kowler, 2012). Covert orienting promotes the preparation of response, modulating visual processing by biasing the neural system for future executable movement towards the attended location (Ptak, 2012). This subsequently results in facilitating target detection and movement towards the location where attention is allocated (Singh et al., 2016).

A commonly used measure of attentional orienting is the Posner-style spatial cueing paradigm that manipulates attention either exogenously, by the presentation of a salient visual event, or endogenously by a symbolic cue, prior to target presentation. In MS, endogenous orienting of attention has been characterised using a truncated version of Posner's endogenous cueing paradigm (Clough, Millist, Lizak, Frohman, et al., 2015; Fielding et al., 2009b). Here participants made a saccade (overt shift of attention) towards a target in a direction either correctly

or incorrectly predicted by a preceding symbolic cue (covert shift of attention). These studies revealed that patients diagnosed with MS or a CIS suggestive of MS, were more susceptible to responding erroneously in accordance with a non-informative symbolic cue, irrespective of cue validity. The authors interpreted this as poor inhibitory control.

Although the exogenous orienting of attention has been investigated using a Posner-style spatial cueing paradigm by numerous researchers, using a range of response modalities (Chica, Bartolomeo, & Valero-Cabré, 2011; Smith, Schenk, & Rorden, 2012; Tian, Klein, Satel, Xu, & Yao, 2011; Yang, Yao, Ding, Qi, & Lei, 2012), no study to date has explicitly done so in MS. Here, participants are presented with a peripheral stimulus or cue that corresponds, or not, with the location of an upcoming target, covertly directing attention to a particular spatial location prior to target onset. With relatively short intervals between cue and target presentation, referred to as stimulus onset asynchrony (SOA), spatially corresponding, or valid cues, promote faster response times to the target than spatially non-corresponding or invalid cues. However, with longer SOAs, typically beyond 250ms, this relationship is reversed with protracted response times for valid compared to invalidly cued targets (Posner, 1980; Posner, Rafal, Choate, & Vaughan, 1985). This effect, known as inhibition of return (IOR), is considered a consequence of initial capturing and subsequent removal of attention at a cued location, with an inhibitory bias generated against returning attention to a previously attended location (Posner, 1980; Posner et al., 1985).

This study explored attentional orienting in MS using a saccadic Posner-style exogenous cueing paradigm. Four SOAs ranging from 67ms to 500ms; were selected to capture both the early facilitatory effects of a valid cue and the later IOR effect. Specifically, the study examined whether:

1) MS patients perform differently to neurologically individuals on this paradigm

2) MS patients generate more erroneous responses than neurologically healthy individuals, implicating poor inhibitory control as previously proposed using an endogenous cueing paradigm.

3.2. Methods

3.2.1. Participants

Twenty-eight patients who met the McDonald criteria for MS (Male: 7; Female: 21) participated in this study. The mean age of patients was 43.85 years (*Min* = 22 years, *Max* = 65 years), mean disease duration 95.76 months (range 1 – 312) and mean EDSS 2.07 (range 0 – 6). Patients did not demonstrate significant fatigue at the time of testing as indicated by the MFIS scale (> 38 total score). Thirty-one individuals (*Male* = 12; *Female* = 19) with no history of neurological, psychiatric or drug abuse condition served as controls. The mean age of controls was 37.19 years old (*Min* = 29, *Max* = 59). Exclusion criteria for both groups were a history of traumatic brain injury, neurological disorder (other than MS for the MS group), psychiatric illness, drug abuse or regular intake of psychoactive drugs. Both IQ, as determined using the NART (Controls *M* = 118.2; MS patients *M* = 111.07) and depressive state, examined using the BDI (Controls *M* = 5.35; MS patients *M* = 8.85), were comparable across groups.

3.2.2. Materials

Horizontal displacement of the eye was recorded using an Eyelink II dark pupil, video-oculography system (SR-Research Ltd, Mississauga, Canada), which features high resolution (noise limited at <0.01º), and a high acquisition rate (500 Hz). All screen-based stimuli were generated using Experiment Builder (version 1.10.165), and displayed on a 22-inch CRT

monitor. Participants were seated in a dark room, located 840mm directly in front of the monitor, with heads stabilised.

The stimulus display comprised a white centrally positioned fixation cross on a black background, flanked by two white boxes (53mm×53 mm) positioned such that their centres were 8◦ to either side of fixation with respect to the participant's right eye. Target stimuli were blue crosses measuring 17mm×17mm which appeared in the centre of one of the two flanking boxes, or at centre to signify the conclusion of a trial.

3.2.3. Experimental Paradigm

Participants were instructed to fixate a central cross at the commencement of each trial (850ms) and to maintain fixation during the presentation of a peripheral cue represented by 50 s of brightened illuminance in either the left or right peripheral box. Cue presentation was followed by varying fixation intervals of 17, 100, 250, 450ms, effectively creating stimulus onset asynchronies (SOA) of 67, 150, 300, 500ms respectively. A blue target cross was subsequently presented in one of the peripheral boxes for 1500ms, and participants were instructed to direct an eye movement towards the cross as soon as it appeared. Participants were then instructed to return gaze back to centre after the target extinguished, concomitant with the appearance of a central re-fixation cross (400ms).

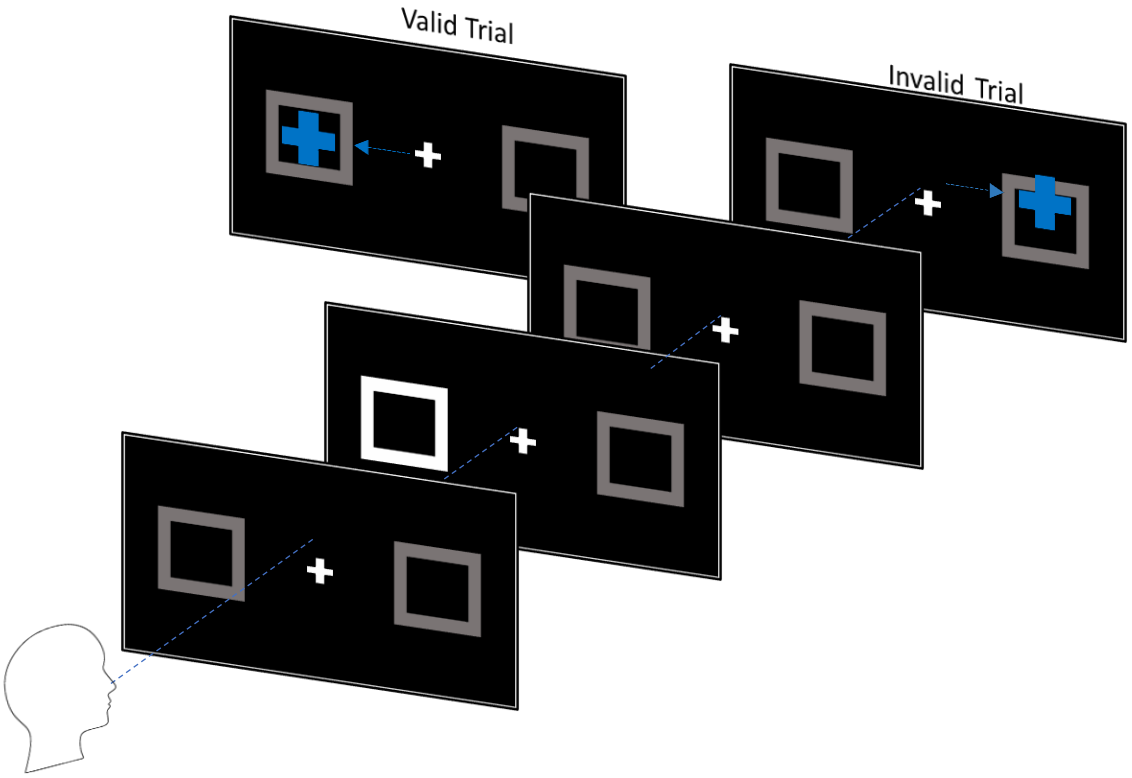

Figure 6. Schematic diagram of a valid and invalidly cued trial

Trial *type* was determined by the type of cue presented prior to target onset:

- valid trial: the peripheral cue was presented in the location corresponding with the subsequent target
- invalid trial: the peripheral cue was presented in the location opposite to the subsequent target.

Valid and invalid trials occurred pseudorandomly, with equal probability (64 trials each) to ensure that cues were unpredictive of target location. Catch trials comprised presentation of cue but no subsequent target, and served to discourage anticipatory responses. Neutral trials, typically

presented to ascertain the relative influence of either trial type, were not included in this study to minimise the impact of fatigue, known to detrimentally impact performance in MS patients.

3.2.4. Data Analysis

Variables of interest were (1) latency (ms), defined as the time period between target onset and saccade onset, calculated using a velocity criterion of 30º per second, and (2) error, defined as an erroneous response to the cue (>90ms prior to target presentation), or < 100ms of target onset to the correct or incorrect location (anticipation).

Trials were removed from latency analysis where 1) an error occurred, 2) fixation failed to fall within 2º of central fixation cross, or 3) a blink occurred immediately before, during or after the initiation of a saccade. A comparable number of total trials were removed due to saccade anticipations, poor fixation and blinks for both controls (2.36%) and MS patients (3.3%), t (62) = -1.005, p = .32.

Latency data were analysed using a repeated-measures ANOVA (Cue: valid, invalid; x SOA: 67, 150, 300, 500; x Group: MS, controls). Error data were analysed using a repeated-measures ANOVA (SOA: 67, 150, 300, 500; x Group: MS, controls). An alpha level of .05 was set for all statistical tests and Bonferroni type adjustments made for all post hoc comparisons.

3.3. Results

3.3.1. Latency

Table 3 presents the means and standard deviations of latencies for valid and invalid trials.

Table 3. *Means and standard deviations of latencies for valid and invalid trials*

SOA	Valid trial		Invalid trial	
(ms)	Controls	MS	Control	MS
67	279.01	320.55	310.28	356.36
	(38.01)	(57.51)	(39.71)	(49.67)
150	271.83	308.35	308.67	341.54
	(35.19)	(61.28)	(39.70)	(63.05)
300	307.46	317.96	301.1	328.85
	(45.66)	(56.42)	(46.69)	(69.03)
500	312.82	333.78	288.27	320.23
	(48.66)	(43.93)	(46.67)	(61.94)

ANOVA revealed a main effect of Group, F (1, 58) = 7.64, p = .008, with overall latencies prolonged for MS patients, and a main effect of Cue, F (1, 58) = 13.29, p = .001, with shorter latencies for valid compared to invalid trials overall, as well as a significant SOA*Group interaction, F (3, 174) = 4.09, p = .008 and a significant SOA*Cue interaction, F (3, 174) = 45.2, $p < .001$.

3.3.1.1. Within Group Analysis

For controls, post-hoc analyses revealed that latencies for valid trials were comparatively shorter than invalid trials for both 67ms ($p < .001$) and 150ms ($p < .001$) SOAs. As anticipated, this was reversed for later SOAs where IOR was evident (see Figure 7), with relatively *longer* latencies for valid trials with SOAs of 300ms ($p = .28$) and 500ms ($p < .001$). For MS patients, latencies for valid trials were shorter than invalid trials for 67ms ($p < .001$), 150ms ($p = .001$) and 300ms ($p = .29$) SOAs, and only prolonged for 500ms ($p = .11$) SOAs.

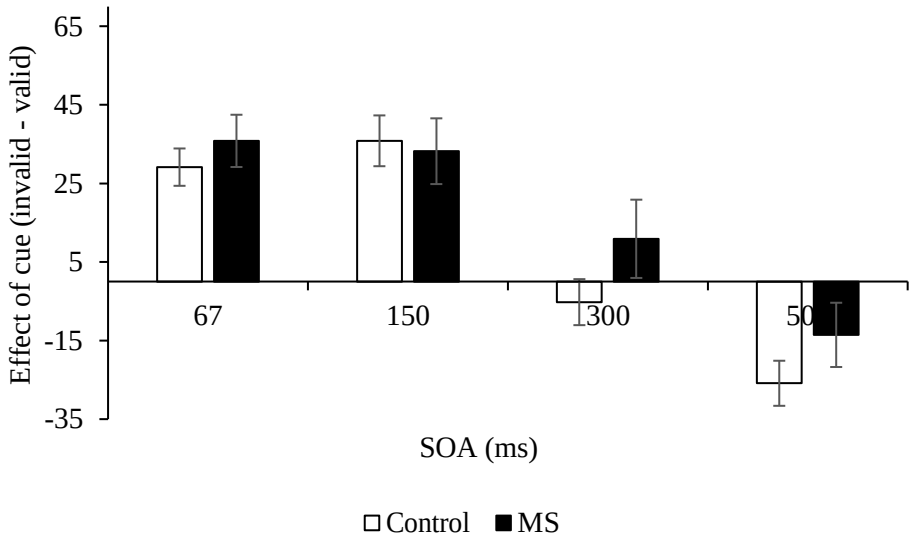

Figure 7. *Cue effect* for control and MS groups, defined as the difference in latencies between valid and invalid trials. Negative values represent IOR, with relatively longer latencies for valid compared to invalid trials.

3.3.1.2. Cue Type Comparisons

Separate ANOVAs for valid and invalid trials (SOA x Group) were conducted to explore the differential effect of cue type on both groups. For valid trials, a main effect of SOA, F (3. 174) = 17.63, $p < .001$, and a significant SOA x Group interaction, F (3, 174) = 4.24, $p = .006$ were revealed. Post hoc analyses revealed that for controls, pairwise comparison of SOAs revealed significantly shorter latencies for 67ms compared to 300ms ($p < .001$) and 500ms ($p < .001$) SOAs, and significantly shorter latencies for 150ms compared to 300ms ($p < .001$) and 500ms ($p < .001$) SOAs. The largest incremental increase in latency was between 150ms and 300ms SOAs. However, for MS patients, no significant differences were found across all SOA comparisons (see Figures 8 and 9).

For invalid cues, a main effect of SOA only, F (3, 174) = 16.87, $p < .001$, was revealed. Although latencies were longer overall for MS patients, for both groups there was a progressive decline in latencies across the 4 SOAs. For controls, pairwise comparison of SOAs revealed significantly shorter latencies for 500ms compared to 67ms ($p = .001$), 15 ms ($p < .01$) and 300ms ($p < .05$) SOAs. For MS patients, pairwise comparison of SOAs revealed significantly shorter latencies for 500ms compared to 67ms ($p = .001$), and 150ms ($p < .05$) (see Figures 8 and 9)

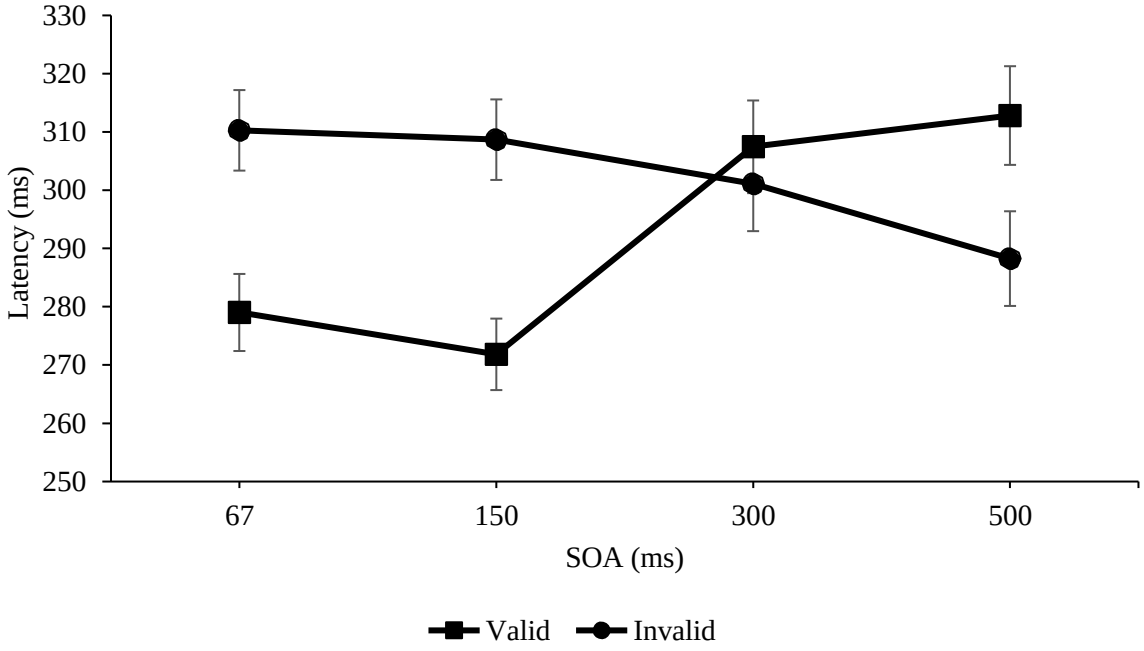

Figure 8. Controls only: Latencies for valid and invalid trials

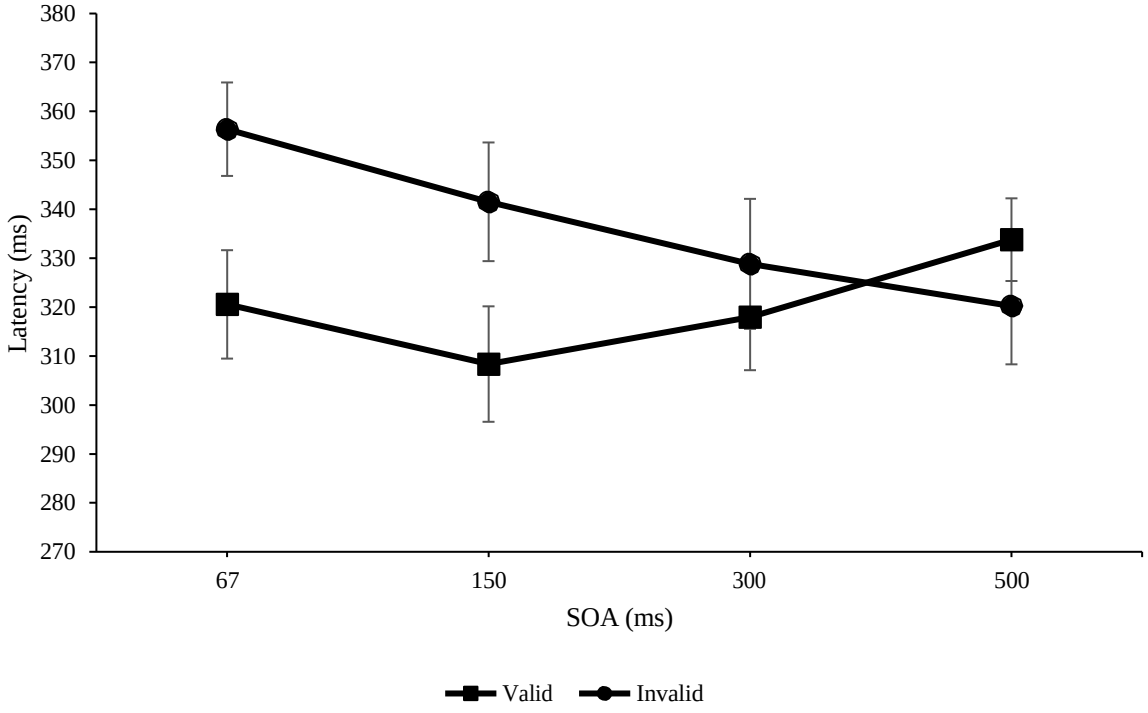

Figure 9. MS patients only: Latencies for valid and invalid trials

3.3.2. Errors

Errors were analysed as a proportion of total trials for a given SOA (32 trials per SOA). ANOVA with Greenhouse-Geisser correction revealed a main effect of SOA, F (3, 174) = 71.664, p < .001, with all participants generating an increased proportion of errors with increasing SOA, and a main effect of group, F (1, 58) = .4.27, p = .043, with MS patients generating proportionately more errors overall (see Figure 10). Although the proportion of errors was consistently higher for MS patients across all SOAs, no significant between group differences were found for any SOA.

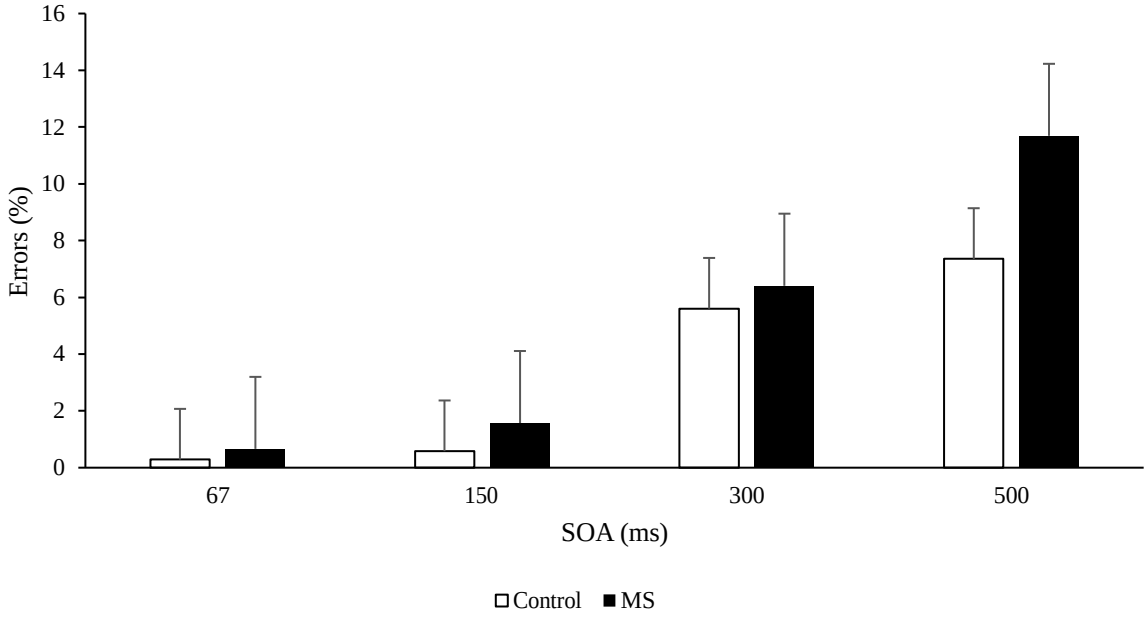

Figure 10. Errors as a proportion of total trials as a function of SOA

3.3.3. Neuropsychological Measures

Table 4 presents the means and standard deviations for PASAT and SDMT scores.

Table 4*. Means and standard deviation for neuropsychological tests*

	Controls		*MS*	
	M	*SD*	*M*	*SD*
PASAT	87.66	11.58	70.7[a]*****	25.48
SDMT	63.19	9.74	54.62[b]*****	13.13

*significantly different from controls: [a]$p = .003$, [b]$p = .006$

A series of Pearson's correlations were conducted between saccade metrics and clinical and neuropsychological measures for MS patients. To reduce the number of correlations, average latency and error across all SOAs and cue types were used. Poorer performance on both the PASAT and SDMT was related to increased error performance; PASAT $r = -.43$, $p = .02$, $r^2 = 18.49\%$; SDMT $r = -.44$, $p = .02$, $r^2 = 19.36\%$. No significant correlation between latency and PASAT or SDMT performance was found.

3.4. Discussion

The present study examined attentional orienting in MS by evaluating the effect of presenting uninformative exogenous cues prior to target onset and varying the temporal relationship between cue and target to elicit IOR. Our results revealed that MS patients exhibited an altered response profile, with IOR evident at a later time point than controls, and a higher proportion of errors, reflecting changes to inhibitory control mechanisms in MS. Increased overall latencies were

considered consistent with reduced information processing speed, a hallmark of the disease process in MS.

When a visually salient cue is presented, attention is automatically captured at the cued location, and is reflected neutrally in changes to activity in cortical and sub-cortical regions of the brain, including the SC, which provides the final premotor command for release of a saccade by the brainstem saccadic burst generator. Simplistically, a motor plan for a corresponding response is pre-prepared (e.g. premotor theory of attention), and held back from release by strong inhibitory input from cortex via the BG. Consequently, if a target appears in the cued location, this pre-preparation results in the facilitation of a response, with a relatively short response latency. In contrast, where a target appears in an un-cued location, attention must firstly be disengaged from the cued location (plan cancelled), then re-oriented, and a new plan prepared and executed, resulting in a relatively prolonged latency. However, this pattern of response varies depending upon the time interval between cue and target presentation (SOA). While this relationship holds for short SOAs, once the time interval reaches approximately 200-300ms, the relationship is reversed (i.e. longer latencies for validly cued targets compared to invalidly cue targets). This phenomenon is known as IOR (Dukewich & Klein, 2015). As anticipated, healthy controls generated shorter latency saccades for validly cued trials with 67 and 150 SOAs, and the inverse with 300 and 500ms SOAs (i.e. shorter latencies for invalidly cued trials compared to validly cued trials). Comparatively, MS patients exhibited a delayed time course of IOR, which was not evident with 300ms SOAs, but present with 500 SOAs, demonstrating alteration to the time-course of IOR.

A large body of work has explored the IOR phenomenon, and while the underlying mechanisms are not resolved, many theorists posit that it does not simply reflect the gradual decay of initial facilitation (where attention is gradually removed from cue), but the relative suppression

of activity representing stimuli that have recently been the focus of attention, encouraging orienting toward novelty or serve as a search or foraging facilitator. This has been widely referred to as an *inhibitory tag* (Dukewich & Klein, 2015). An IOR inhibitory tag purportedly registers and maps the location of a previously attended location, so that as that location is revisited, the strength of preparatory activity in the SC representing that location is attenuated, or inhibited, delaying the release of a saccade.

Although the neural mechanisms underlying IOR are unclear, the involvement of the midbrain SC appears irrefutable, with modulation of activity consistent with the time-course of IOR irrespective of response modality. The regulation of activity over the SC however, derives from convergent excitatory and inhibitory input, largely from cortex including the FEF, PEF) prefrontal cortex, or posterior parietal cortex. Therefore, IOR may be characterised as the relative precedence of inhibitory activity *versus* facilitatory activity over the SC.

Our results demonstrate that IOR occurs in neurologically healthy individuals in under 300ms. Interestingly, in controls it was revealed that latencies for invalidly cued trials declined gradually over increasing SOAs, indicating a decay in the strength of cue-related activity, but that latencies for valid cues increase dramatically between 150ms and 300ms SOAs. In MS patients, results similarly revealed a gradual decline in latency over increasing SOAs, although latencies were longer overall, but no modulation of latency as a function of SOA for validly cued trials. It appears that despite a gradual increase in latency over SOA, as would be expected with a decay in the strength of cue-related activity over time, MS patients did not exhibit the significant increase in latencies post 150ms SOA, indeed at any time point in this study. IOR is at best significantly delayed in MS, most likely a consequence of a deficient, cortically driven *inhibitory tag*.

As discussed, the presentation of a visually salient cue promotes both facilitatory and inhibitory processes, thus generating conflict between the competing bottom-up prepotent command to execute a saccadic response and the top-down command of maintaining the task goal to fixate. This competition is resolved through competitive interaction (all-or-nothing), the winner determining the outcome of a response. With cue presentation, a response plan is *activated*. Whether the plan is *executed* depends on top-down cortically derived inhibitory signals. An overt saccade toward a peripheral cue (error) represents a failure of these inhibitory signals to override the executable command of a premotor plan, effectively a failure to resolve the conflict between competing bottom-up and top-down processes.

Compared to controls, MS patients generated a higher proportion of errors, with more saccades generated directly towards the cue prior to target onset. This represents a relative failure to inhibit the automatically elicited saccade plan, generated in response to the presentation of a cue. Importantly, the successful resolution of response conflict is reliant upon the integrity of the networks subserving the competing processes, which are sensitive to changes affecting signal strength and propagation. Severed or compromised connections, as occurs in MS, either through inflammatory lesions (demyelination) or neurodegenerative changes (neuronal degradation) potentially undermine the successful generation or transmission of signals (both facilitatory and inhibitory) throughout the brain, resulting in difficulty effectively controlling the release of an appropriate response. Perhaps unsurprisingly, poor inhibitory control has been consistently demonstrated across a range of studies in MS, whether utilising novel ocular motor experimental paradigms or more commonly used neuropsychological or experimental measures like the go-no-go task, the stroop task (Ternes, Clough, Foletta, White, & Fielding, 2019a). Increased error rate

also correlated with PASAT, a reference task in MS for cognitive assessment accessing multiple processes including attention.

Although this study demonstrated a delay in the time course of IOR in MS, it remains unclear whether, or if, the typical prolongation of latencies for validly cued trials, which presumably reflects the application of an inhibitory tag, occurs at a later time-point (i.e. with longer SOAs). Further, it is unknown whether IOR persists in MS as it does in controls. Previous work has shown that IOR may persist for up to 3000ms. Thus, future studies are encouraged to explore longer SOA(s) to examine the profile of change over time, to address when or whether IOR subsides in MS. Further, neutral and bi-directional trials were not included in this experiment, simply to avoid the burden of additional trials on patients engaged in a larger research study. Therefore, a cost/benefit analysis was not conducted for each cue type, and this may have provided additional insight into the profile of change in MS. Future studies are encouraged to incorporate these cues for comparison.

Chapter 4: Selective Attention

4.1. Introduction

At any point in time, we are subjected to a barrage of sensory information. Selective attention is the process that allows us to focus on the particular subset of information that is relevant to given situation, and tune out irrelevant information. This fundamental ability is integral to our capacity to function optimally in a busy environment, with deficits of selective attention potentially affecting an individual's capacity to function in work and social situations. Behaviourally, what is ultimately selected for further processing relies on the result of a competitive interaction, whereby information in the environment competes for representation across neural networks, and a winner is 'selected' (Desimone & Duncan, 1995; Luck, Chelazzi, Hillyard, & Desimone, 1997). On a neural level, competition between visual stimuli is expressed through the parallel activation of neurons within their respective receptive fields in the visual and extrastriate cortices. This competition is thought to be resolved through neural biasing, determined by saliency (e.g. novelty) and behavioural relevance (Corbetta & Shulman, 2002).

Patients with MS are proposed to experience deficits of selective attention; however, the few studies that have been conducted in MS, report conflicting results (Adler & Lembach, 2015; Pöttgen, Stephan, Gold, Heesen, & Penner, 2015; Prakash et al., 2008). In the study by Prakash et al. (2008), MS patients performed a flanker task which required them to press the left innermost key on the four-button response pad if a central arrow pointed left, and press the right innermost key if a central arrow pointed to the right. No group differences were revealed. Similarly, Pöttgen et al. (2015) did not demonstrate a performance difference between MS patients and controls using go/no-go task as the chosen measure of selective attention. Conversely, a study by Adler and Lembach (2015) using a computerised oddball paradigm, found that MS patients generated more erroneous responses when responding to a symmetrical pattern stimulus within a sequence of

geometric patterns. Whilst all of these tasks were proposed to measure selective attention, traditionally, go-no-go, odd-ball and flanker tasks are known as measures of inhibitory control (Chikazoe, 2010; Redick, Calvo, Gay, & Engle, 2011). MS patients have been consistently found to have significant inhibitory control deficits, and may better explain performance on these tasks rather than selective attention per se.

The process of selecting a subset of information while explicitly refraining from responding to irrelevant information, or selective attention, is commonly explored using an interference paradigm (Awh, Armstrong, & Moore, 2006; Eimer & Grubert, 2014; Grubert & Eimer, 2015; Pooresmaeili, Poort, & Roelfsema, 2014). In such a paradigm, an observer must generate a response to a target presented alongside (or close in temporal proximity to) one or more visually salient non-target(s). This require the generation and maintenance of an attentional template that carries the description of a target (Carlisle, Arita, Pardo, & Woodman, 2011). When both a target and non-target are presented simultaneously, a selection process takes place, whereby the stimulus that matches the attentional template is selected the non-target stimulus inhibited (Carlisle et al., 2011). This selection process, underpinned by the fronto-parietal network, creates, maintains and enforces an attentional template (Barcelo, Suwazono, & Knight, 2000; Miller, Erickson, & Desimone, 1996; Schafer & Moore, 2011).

Assessment of saccades offers a unique opportunity to assess selective attention. Indeed, selective attention is considered imperative to, and even a precursor of, any eye movement (Giacomo Rizzolatti & Craighero, 2010). Further, the neural substrates of 'selecting' are tightly integrated/associated with the ocular motor system, sharing multiple regions including the DLPFC, FEF and parietal cortex (Ptak, 2012; Wardak, Olivier, & Duhamel, 2011). As discussed, these regions generate a bias that determines where selection takes place and pre-plan an upcoming

saccade to the selected location (Ptak, 2012; Wardak et al., 2011). This is extended to the SC, where local activity (build-up neurons that initiate saccades, and fixation neurons that initiate fixation) directly reflects top-down modulation of a motor command, shaping the final pre-motor response based on the target stimulus 'selected' by the attentional and the visual processing systems (Knudsen, 2011; Krauzlis, Lovejoy, & Zénon, 2013).

Saccadic interference paradigms have been designed to assess selective attention. Specifically, an observer must generate a response to a target presented alongside (or close in temporal proximity to) one or more visually salient non-target(s). When both a target and non-target are presented simultaneously, a selection process takes place, whereby the stimulus that matches the attentional template is selected and the non-target stimulus inhibited (Carlisle et al., 2011). The competing non-target presented during the eye movement planning stage invariably interferes with the saccade plan (Ludwig, Gilchrist, & McSorley, 2005; McSorley, McCloy, & Lyne, 2012). For example, concurrently presenting a competing non-target in the opposite hemifield of a target delays the release of the subsequent target response, which is evidenced as increased saccade latency (Benson, 2008; Bompas & Sumner, 2009). This effect is strongest when the competing event is presented near fixation, with the magnitude of the effect decreasing as the position of the competing visual stimulus moves further away (McSorley et al., 2012). This effect is attributed to the competitive interplay between non-target and target related activity in the SC (Findlay & Walker, 1999; Walker, Deubel, Schneider, & Findlay, 1997). According to this view, a remotely presented non-target (within 10 degrees of central fixation) will still activate a subset of fixation neurons (rostrolateral) responsible for maintaining fixation, although the degree of activation is relative to non-target proximity. Further activation of fixation neurons generates

lateral inhibition upon the build-up neurons responsible for initiating a saccade to a target (Olivier, Dorris, & Munoz, 1999).

This study investigated selective attention in MS using a saccadic interference paradigm that required a two-choice selection based on 4 target locations. Given the typically widespread distribution of inflammatory and neurodegenerative changes across cognitive networks in MS, it was predicted that MS patients would exhibit poorer performance overall, specifically, longer saccade latencies and increased responsive errors towards non-target stimuli. However, it was unclear whether latencies for MS patients would be differentially affected by non-target stimuli at four degrees compared to eight degrees eccentricity.

4.2. Methods

4.2.1. Participants

Twenty-nine patients (*Male* = 8; *Female* = 21) who met the McDonald criteria for MS were recruited into the study. The mean age for patient group was 43.24 years old (*Min* = 22, *Max* = 65 years). On average, MS patients had a disease duration of 92.64 months (range 4 – 312), and mean Extended Disability Scale Score (EDSS) 1.91 (range 0 – 6). Patients did not demonstrate significant fatigue at the time of testing as indicated by the MS fatigue scale (> 38 total score). Thirty-two individuals (*Male* = 13; *Female* = 21) served as controls. The mean age of controls was 37.56 years old (*Min* = 29, *Max* = 59). Exclusion criteria for both groups were a history of traumatic brain injury, neurological disorder (other than MS for the MS group), psychiatric illness, drug abuse or regular intake of psychoactive drugs. Both IQ, as determined using the NART (Controls *M* = 118.27; MS patients *M* = 111.24) and depressive state, examined using the BDI (Controls *M* = 5.56; MS patients *M* = 8.72), were comparable across groups.

4.2.2. Materials

Horizontal eye movements were recorded using the Eyelink II tracker, with output sampled at 500 Hz. Participants were seated in a dark room, situated 840mm directly in front of the monitor, with their heads stabilised by a chin rest. All test stimuli were generated using experiment builder ver. 1.10.165, imposed on a black background on a 21-inch CRT monitor test stimuli comprised a blue target cross, measuring 42 mm X 42 mm, a blue competing square (42 mm x 42 mm), 3) a white central fixation cross (21 mm x 21 xx mm) and 4) a refixation square (16 mm x 16 mm).

4.2.3. Experimental paradigm

Participants were instructed to fixate a central cross at the beginning of each trial and perform a saccade to a blue target cross as soon as it appeared on the screen. The target was either presented alone (N) or concomitant to a blue square non-target (C) located in the mirror opposite location. The target was presented for 1500ms, after which, a central refixation square was presented reorienting the eyes to centre. Each participant completed 48 trials of the paradigm, split into 2 blocks of 24 trials, with a break in-between. Four conditions were assessed, with each condition representing a unique target spatial position, either with or without a competing non-target: (1) 4^{o} target *without* a competing non-target (N4); (2) 4^{o} target *with* a competing non-target (C4); (3) 8^{o} target *without* a competing non-target (N8); (4) 8^{o} target *with* a competing non-target (C8). Trials presentation was randomised. An even number of trials was performed for each condition (i.e., 12 trials per condition).

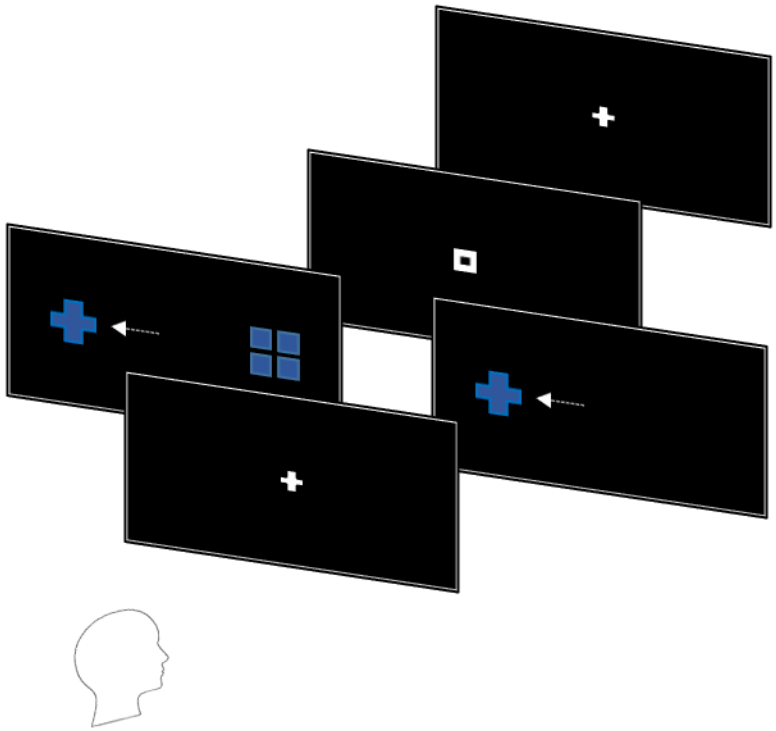

Figure 11. Illustration of the saccadic interference paradigm. (1) Participant fixates a central cross. (2A) example of a *compete* condition, (2B) example of a *non-compete* condition. For both conditions the participant must perform a saccade to the target cross. (3) Participant reorients to the centre in preparation for the next trial.

4.2.4. Data analysis

Variables of interest were (1) latency (ms), defined as the time period between target onset and saccade onset, calculated using a velocity criterion of 30º per second, and (2) error, defined as an erroneous response to the cue in the non-target compete conditions (C4 and C8).

Trials were removed from latency analysis where 1) an error was performed, 2) a saccade was initiated within 100ms of target onset, 3) fixation failed to fall within 1.5º of central fixation,

4) a blink occurred immediately prior, during or after the initiation of a saccade that affected the interpretation of saccade onset.

Latency data were analysed using a repeated-measures ANOVA (Condition: compete, non-compete; x Spatial position: 4 degrees, 8 degrees; x Group: MS, controls). Error data were analysed using a repeated measures ANOVA (Spatial position: 4 degrees, 8 degrees; Group: MS, controls). An alpha level of .05 was set for all statistical tests and Bonferroni type adjustments made for all post hoc comparisons.

4.3. Results

Table 5 presents the means and standard deviations of saccade metrics.

Table 5*. Means and standard deviations of saccade metrics for MS and Control groups*

	MS		Control	
	M	*SD*	*M*	*SD*
Latency				
N4	263.28	64.67	265.7	48.04
C4	309.93	53.88	299.3	52.51
N8	259.3	56.47	260	48.45
C8	298.73	72.11	289.67	46.44
Error				
C4	21.84	20.1	11.62	13.33
C8	30.17	19.47	19.19	15.8

*Note: *N4 = 4-degree target without non-target; *C4 = 4 degree target with non-target; *N8 = 8 degree target without non-target; *C8 = 8 degree target with non-target*

4.3.1. Latency

ANOVA revealed a significant main effect of condition, F (1, 60) = 60.67, p < .001, with latency prolonged for compete trials compared to non-compete trial and a main effect of spatial position, F (1, 60) = 5.93, p < .018, with latency prolonged for four degrees trials compared to eight degrees trials. However, no significant main effect of group, F (1, 60) = .11, p = .745) or significant interactions were found (group x condition, F (1, 60) = 1.42, p = .24; group x spatial position, F (1, 60) = 1.44, p = .24; group x condition x spatial position, F (1, 60) = .13, p = .72) (see figure 12).

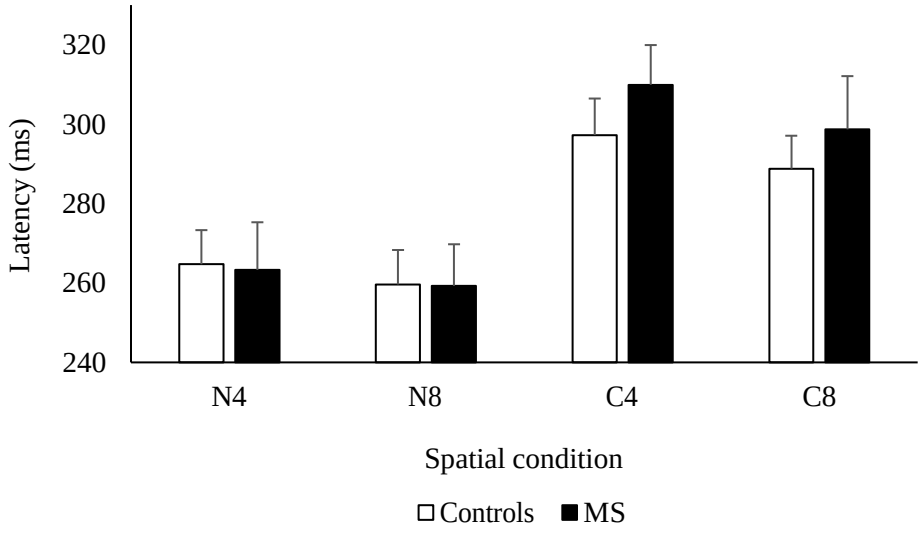

Figure 12. Latency across spatial positions and competing conditions for control and MS groups. Where C represents compete trials and N represents non-compete trials, and numbers (4 and 8) represent spatial location in degrees relative to centre. (C = compete, N = non-compete).

4.3.2. Errors

Errors were analysed as a proportion of total trials. ANOVA revealed a main effect of group, F (1, 60) = 7.53, p = .008, with MS patients performing significantly more errors than controls. Further, a significant main effect of spatial position was found, F (1, 60) = 14.76, p < .001, with significantly more errors performed at 8 degrees relative to 4 degrees. However, no group interaction was found, F (1, 60) = .03, p = .86 (see figure 13).

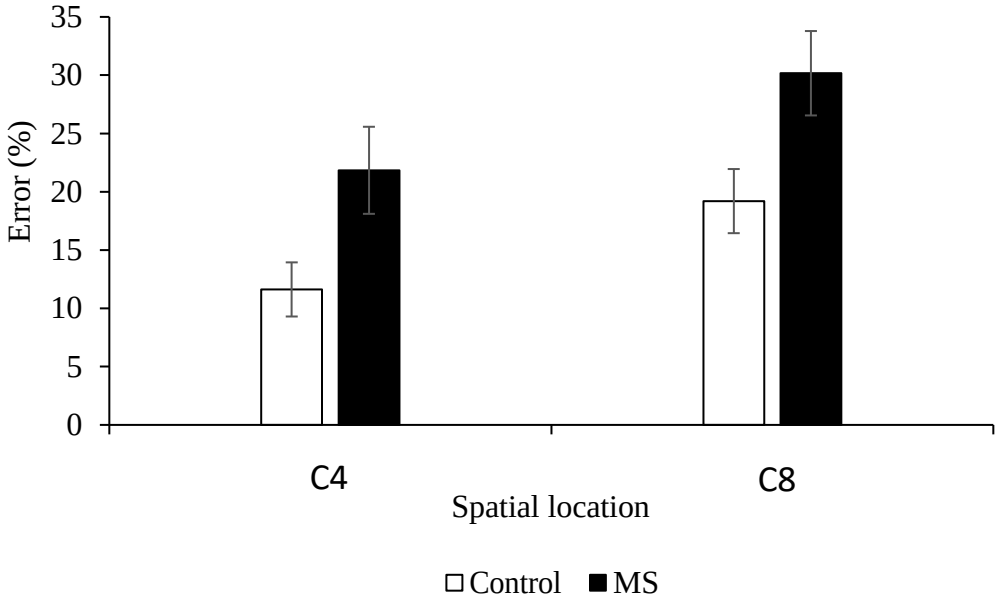

Figure 13. Error rates across spatial location for control and MS groups

4.3.3. Neuropsychological Measures

Table 6 presents the means and standard deviations for PASAT and SDMT scores.

Table 6*. Means and standard deviations for neuropsychological measures*

	Controls		*MS*	
	M	*SD*	*M*	*SD*
PASAT	87.21	11.67	73.84 [a]*	21.32
SDMT	63.19	9.75	55.24 [b]*	13.46

*significantly different to controls: [a]$p = .003$, [b]$p = .013$

A series of Pearson's correlations were conducted between saccade metrics and clinical and neuropsychological measures for MS patients. To reduce the number of correlations, average latency and error rate across all conditions were used. No relationship between error rate or latency and performance on either the SDMT or PASAT were found.

4.4. Discussion

The present study examined selective attention in MS by evaluating performance on a saccadic interference, two-choice selection paradigm. As predicted, MS patients exhibited a higher error rate than controls, generating more saccades towards non-target stimuli. However, whilst both MS patients and controls exhibited longer latencies to 4 degree relative to 8 degrees target, no significant difference in latencies were found between groups. This may well reflect increased difficulty in inhibiting a response to a task-related stimulus, whether correct or incorrect, prior to

the selection of the appropriate target. This is similarly reflected in increased erroneous responding by MS patients.

To selectively attend to a stimulus, attention must bias processing in favour of the behaviourally relevant stimulus and suppress the processing of other irrelevant stimuli that may compete for dominance. This competitive process is aptly captured by the concurrent presentation of a target and a non-target in our saccadic interference, two-choice selection paradigm. When two stimuli are presented simultaneously, activation of neurons in their respective visual fields within the visual cortex occurs (Dugue, Merriam, Heeger, & Carrasco, 2018; Moore & Zirnsak, 2017; Zhang et al., 2014). To select and respond to the appropriate target, the attentional system must first identify the visual input that matches the target's attentional template (attentional set) (Carlisle et al., 2011; Olivers & Eimer, 2011). This is dependent on the outcome of a competitive interaction between populations of neurons representing the stimuli that is modulated by top-down processes, reflecting intent, as well as bottom-up feedback from the visual pathways (Moore & Zirnsak, 2017). The top-down selection process strengthens/enhances target-related-activation in the cortex, via cross-regional communication between multiple regions including the DLPFC and FEF. This strengthened neural activity triggered by attentional bias further inhibits the activity of a non-target stimulus via lateral inhibition, decreasing the potential for 'selecting' the competing non-target. Thus, a response generated toward a non-target reflects a momentary breakdown of competition, guided by failure to 'select' or balance neuronal activities in favour of the appropriate target.

Consequently, the increased error rate found for MS patients suggests a failure to resolve competition when faced with two competing stimuli. This increased overall error rate also correlated with scores on the PASAT, a neuropsychological measure known for measuring a range

of cognitive processes including attention. Conceivably, MS patients may have difficulty in appropriately altering the balance of activity in visual regions and the spatiomotor map of the SC to favour the target stimulus. An impaired bias mechanism conceivably reflects weakened inhibitory processes; whereby insufficient inhibition is applied to the non-target region. On a neural level, a deficit to biased processing implicates impairment to top-down processing regions critical for resolving attentional competition and inhibitory control (Beck & Kastner, 2009; Shomstein, Lee, & Behrmann, 2010). Neuronal injury or damage any point within this network will likely cause impaired/breakdown of regional communication or communication inefficiency, affecting biased processing/top down modulation of critical regions important for target selection. Pathologically, inflammatory and/or neurodegenerative injury to neurons and/or chronic demyelination are likely responsible for such disruption (DeLuca, Yates, Beale, & Morrow, 2015).

Alternatively, the heightened error rate among patients may reflect a failure to maintain or match a target to its corresponding attentional set. MS patients have previously exhibited poorer maintenance of attentional template or task elements across a range of neuropsychological and ocular motor paradigms (Clough et al., 2015; Fielding et al., 2009c; Simone Freitas Fuso, Callegaro, Pompéia, & Bueno, 2010; Hulst et al., 2015). The prefrontal cortex is known as an important 'coordinator' for actively maintaining and/or enforcing the attentional template (Barcelo et al., 2000; Miller et al., 1996). Imaging studies in MS have reported altered functional connectivity and aberrant prefrontal activation during memory tasks (Cader, Cifelli, Abu-Omar, Palace, & Matthews, 2005; Céline Louapre et al., 2014; Roca et al., 2008; Rocca et al., 2014).

Presenting a competing non-target in the opposite hemifield of a target typically delays a subsequent response (Benson, 2008). In the context of eye movement, this delay reflects resolution of the response competition between competing premotor plans represented at the level of the SC

(Findlay & Walker, 1999; Walker et al., 1997). Prior to initiating a saccade, the SC receives and integrates top down signals that shape the premotor plan and determine where a saccade is executed (Johnston & Everling, 2008; Matsumoto, Inoue, & Takada, 2018). Generating a premotor plan involves altering the balance of activity across the spatiomotor map, which comprises fixation neurons that govern fixation maintenance and retinotopically mapped neurons that code a saccade in the contralateral visual field (intermediate layer of SC) (Krauzlis et al., 2013; Leigh & Zee, 2015; White & Munoz, 2011b). To initiate a saccade to the appropriate target, fixation neurons must firstly be inhibited, whilst build-up neurons representing the target receive inputs enhancing their activity (Leigh & Zee, 2015; White & Munoz, 2011b). This push-pull mechanism governs how a saccade is initiated.

However, when the target presents with a competing event in the opposite hemifield, two premotor plans that discretely activate two groups of build-up neurons will generate and compete against each other within the SC (Walker & Benson, 2013; Walker et al., 1997). Alongside the target regions, regions representing the competing event will also be enhanced, racing against target regions to reach saccadic threshold (Krauzlis et al., 2013; Leigh & Zee, 2015). Simultaneous activation of these two distant regions consequently create bilateral inhibition that mutually suppress each region's activities, delaying the activation of both regions and the subsequent target response (Olivier et al., 1999; Walker & Benson, 2013). Finally, in a winner takes all fashion, the neuronal group to first reach the saccadic threshold determines where and when the final response is executed (Leigh & Zee, 2015). Here, MS patients did not demonstrate differences in latency. Given the increased error rate, rather than delaying the selection process, MS patients failed more often to resolve the competition between the stimuli.

The delay of a correct response may vary as a function of the non-target's eccentricity (distance away from central fixation), with decreasing eccentricity corresponding to an increase in the size of delay (Walker & Benson, 2013). This relationship is thought to reflect differential activation and competitive interaction between local fixation and build-up neurons in the SC (Findlay & Walker, 1999; Walker et al., 1997). Structurally, the rostral part of the SC is most populated by fixation neurons that activate during central fixation or when a stimulus presents at/near the focal fixation (White & Munoz, 2011b). As it extends toward the caudal SC, fixation neurons become less populated and gradually replaced by build-up neurons that activate when encoding saccades in the periphery (Findlay & Walker, 1999; Walker et al., 1997). Consequently, a competing event presented centrally, or neighbouring central fixation point activates a relatively larger proportion of fixation neurons (Findlay & Walker, 1999; Walker et al., 1997). This in turn, creates further competition as it requires a relatively higher degree of inhibition to suppress fixation neurons, while simultaneously activating build-up neurons that launch a saccade.

Although both MS and controls exhibited prolonged latencies at 4 degrees relative to 8 degrees, MS patients did not exhibit an exaggerated effect. The lack of group difference here suggests patients have a specific deficit concerning the resolution of competition (hence error), as opposed to resolving competition at a reduced capacity (delaying) within the given timeframe of the paradigm. It is likely that when both target and non-target were presented, MS patients could not resolve the competition quickly and rather than delaying the resolution process, simply selected/responded to either one of the targets or non-targets without properly resolving the competition.

Although beyond the scope of the study, future studies are encouraged to explore selective attention across varying levels of complexity in MS. Studies may vary the saliency of the

competing non-target, detecting where selectivity falters, adding to an understanding of selective attention in the individual patient. Future studies might also examine selective attention longitudinally to observe changes to the sub-domains over time. Selective attention may serve as a disease marker, which may assist disease management and signal early intervention yielding better treatment outcome.

Selective attention impairment has significant real-world implications. Difficulty selecting relevant/filtering irrelevant events may detrimentally affect daily functioning and well-being of patients, bombarding patients with irrelevant information. This may well also contribute to cognitive fatigue which is often reported by patients.

Chapter 5: Divided Attention

5.1. Introduction

As the name suggests, divided attention refers to the ability to attend to and process multiple pieces of information simultaneously. More specifically, this requires the distribution of attentional resources across multiple streams of information concurrently (Bowman, Waite, & Levine, 2015; Künstler et al., 2018). This ability appears fundamental to successful interaction within a complex and demanding environment, allowing multiple tasks to be completed at the same time (Bowman et al., 2015; Deprez et al., 2013). Consequently, deficits in divided attention may huge impact on an individual's capacity to function, particularly in in the context of work and social situations.

Theories of divided attention (e.g. resource capacity models) (Kahneman, 1973; Pashler, 1994), propose that the degree of division of attention is proportionate to the level of demand of the given tasks. When the degree of division of attention required exceeds the attentional resources present, performance becomes compromised (Künstler et al., 2018; K. Watanabe & Funahashi, 2014). Divided attention may be assessed experimentally by requiring participants to perform two discrete tasks simultaneously (dual task) (Künstler et al., 2018; Loose, Kaufmann, Auer, & Lange, 2003; Stelzel, Brandt, & Schubert, 2009; Vohn et al., 2007). Dual task paradigms usually comprise two tasks that engage discrete modalities (visual, auditory, cognitive and motor modality); complexity is varied depending on whether the tasks involve simple, automatic processes, more complex controlled processes or a combination of the two. Dual tasks performance is determined by comparing an individual's performance on each task individually, to their performance when the two tasks are completed simultaneously (dual task), with performance relatively worse under dual task conditions those tasks (Etemadi, 2017; Lemmens, Ferdinand, Vandenbroucke, Ilsbroukx, & Kos, 2018; Wajda, Motl, & Sosnoff, 2013). This performance decrement represents a dual task

interference effect, presumably a reflection of the cost of heightened attentional competition and demand from a limited pool of available resources during dual tasking (Bowman et al., 2015; K. Watanabe & Funahashi, 2014). Dual task interference is evident across a range of performance metrics, including prolonged task latencies and increased performance errors (Etemadi, 2017; Lemmens et al., 2018; Leone, Patti, & Feys, 2015; Wajda et al., 2013).

Divided attention is supported by a widely distributed network, which extends throughout fronto-parietal regions (Deprez et al., 2013; Stelzel et al., 2009; K. Watanabe & Funahashi, 2014). Imaging studies, for example, report the involvement of lateral and medial prefrontal cortices, parietal cortex, in particular the lateral intraparietal area, and anterior cingulate during (Adcock, Constable, Gore, & Goldman-Rakic, 2000; Deprez et al., 2013; Loose et al., 2003; Salo, 2017; Stelzel et al., 2009; Szameitat, Schubert, Müller, & Von Cramon, 2002; Vohn et al., 2007; Watanabe & Funahashi, 2014). These areas show enhance activation during simultaneous performance of two or more tasks or when one task interferes with the simultaneous execution of a secondary task (Adcock et al., 2000; Loose et al., 2003; Stelzel et al., 2009; Watanabe & Funahashi, 2014). The prefrontal cortex appears to apply top down control, coordinating concurrent processing during performance of simultaneous tasks (Deprez et al., 2013; Loose et al., 2003; Watanabe & Funahashi, 2014). Activity in parietal regions likely reflects attentional shifts between tasks, whilst activity in anterior cingulate cortex reflects a role in maintaining stable performance and monitoring between actions and outcomes (Deprez et al., 2013; Loose et al., 2003; Vohn et al., 2007).

In MS, changes within networks that involve the PFC are consistently found, and are associated with changes in the cognitive control of behaviour (Audoin et al., 2008; Louapre et al., 2014; Roca et al., 2008; Wojtowicz, Mazerolle, Bhan, & Fisk, 2014). Indeed, previous studies in

MS that have required patients to simultaneously perform a motor task (e.g. walking, stand balance) and a cognitive task (e.g. neuropsychological test) (Butchard-MacDonald, Paul, & Evans, 2018; Lemmens et al., 2018; Leone et al., 2015; Sosnoff et al., 2014; Wajda et al., 2013), report greater performance decrement in patients compared to controls, evident as a greater reduction in gait speed, step length, balance and postural stability during dual tasking relative to single task condition (Chaparro et al., 2017; Hamilton et al., 2009; Wajda et al., 2013). These differences have been interpreted as evidence of a more limited central resources in MS patients, rendering them more susceptible to cognitive overloading during dual tasking or concurrent tasks that compete within a shared network (Hamilton et al., 2009).

However, most dual task studies in MS have evaluated the effect of dual tasking on motor performance, with very few studies reporting the effect of dual tasking on cognitive performance (Beste, Mückschel, Paucke, & Ziemssen, 2018; Downer, Kirkland, Wallack, & Ploughman, 2016; Hamilton et al., 2009). Of those studies that have investigated a dual task effect on cognition, Hamilton et al (2009) found a larger dual task effect on cognitive performance in MS patients when using a walking task alongside a cognitive task that required retention/repetition of a digit sequence. Similarly, Downer et al. (2016) revealed a significant deterioration of cognitive performance in MS patients when examining the effect of a walking task on a cognitive task involving simple arithmetic and working memory. Finally, Beste et al. (2018) found that patients generated a higher proportion of errors during simultaneous performance of a visual and auditory discrimination task when task difficulty increased. In each of these studies, a cognitive task was paired with a complex motor task such as walking and balance. However, it is unknown whether divided attention is similarly affected in MS, when a cognitive task is paired with a simple motor task.

This study examined the impact on cognition of simultaneously engaging in simple motor task in MS by employing a dual task paradigm that required the simultaneous performance of a simple button press task and an antisaccade task. The button press task required participants to respond by repetitively pressing a button using the same rhythm as memorised using a tone stimulus prior to task commencement. Based on previous findings, it was expected that:

1) all participants would exhibit a dual task decrement for both tasks; specifically, all participants would exhibit increased antisaccade latencies and error rates, and a temporal discrepancy under the dual task condition relative to the single task condition
2) the performance decrement in MS patients would be significantly greater than controls.

5.2. Methods

5.2.1. Participants

Twenty-seven patients who met the McDonald criteria for MS (Male: 7; Female: 20) participated in this study. The mean age of patients was 42.74 years (*Min* = 22, *Max* = 65 years), mean disease duration 93.24 months (range 4 – 312), and mean EDSS of 2.03 (range 0 – 6). Patients did not demonstrate significant fatigue at the time of testing as indicated by the MS fatigue scale (> 38 total score). Thirty-two individuals (*Male* = 14; *Female* = 18) with no history of neurological, psychiatric or drug abuse condition served as controls. The mean age of controls was 37.56 years old (*Min* = 29, *Max* = 59). Exclusion criteria for both groups were a history of traumatic brain injury, neurological disorder (other than MS for the MS group), psychiatric illness, drug abuse or regular intake of psychoactive drugs. Both IQ, as determined using the NART (Controls *M* = 118.27; MS patients *M* = 115.33) and depressive state, examined using the BDI (Controls *M* = 5.56; MS patients *M* = 9.37), were comparable across groups.

5.2.2. Materials

Horizontal eye movements were recorded using an Eyelink II dark pupil, video-oculography system (SR Research Ltd, Canada). This system is high resolution (noise limited at <.01°), with an acquisition rate of 500 Hz. Participants were seated in a darkened room, 840mm from a 75Hz CRT monitor (resolution: 1024 X 768), with their heads resting on a chin rest. All test stimuli used in the antisaccade task (cognitive task) were generated using Experiment Builder version 1.10.165, and were imposed on a black background. Test stimuli comprised a blue non-target cross, measuring 30mm x 30mm and a refixation square (16 mm x 16 mm).

Button presses were recorded from the participants' index finger on a conventional PC controller. Participants were required to replicate a rhythm previously demonstrated using a series of tones spaced 1000ms apart.

5.2.3. Experimental paradigm

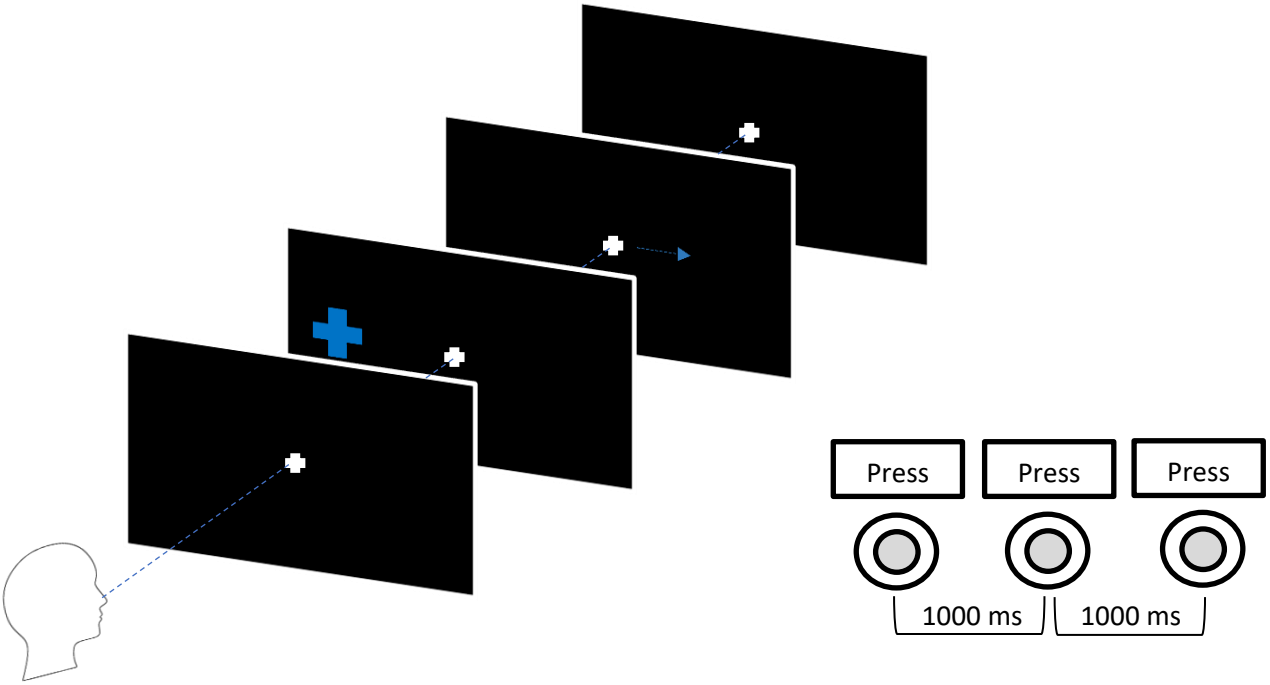

Figure 14. Illustration of the divided attention paradigm. (1) Participants repeatedly perform taps on a controller button and maintain taps 1000 ms apart. (2) Participant fixates a central cross and maintain central fixation when a non-target cross appears. (3) The non-target cross extinguished (4) Participant performs a saccade in the direction opposite to where the non-target cross appeared. (5) Participant reorients to the centre in preparation for the next trial.

The testing session comprised two trial types; single task trials, where participants were required to perform two discrete tasks independently, and dual task trials, where participants were required to perform the two discrete tasks concurrently. For the single task trials, participants completed an antisaccade task followed by a rhythmic button press task. For the antisaccade task, participants were firstly instructed to fixate onto a fixation cross presented at the centre of the screen. After a period of 1000ms, a blue peripheral cross was presented in either horizontal directions 10^{o} away from fixation. Participants were instructed to refrain from looking at the blue peripheral cross and make a saccade in the mirror opposite location as quickly and as accurately as possible. The blue peripheral cross was extinguished after 1000ms. This was accompanied by

the presentation of a re-fixation stimulus presented for 150ms, which served to redirect gaze back to centre prior the onset of next trial. The task comprised 24 trials, randomly, and even distributed to the left or right. See figure 14 for details.

5.2.4. Data analysis

Variables of interest were (1) latency (ms), defined as the time period between target onset and saccade onset, calculated using a velocity criterion of 30º per second, (2) error, defined as a saccade made towards the target, (3) press discrepancy, which reflected the temporal discrepancy between the demonstrated tonal rhythm and actual button press rhythm (% of misalignments), and (4) dual task performance, measured by comparing performance between dual task and single task conditions.

Trials were excluded from analysis of latency where 1) a saccade was performed towards the target, 2) a saccade was initiated within 100ms post target onset, 3) eye fixation fell >2º outside of the central fixation target and/or a blink occurred immediately prior to, during or after the initiation of a saccade affecting and interfered with saccade onset.

All data were analysed using repeated measures ANOVA (Condition: single-task, dual-task; Group: MS, Controls). An alpha level of .05 was set for all statistical tests and Bonferroni type adjustments made for all post hoc comparisons.

5.3. Results

5.3.1. Antisaccade latency

ANOVA revealed a significant main effect of Condition, F (1, 57) = 55.69, p < .001, with longer antisaccade latencies found for the dual-task condition, but no significant main effect of Group, F (1, 57) = 2.53, p = .12, or Group x Condition interaction F (1, 57) = .49, p = .49 (see Figure 15).

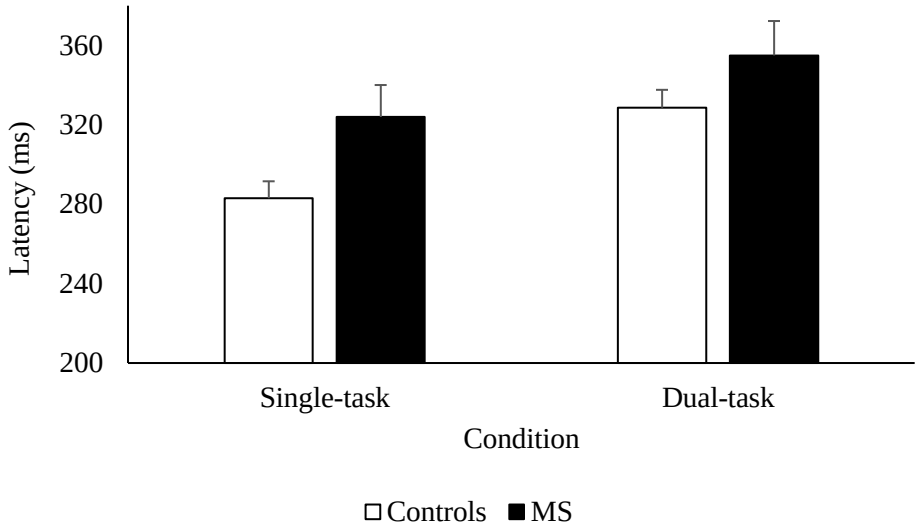

Figure 15. Antisaccade latencies for control and MS groups across single-task and dual-task conditions.

5.3.2. Antisaccade error

Errors were analysed as a proportion of total trials. ANOVA revealed a significant main effect of Condition, F (1, 56) = 9.22, p = .004, with more errors found for the dual-task condition, and main effect of Group, F (1, 56) = 9.28, p = .004, with more errors found for MS patients. No significant Group x Condition interaction was found, F (1, 56) = .015, p = .903 (see Figure 16).

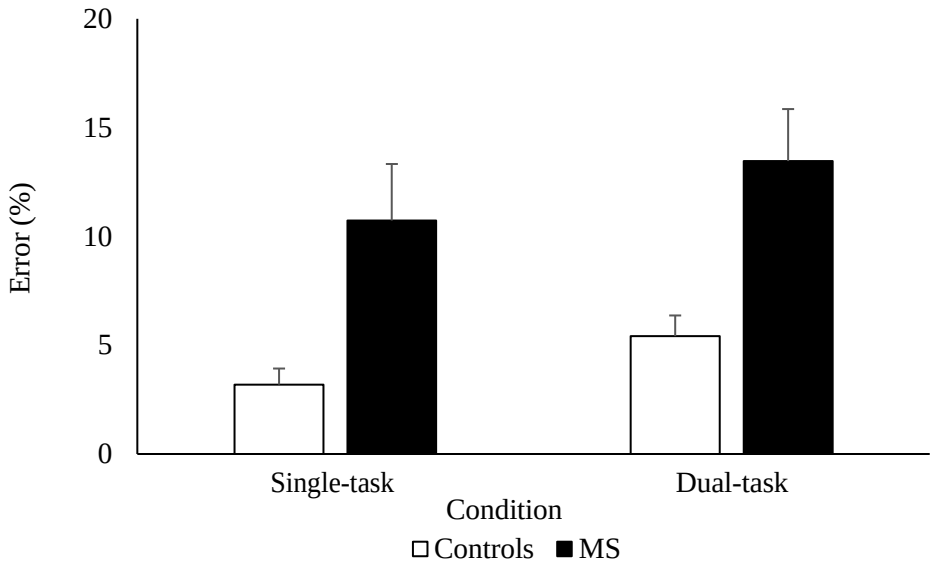

Figure 16. Antisaccade error rates for control and MS groups across single-task and dual-task conditions.

5.3.3. Press discrepancy

ANOVA revealed a significant main effect of Condition, F (1, 58) = 84.41, p < .001, with greater discrepancy found for the dual-task condition (see Figure 17). No significant main effect of Group, F (1, 58) = .107, p = .745 or Group x Condition interaction was found, F (1, 58) = .004, p = .95.

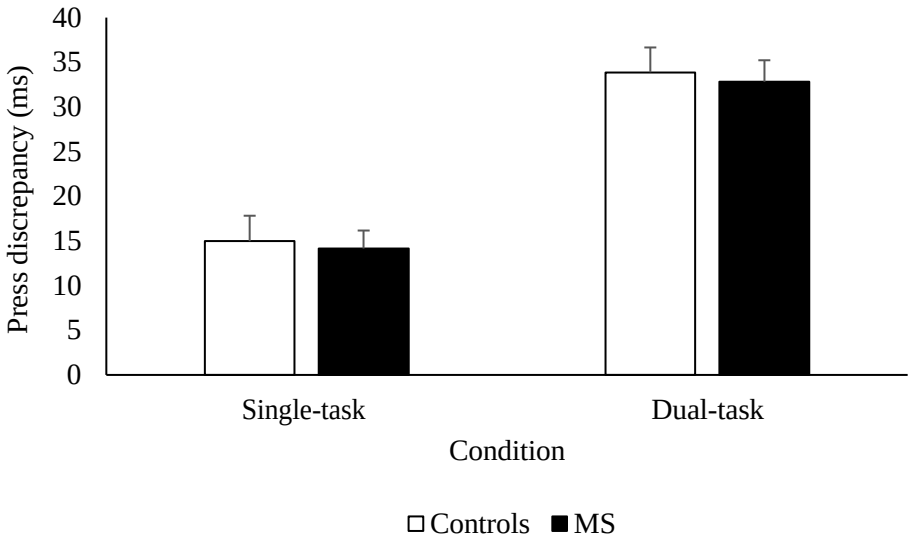

Figure 17. Press discrepancy for control and MS groups across single-task and dual-task conditions.

5.3.4. Neuropsychological tests

Table 7 presents the means and standard deviations for PASAT and SDMT scores.

Table 7*. Mean and standard deviation for neuropsychological tests*

	Controls		*MS*	
	M	*SD*	*M*	*SD*
PASAT	87.66	11.58	72.4[a]*****	21.45
SDMT	63.19	9.74	55.24[b]*****	13.45

*significantly different from controls: [a]$p = .003$, [b]$p = .013$

A series of Pearson's correlations were conducted between saccade metrics and clinical and neuropsychological measures for MS patients. To reduce the number of correlations, average latency and error rate across all conditions were used. Poor performance on the PASAT was related

to increased proportion of antisaccade errors, r = -.41, p = .04, r^2 = 16.81%, and prolonged latency, r = -.45, p = .02, r^2 = 20.25%. No correlations between SDMT performance and any saccade measure was found.

5.4. Discussion

The present study examined divided attention in MS by using a dual task design comprising an antisaccade task (cognitive task) and a simple button-press task (motor task). As expected, all participants exhibited a dual task decrement for both cognitive and motor tasks. Specifically, all participants exhibited increased antisaccade latencies and error rates, and a temporal discrepancy under the dual task condition relative to the single task condition. However, although MS patients generated more antisaccade errors compared to controls under individual and dual task conditions, they did not exhibit a significantly higher dual task decrement in either the cognitive or motor task.

Performing two or more tasks simultaneously requires that attentional resources be divided across the different tasks. According to resource sharing theory, attention can be construed as a central resource that can be assigned or allocated to different parts of the tasks, which enables parallel processing and simultaneous tasks performance (Kahneman, 1973; Pashler, 1994; Wickens, 1980). When tasks demand attentional resources that exceed the attentional limit, performance decrement of one or all tasks performed ensues (Gopher, 1980; Pashler, 1994). Consequently, in a disease like MS where attentional deficits are a known feature of the disease, it is thus surprising that a significantly larger dual task decrement was not found compared to controls. This finding may reflect the fact the tasks used in this study may not be difficult/complex enough to dissociate potential differences between MS patients and controls.

The competition for the limited attentional resources between various task events is influenced by a range of task factors, including the level of task complexity and task modalities (Gopher, 1980; Scerra & Brill, 2012; Wickens, 1980, 2008). Naturally, complex tasks that demand higher order processing consume higher levels of attentional resources than simple, relatively automated tasks, and completing two high complexity tasks simultaneously would necessarily create a stronger interference effect/performance decrement than completing a complex task with simple task simultaneously (Gopher, 1980). Interestingly, compared to controls, patients only exhibited impaired performance on the antisaccade task and not the button-pressing task. The difference here suggested that that the antisaccade task was a relatively attentionally demanding task that, when completed with another task, places a higher cognitive load overall and exhausts attentional capacity. Indeed, antisaccade errors also correlated with PASAT scores, a neuropsychological measure commonly used in MS to measure cognitive function.

Conversely, the motor button pressing task was a relatively automatic and adapted task, that when paired with another task, might not necessitate the level of attentional demand that would differentiate performance between member groups. This explanation could also explain why this study failed to find a dual task decrement when other studies in MS have. Other studies have required the completion of two complex tasks together (e.g. neuropsychological and walking tasks).

Although unlikely, given the disease severity scores of many of the patients tested, it is conceivable that performance deficits might have been masked/partly driven by compensatory mechanisms often observed in MS patients. Indeed, multiple imaging studies reveal compensatory changes in MS accompanied by stable cognitive task performance (Lopez-Gongora et al, 2015; Audoin, et al, 2003; Staffen et al, 2002; Franklin, Edgar, & Smith, 2012; López-Góngora et al.,

2015). Neuro-compensation is formation of new communication pathways via recruiting additional brain regions (Bonavita et al., 2011; Victoria M Leavitt, Wylie, Genova, Chiaravalloti, & DeLuca, 2012; Loitfelder et al., 2011). Past research has shown that MS patients exhibit compensatory changes in prefrontal regions during dual tasking, revealing stronger activation of the prefrontal cortex and recruitment of an increased number of regions compared to controls during dual task performance (Chaparro et al., 2017). To further explore divided attention in MS, future studies are encouraged to employ more complex motor tasks or explore different levels of complexity.

Chapter 6: Attentional Performance and Patient Disability

6.1. Introduction

It is evident from the results of the previous chapters in this thesis that MS patients exhibit deficits across multiple attentional sub-domains; specifically, (Chapter 3) attentional orienting, MS patients exhibited significantly prolonged latencies, an altered response profile, with IOR evident at a later time point than controls, and increased errors in MS patients; (Chapter 4) selective attention, MS patients performed a higher proportion of errors towards non target stimuli; (Chapter 5), divided attention, MS patients generated an increased proportion of errors towards non-target stimuli. However, the degree of cognitive impairment is known to worsen with advancing disease, with the magnitude of existing deficits and the number of domains implicated increasing as the disease worsens (Amato et al., 2001). Consequently, what is unclear from the results presented thus far in this thesis is whether these OM attentional deficits emerge only as a consequence of more advanced disease, or whether a specific and dissociable pattern of deficits is evident at milder disease compared to more advance disease.

This chapter aimed to explicitly investigate the effect of increased disability (EDSS) on performance on each attentional task investigated in this thesis. Further, this chapter aimed to determine whether certain OM attentional measures better discriminated patients with low disability from high disability, and whether this was similarly evident on the current gold standard measures of cognition used in MS (PASAT and SDMT).

6.2. Methods

6.2.1. Participants

Patients and controls included in this chapter represent a subset of patients from previous experimental chapters (Chapter 3, Chapter 4, Chapter 5). The MS group was dichotomised into two subgroups based on their EDSS scores: (1) low disability, EDSS $\leq$ 2; (2) high disability > 2. Table 8 contains the new descriptive statistics for the new MS groups as well as the descriptive statistics for the control group.

Table 8. *Descriptive statistics for controls, low and high disability groups*

	n	*Age*	*BDI*	*NART*	*Disease duration (Months)*	*EDSS*
Controls	33	37.7 (8.75)	5.63(.78)	118.27(.94)	-	-
Low Disability	15	38.53 (9.88)	8.00(2.21)	115.63(1.51)	74.53 (82.57)	.53 (.61)
High Disability	12	50 (11.34)	9.61(2.06)	105.85(8.88)	120.46 (69.6)	3.54 (1.26)

6.2.2. Materials

Description of experimental setup and tasks can be found in the relevant chapters: Chapter 3: Attentional orienting (page 50), Chapter 4: Selective attention (page 67), Chapter 5: Divided attention (page 83). For neuropsychological measures (PASAT, SDMT) a full description can be found in the general methods section (Chapter 2). Below is a brief description of the OM attention task variables pertinent to the analyses performed in this chapter

6.2.3. OM attention tasks

1) Attentional orienting:

Two trial types were assessed. Trial *type* was determined by the type of cue presented prior to target onset:

- valid trial: the peripheral cue was presented in the location corresponding with the subsequent target
- invalid trial: the peripheral cue was presented in the location opposite to the subsequent target.

Valid and invalid trials occurred pseudo-randomly, with equal probability (64 trials each) to ensure that cues were non predictive of target location. Catch trials comprised presentation of cue but no subsequent target, and served to discourage anticipatory responses. Neutral trials, typically presented to ascertain the relative influence of either trial type, were not included in this study to minimise the impact of fatigue, known to detrimentally impact performance in MS patients. Four stimulus onset asynchronies (SOAs) were examined, and represented the fixation intervals between cue presentation and the onset of the target cross: 67, 150, 300, 500ms.

2) Selective attention

Four conditions were assessed, with each condition representing a unique target spatial position, either with or without a competing non-target:

- 4^{o} target *without* a competing non-target (N4)
- 4^{o} target *with* a competing non-target (C4)
- 8^{o} target *without* a competing non-target (N8)
- 8^{o} target *with* a competing non-target (C8).

Trials presentation was randomised. An even number of trials was performed for each condition (i.e., 12 trials per condition).

3) Divided attention

Two trial types were assessed.

- single task trials; participants were required to perform an antisaccade task and a rhythmic button press task independently.
- dual task trials; participants were required to perform an antisaccade task and rhythmic button press task concurrently

6.2.4. Data analysis

6.2.4.1. Latency

For all tasks, saccade latency (ms) was calculated from a monocular recording as the temporal difference between target and saccade onset with saccade onset/offset calculated using a velocity criterion of 30^{o} per second. Trials were excluded from analysis of latency where, 1) a task relevant error was performed (see descriptions below), 2) a saccade was initiated within 100 ms post target onset, 3) central fixation fell >2^{o} outside of the central fixation target and/or a blink occurred immediately prior to, during or after the initiation of a saccade affecting and interfered with saccade onset.

6.2.4.2. Errors

1) Attentional orienting (errors): saccades performed in response to the cue either prior to target presentation (valid trials and invalid trials) and/or upon target presentation (invalid trials only).

2) Selective attention: saccades performed to a competing non-target. Consequently, errors were only evident during the compete conditions (C4 and C8), and were calculated as the proportion of competing trials for each spatial condition (12)

3) Divided attention: saccades performed to the target cross (antisaccade task)

Statistical analyses were only performed for variables that were reported as significant within previous chapters.

6.3. Attentional Orienting Task

6.3.1. Latency

Overall, a significant effect of group was found for all SOA/cue type permutations, except for valid 300 and valid 500; valid 67 F (2, 59) = 5.83, p = .005, valid 150 F (2, 59) = 4.90, p = .01, invalid 67 F (2, 59) = 9.98, p < .000, invalid 150 F (2, 59) = 6.35, p = .003, invalid 300, F (2, 59) = 5.84, p = .005, invalid 500 F (2, 59) = 5.43, p = .007 . For significant effects, post hocs revealed that the high disability group had significantly prolonged latencies compared to controls for all SOA/cue type permutations; valid 67 p = .026, valid 150 p = .016, invalid 67 p < .000, invalid 150 p = .002, invalid 300 p = .005, invalid 500 p = .005. In comparison, the low disability only demonstrated significantly prolonged latencies compared to controls for the shortest SOA irrespective of cue type; valid 67, p = .023, invalid 67, p = .028. Lastly, the high disability group

only demonstrated significantly prolonged latencies compared to the low disability at one SOA/cue type; invalid 300, $p = .024$.

6.3.2. IOR profile

As reported in Chapter 3, controls revealed the classic IOR effect, with latencies for valid trials comparatively shorter than invalid trials for both 67 ms ($p < .000$) and 150 ms ($p = .001$) SOAs, with this effect reversing at later SOAs (IOR), with relatively *longer* latencies for valid trials with SOAs of 300 ms ($p = .28$) and 500 ms ($p < .000$); IOR emerged between 150 and 300 ms. Further, analyses revealed that the IOR was generated by modulation of latency with increasing SOA for both cue types, with valid trials demonstrating a significant increase in latency with increasing SOA, F (3, 93) = 20.24, p = .000, and invalid trials demonstrating a significant decrease in latency with increasing SOA, F (3, 96) = 9.5, p = .001. (see Figure 18)

Similar to controls, the low disability MS group revealed a comparable IOR effect with IOR emerging between 150 and 300ms, and evident as latencies for valid trials being significantly shorter than invalid trials for both 67 ms ($p = .003$) and 150 ms ($p = .04$) SOAs, and latencies significantly *longer* for valid trials at later SOAs: 300 ms ($p = .40$) and 500 ms ($p = .009$); IOR emerged between 150 and 300ms. Again, similar to controls, the IOR effect was generated by modulation of latency across SOA for both cue types with valid trials demonstrating a significant increase in latency with increasing SOA, F (3, 42) = 3.37, $p = .027$, whilst invalid trials demonstrated a significant decrease in latency with increasing SOA, F (3, 42) = 10.18, $p = .001$.

In contrast to both controls and the low disability group, the high disability group did not reveal an IOR effect within the SOAs used in this experiment. Specifically, latencies for valid trials were significantly shorted than invalid latencies for 67 $p = .001$, 150 $p = .004$ and 300 $p =$

.013, with no difference found for 500 SOA, $p = .55$. Further analyses revealed that the absence of IOR was due to neither cue type demonstrating latency modulation with increasing SOA: valid, $F(3, 33) = .78$, $p = .51$, invalid cues, $F(3, 33) = 1.77$, $p = .17$.

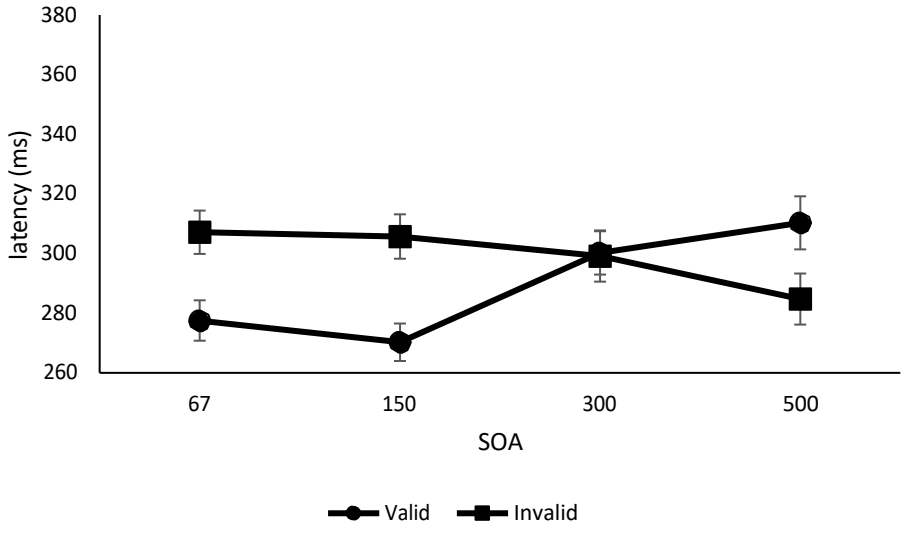

Figure 18. Valid and invalid trial latencies for controls

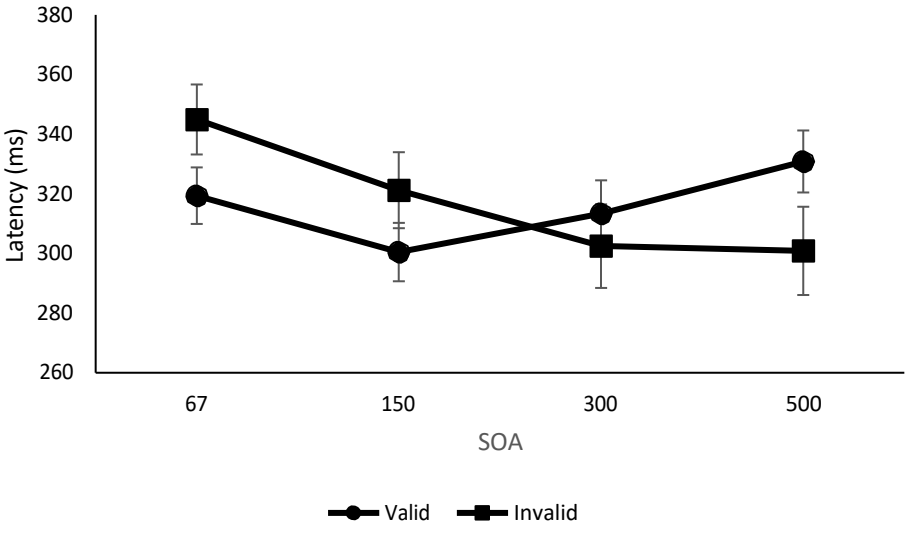

Figure 19. Valid and invalid trial latencies for the low disability group

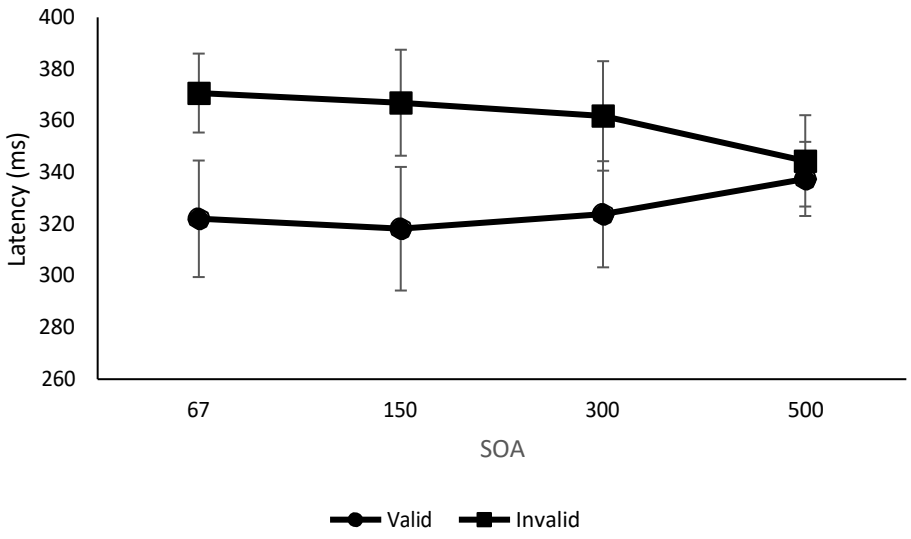

Figure 20. Valid and invalid trial latencies for high disability group

6.3.3. Errors

A significant effect of group was found for valid cue 67 F (2, 58) = 3.21, p = .04, and 150 F (2, 59) = 4.21, p = .02, and invalid cue 500 F (2, 59) = 4.89, p = .01. For significant effects, post hocs revealed that the high disability group performed significantly more errors than controls for valid cue 150 (p = .02) and invalid cue 500 (p = .01). In contrast, no difference in error rate was found between the low disability group and controls, or between the low and high disability groups (see figure 21).

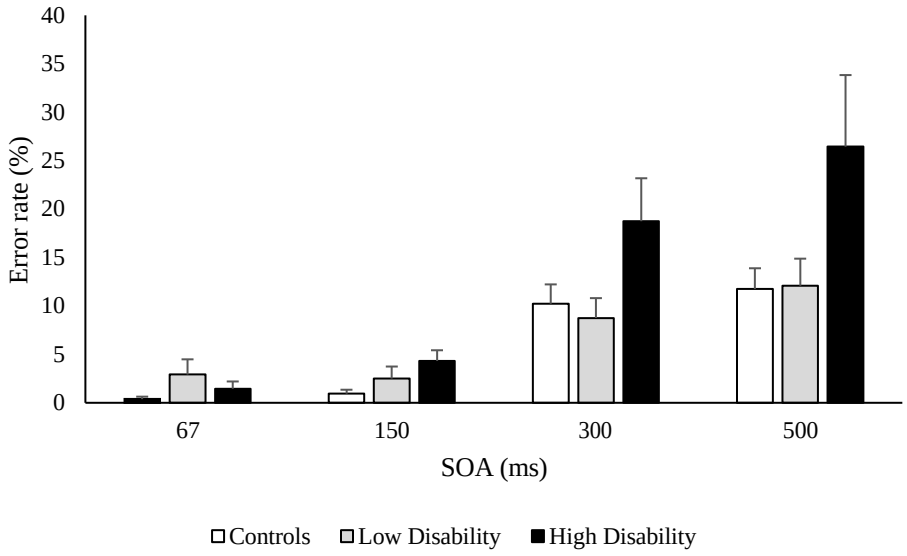

Figure 21. Error rates for controls, low disability and high disability groups

6.4. Selective Attention Task

6.4.1. Errors

A significant effect of group was found only for the 8 degree spatial location F (2, 60) = 5.17, p = .009. Post hoc analyses revealed that controls performed significantly less errors than both the high disability group (p = .004) and the low disability group (p = .04). No other differences were found (see figure 22).

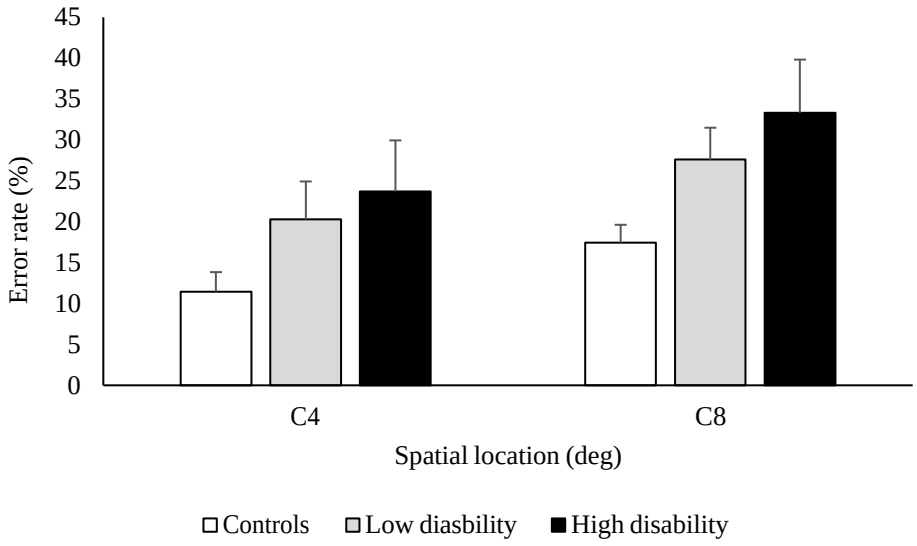

Figure 22. Error rates as function of non-target location for controls, low disability MS and high disability MS groups.

6.5. Divided Attention Task

6.5.1. Errors

A significant effect of group was found for both the single task condition (F (2, 57) = 6.97, p = .002) and the dual task condition (F (2, 57) = 6.67, p = .003). Post hoc analyses revealed that the high disability group performed significant more errors than controls for both conditions; single task p = .008, dual task p = .015, and the low disability group performed significantly more errors than controls on the dual task condition only, p = .027. No significant differences were found between the high and low disability groups (see figure 23).

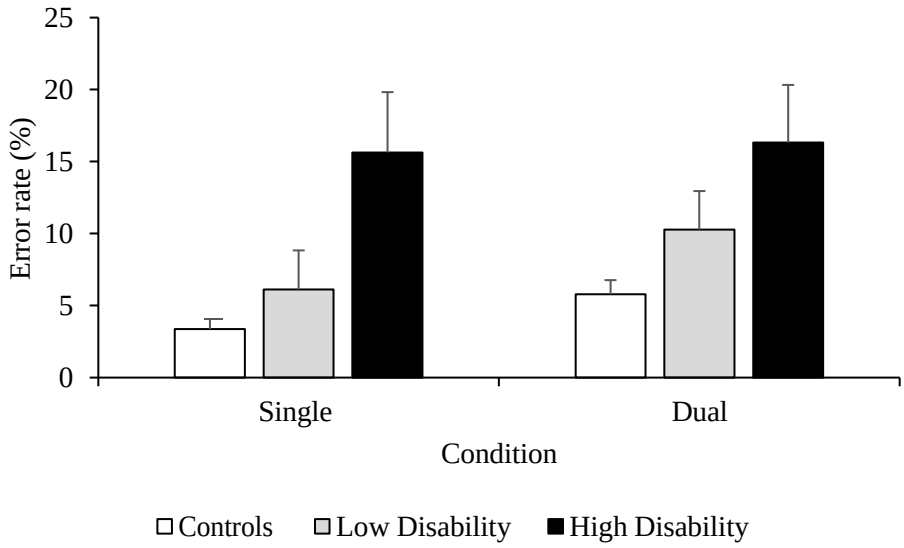

Figure 23. Antisaccade error rates for single and dual task conditions across groups.

6.6. Neuropsychological tests

6.6.1. PASAT

A significant effect of group was found, F (2, 57) = 7.35, p = .001. Post hoc analyses revealed that the high disability group (M = 61.16, SD = 24.03) performed significantly worse than controls (M = 87.22, SD = 11.67), p = .001. However, no difference between controls and low disability groups, and low disability and high disability groups was found.

6.6.2. SDMT

A significant effect of group was found, F (2, 57) = 9.07, p < .000. Post hoc analyses revealed that the high disability group performed significantly worse than controls (p < .000) and the low impairment group (p = .013). However, no difference was found between the low and high disability groups.

Table 9. *Neuropsychological tests scores*

	n	*PASAT*	*SDMT*
Controls	33	87.22(11.67)	63.19(9.74)
Low Disability	15	82.97(11.68)	60.13(12.51)
High Disability	12	61.16(24.03)	47.75(10.73)

6.7. Discussion

Overall, by subgrouping the MS group into those with high and low disability, it was revealed that the high disability group performing significantly differently from controls on all tasks. However, tasks with higher executive requirements (selective attention task, divided attention task), were able to dissociate between patients with low disability and controls. This was not similarly evident from performance on standard neuropsychological measures.

Collectively, it would appear that for those with low disability, attentional deficits are largely isolated to be cognitively challenging tasks that require engagement of executive control. However, as the disease progresses, wider implication of attentional domains occurs and subconscious attentional processes (attentional orienting) become compromised. This will be discussed in further detail in the general discussion.

Chapter 7: General Discussion

7.1. General Discussion

MS is a debilitating disease of the central nervous system, with unclear aetiology and disease pathology (Bishop & Rumrill, 2015; Ransohoff, Hafler, & Lucchinetti, 2015). Although widely understood as a disease affecting sensory and motor processes, cognitive symptoms are an early and prominent symptom of the disease (DeLuca et al., 2015), with a profound impact on quality of life (Feuillet et al., 2007; Langdon, 2011; Prayoonwiwat et al., 2009). As previously discussed, cognitive deficits have been shown to occur across a number of domains, and are variously reported as deficits of working memory, information processing speed, episodic memory, executive functioning, and attention (Amato et al., 2010; Strober, Rao, Lee, Fischer, & Rudick, 2014). There is a body of evidence that suggests that attentional deficits are an especially common feature. However, attention is not a unitary construct, comprising instead, a set of sub processes or sub domains that, under certain circumstances, function to facilitate the processing of relevant information and inhibiting or filtering of irrelevant information. Currently it is unclear how MS affects these attentional sub domains, and whether deficits occur in isolation or are globally effected. The purpose of this thesis was to contribute to a greater understanding of attentional deficits in MS, by exploring some its sub domains.

Ocular motor tasks were used to investigate three subdomains of attention, orienting, selecting, and dividing. These sub-domains were selected to reflect various levels of complexity, from basic attentional orienting, to more challenging selective and divided attention. In order of complexity, the following tasks were administered:

1. Attentional orienting:
    a. Evaluates the *subconscious* process dubbed ‘Inhibition of Return’, which prolongs the return of attention to a previously attended location

b. Evaluates the capacity to inhibit a reflexive saccade towards a suddenly appearing non-target stimulus

2. Selective attention:
    a. Evaluates the capacity to inhibit of a response to one of two task-related stimuli prior to the selection of a 'correct' target
    b. Evaluates the capacity to select and response to a 'correct' target
3. Divided attention:
    a. Evaluates the capacity to efficiently carry out an attentional task while simultaneously engaged in a second task
    b. Evaluates the capacity to inhibit a reflexive response to a suddenly appearing non-target stimulus AND redirect gaze in the opposite direction

Finally, this thesis aimed to explicitly investigate the effect of disability level on performance on each attentional task investigated, determining whether certain OM attentional measures better discriminate patients with low disability from those with high disability (EDSS).

The following table summarises the results of this study.

Attention Sub-domain	**Key Findings**	**Conclusions**
Attentional Orienting	MS vs. controls (Chapter 3) • Delayed IOR • Increased proportion of errors Disability level sub-analyses (Chapter 6) • IOR absent for high disability group • IOR comparable to controls for low disability group • Increased proportion of errors for high disability group only	• Deficient, cortically driven inhibitory tag • Impaired inhibitory control • Results driven by high disability group
Selective Attention	MS vs. controls (Chapter 4) • Increased proportion of errors Disability level sub-analyses (Chapter 6) • Increased proportion of errors for both low and high disability groups	• Failure to inhibit a response to a task-related stimulus • Impaired conflict monitoring/ resolution • Both low and high disability groups impaired
Divided Attention	MS vs. controls (Chapter 5) • Increased proportion of antisaccade errors for both single and dual task conditions • No significant difference in dual task decrement Disability level sub-analyses (Chapter 6) • Increased proportion of errors for single and dual task conditions for high disability group. • Increased proportion of errors for dual task condition only for low disability group	• Impaired inhibitory control/conflict resolution • Secondary task insufficiently complex to promote dual task decrement • Both low and high disability groups impaired

The results presented above demonstrate that MS patients exhibited deficits across all attentional tasks. Specifically, MS patients generated a larger proportion of erroneous responses, irrespective of task complexity, highlighting an overall failure of inhibitory control, from the most basic of tasks requiring a participant to stop an inappropriate response (attentional orienting) to the more complex behaviours governed by executive processes. These executive processes involve the suppression and selection, or interpretation of competing responses, with tasks evaluating conflict resolution and error monitoring capacity.

Interestingly, when level of disability was factored into these analyses, inhibitory deficits were exacerbated with greater levels of disability, with those with the highest EDSS scores exhibiting inhibitory control deficits across all tasks and those with low EDSS scores only exhibiting deficits for more complex, or executive attentional tasks. This demonstrates that executive attentional deficits may become evident only with greater levels of pathology.

7.2. Attention and inhibitory control

Attention refers to the ability to select and enhance the processing of a subset of information from the environment, while filtering out any unwanted, or irrelevant information. These processes, which help prioritise the processing of information, are thought to be driven the constant competition between top down control, that directs attention based on internal goals, and bottom up activity, that directs attention based on external novelty and unexpected events. On a neural level, the ‘winner’, as determine by relative activation, determines where attention is eventually deployed. Two prominent models are those of (1) Posner (Petersen & Posner, 2012), which characterises attention as comprised of three components with distinct underlying networks: alerting, orienting and executive attention, and (2) Corbetta (Corbetta & Shulman, 2011), which proposes two anatomically integrated but distinct networks that guide these processes; the DAN,

which exerts top-down cognitive control by assessing the salience of stimuli based on pre-existing goals, and the VAN, which allows the reorienting of attention and enables attentional vigilance by maintaining arousal. As discussed earlier, each model recognises the same basic attentional processes (i.e. arousal/vigilance, selection, shifting and goal-directed attention). For both models, more posterior and inferior structures (including subcortical nuclei) modulate bottom-up attentional processes, and more anterior structures exert top-down control such as response inhibition and the orienting of attention based on pre-existing goals. Corbetta's DAN is analogous to Posner's orienting and executive components of attention, and Corbetta's VAN is analogous to Posner's alerting component.

A synthesis of these models is provided by Cohen (2014), who proposes a 'general attention model' with an overall flow of information from sensory cortex, to subcortical nuclei, to posterior cortex, to anterior cortex, to the brainstem. Here visual information is projected to the lateral geniculate nucleus in the thalamus and SC, as well as the midbrain reticular system which facilitates arousal in order to attend to a stimulus. Visual information then reaches the primary visual cortex where projections extend to the parietal and superior temporal cortices and then on to frontal and limbic areas including the prefrontal cortex and the anterior cingulate cortex. These frontal regions are thought to provide top-down control of attention by controlling responses based on higher-order information such as goals and motivation. Consistent with the aforementioned models, there is an anterior/posterior dichotomy; simplistically, more subcortical and posterior structures facilitate bottom-up processing of attention, and more anterior structures top-down control of attention, including response inhibition (Cohen, 2014).

7.3. Attention and inhibitory control in MS

7.3.1. Attentional orienting

For the attentional orienting task, a delayed IOR in MS suggests deficit at the most basic or even subconscious level of attention, although specifically of inhibitory control. While it is still not entirely clear how IOR develops, it is often assumed that IOR is a consequence of an inhibitory tag (Dukewich & Klein, 2015) which registers and maps the location of a previously attended location, presumably within parietal regions, and which in turn attenuates the preparatory activity in the SC for the tagged location, delaying a response. Importantly, this inhibitory tag appears to be compromised only with more advanced disease (i.e. in the high EDSS disability group), consistent with failure across a more extensive network. Likewise, an increased proportion of errors on this task was compromised only for the high EDSS disability group, again suggesting inhibitory failure in the context of relatively low attentional demands. Greater disability, likely equates to greater disease burden, with greater potential for network dysfunction. Importantly, for this task, the cue bears no relationship to the subsequent task, which simply requires participants to *ignore* the irrelevant cue and generate a saccade towards a peripheral target. This is arguably represents the simplest (most basic) form of inhibitory control, with relatively less involvement of prefrontal control.

7.3.2. Selective attention

Increased selection errors in MS similarly suggests inhibitory failure, although where the demands of the task require a participant to covertly determine which of two visual stimuli is the correct target before generating a self-directed saccade towards that target. Thus, the task requires both a greater level of top down inhibitory control (inhibiting an overt response while covertly

orienting towards the target for informational content) and the generation of a separate volitional response to a target stimulus, i.e. represent a conscious decision. The relatively normal latencies in MS for saccades where there is no competing stimulus, are consistent with previous literature (Fielding et al., 2009b). Unlike the attentional orienting task, both MS groups performed more poorly on this task, arguably a consequence of greater attentional demands, and the implication of a more extensive inhibitory network.

7.3.3. Divided attention

The finding of no dual task decrement for MS patients suggests the secondary task used here may not have been sufficiently disruptive to the primary task. However, the proportionately larger error rate for antisaccades, with or without a secondary task, are again consistent with poor inhibitory control. Like the selective attention task, this task requires both top down inhibitory control (inhibiting an overt response while covertly orienting towards the target for informational content) and the generation of a separate response to a target stimulus. Again both high and low disability groups generated significantly more errors, however, for the low disability group, only in the context of the secondary task. Seemingly, performing the antisaccade task alone, may have been less onerous than either the combined antisaccade/tapping task or the selective attention task for those with less disability.

7.4. Executive control and response conflict

Executive control refers to the ability to flexibly adapt behaviour according to task rules or goals, which support complex behaviours like setting goals, focusing on a task, and making a decision (Coutlee & Huettel, 2012). Integral here, is the capacity to selectively attend, and respond

to, task relevant information while ignoring interference from information that is not relevant to the task. These opposing facilitatory and inhibitory processes enable the execution of an appropriate response, as well prevent an erroneous response (Brydges et al., 2012). It is thought that a conflict monitoring system firstly detects conflict then executive processes resolve this conflict via attentional mechanisms that bias information processing in favour of task relevant versus task irrelevant information (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Egner & Hirsch, 2005).

A range of studies have demonstrated a 'control-conflict loop' that consists of the ACC, pre-supplementary area (preSMA) and DLPFC, with evidence that conflict monitoring and detection takes place within the ACC and preSMA (Botvinick et al., 2001; Egner & Hirsch, 2005; Gratton, Cooper, Fabiani, Carter, & Karayanidis, 2018). Once conflict is detected, the ACC engages executive control via reciprocal connections with prefrontal cortex, activating the DLPFC. Collectively, this top-down control culminates in successful task completion (i.e. inhibiting an erroneous response and executing an appropriate response) (Botvinick et al., 2001; Coutlee & Huettel, 2012; Egner & Hirsch, 2005; Gratton et al., 2018).

Failure to correctly respond to a task requiring executive control may represent failure to actively maintain goal relevant information rather than a failure to inhibit a reflexive response per se. This may be conceptualised as working memory, which implicates thalamo-cortico-striatal circuits connecting prefrontal cortex and basal ganglia with the thalamus. The integrity of this closed circuit is crucial to successfully maintaining goal relevant information and, subsequently executing a goal relevant response (Awh & Vogel, 2008; Baddeley, 2012).

7.5. Executive control and response conflict in MS

The findings presented within this thesis provide evidence of impaired executive control in MS, irrespective of level of disability, reflecting impaired conflict resolution. MS patients are more likely to respond in a reflexive manner rather than inhibiting a more automatic response in favour of a controlled volitional response. These results support previous findings from a small body of literature that has demonstrated executive control deficits in MS (Clough, Millist, Lizak, Beh, et al., 2015; Dobryakova et al., 2016; Ferreira et al., 2018; Fielding, Kilpatrick, Millist, Clough, & White, 2012a; Ternes et al., 2019a; Ternes, Clough, Foletta, White, & Fielding, 2019b).

The successful completion of any attentional task requires actively maintaining task relevant information. Throughout a task which generates conflict, like either the selective attention or the divided attention task herein, it is thought that the executive control system resolves this conflict by upregulating the processing of task relevant information, rather than inhibiting the processing of task irrelevant information (Egner & Hirsch, 2005; Munakata et al., 2011; Sheu & Courtney, 2016). This is reliant on the integrity of neural transmission within fronto-striatal circuitry, where any reduction in capacity (e.g. impaired transmission as a consequence of lesion load or neural degeneration) may result in a failure to activate a controlled or volitional response, resulting in the reflexive execution of an erroneous response (Awh & Vogel, 2008; Baddeley, 2012; Gratton et al., 2018).

In MS, cortico-striatal regions that are key to successful executive control, are susceptible to volume loss and altered connectivity (Bergsland et al., 2012; Calabrese et al., 2015; Orbach, Menascu, Hoffmann, Miron, & Achiron, 2018). Previous studies have also demonstrated a relationship between frontal pathology and executive control deficits (Dobryakova et al., 2016;

Ternes et al., 2019a, 2019b), shedding light on the neuropathological underpinnings on the deficit described herein.

7.6. Significance

Behaviourally, our capacity to inhibit or control an inappropriate response in favour of an appropriate response is adaptive. For example, it ensures that we suppress the urge to behave in a socially inappropriate way, or complete a job without becoming distracted. Accordingly, impaired attentional control has the potential to significantly impact our quality of life (Munakata et al., 2011). Providing a greater understanding of the underlying deficit in MS patients has the potential to assist in the management of this often debilitating symptom.

This research in MS, while not exhaustive in terms of sub-domains investigated, demonstrates that only patients with a relatively high level of disability, exhibit deficits during tasks requiring very low level inhibitory control, but all patients irrespective of level of disability, experience difficulty with task requiring the resolution of response conflict. This suggests that inhibitory dysfunction in MS does not represent a global failure of inhibition. Therefore, those assessing cognitive function in an MS patient with low disability should be aware that tasks that measure more basic response suppression are unlikely to reveal deficit, however this is not necessarily indicative of intact inhibitory control. Changes in performances may be evident using more complex tasks requiring executive control.

At present, there is no specific treatment for the cognitive symptoms of MS, and the capacity for current medications to halt or slow the progress of cognitive changes is limited (Niccolai, Goretti, & Amato, 2017). However, there is an emerging literature that focuses on developing targeted cognitive rehabilitation strategies in, with the potential to restore, to some

degree, cognitive function, largely by implementing compensatory strategies to reduce its functional impact. These interventions primarily involve using cognitive compensatory strategies, and computer-assisted cognitive rehabilitation. (e.g. internal and external compensatory strategies including mnemonics, using daily planner, computerized memory training programs). Developing theoretical and physiological models of MS-specific cognitive symptoms will crucially inform these techniques (Sumowski et al., 2018). This research demonstrates that while inhibitory control deficits might be process specific, and dependent upon the patients overall level of disability, deficits are globally evident when a task requires the active maintenance of goal-relevant information in the presence of conflicting stimuli. In patients with lower level disability, future interventions should target these higher order behaviours, and switch focus to more simple behaviours involving the suppression of a reflexive responses to an irrelevant stimulus in patients with greater disease burden.

7.7. Limitations/future directions

Limitations and recommendations specific to each experimental study have been outlined within the relevant chapters. Briefly, for the attentional orienting task it remains unclear whether, or if, the typical prolongation of latencies for validly cued trials, which presumably reflects the application of an inhibitory tag, occurs at a later time-point in MS. Further, neutral and bi-directional trials were not included, disallowing a cost/benefit analysis. Extending SOAs and including neutral cues were suggested for further studies. For the selective attention task, assessment was restricted in terms of complexity. Varying the saliency of the competing non-target, and detecting where selectivity falters, was proposed, to add to an understanding of selective attention in the individual patient. For the divided attention task, the greatest limitation was the fact that we were unable to demonstrate dual task decrement in MS. This was unexpected, given

the reduced processing efficiency in these individuals. This was considered a consequence of

choosing a very simple secondary task. Future studies were encouraged to consider a more attentionally challenging second task.

However, there are a few limitations applicable to all studies. Firstly, these analyses were restricted to the assessment of only three attentional sub-domains. Assessment of a more comprehensive range of sub-domains would inevitably facilitate a more extensive characterisation of deficit, in turn informing therapeutic intervention. Secondly, the sample of participants characterised in the current studies were all those with a relapsing-remitting time course. The sample did not include patients with more progressive MS, nor did it include those with CIS. Extending this investigation to a broader range of patients may lead to identifying the key stages at which these symptoms emerge and progress, again informing therapeutic intervention.

Thirdly, these results derive from a relatively small sample of patients. While this provided adequate power for the analyses adopted herein, a larger sample would inevitably facilitate more sophisticated and potentially more informative analyses. For example, this might allow the subdivision of groups beyond level of disability, such as those with and without cognitive impairment, or those with/without neuropathological changes within discrete regions of cortex, and allow the assessment of differing MS phenotypes.

Finally, this work payed little attention to the likelihood of information processing speed (IPS) deficits in these individuals. While latencies for the attentional orienting task were longer than controls, and acknowledged as representing impaired IPS, comparable latencies found across the other tasks were largely overlooked in favour of focusing on clearly attentional deficits. It is likely that, in MS, latencies reflected a combination of both IPS changes and the inclusion of more reflexive responses. Further studies might investigate this 'trade-off' with larger studies.

7.8. Concluding remarks

Attentional deficits are now widely recognised as a core and debilitating symptom of MS. They emerge early in the disease course and may affect a range of sub-domains. While impaired attentional control has been reported previously, an understanding of whether the various sub-domains are differentially affected remains elusive. The research presented herein suggests that while inhibitory control deficits occur globally in MS, sub-domain specific deficits appear dependent upon a patient's level of overall disability. Only those patients with high levels of disability were impaired on the simplest task presented, specifically the task placing few attentional demands on patients, simply requiring the suppression of a reflexive response to a task-irrelevant visual stimulus. All patients demonstrated some level of deficit, irrespective of disability, in the context of competing inhibitory and facilitatory processes, i.e. those tasks that generated response conflict. This likely occurs due to neuropathological changes which more extensively encompass wide ranging fronto-striatal circuitry. This extended characterisation of deficit represents a first-step in the comprehensive characterisation of attentional deficit in these individuals, with the potential to help inform the development and implementation of cognitive and pharmaceutical interventions targeting attentional changes in MS.

Chapter 8: References

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