INTRA-INDIVIDUAL VARIABILITY IS AN IMPORTANT CHARACTERISTIC OF COGNITIVE FUNCTIONING IN PERSONS WITH MULTIPLE SCLEROSIS

by

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TABLE OF CONTENTS

LIST OF TABLES ..... **vii**

LIST OF FIGURES ..... **viii**

ABSTRACT ..... **ix**

LIST OF ABBREVIATIONS USED ..... **x**

ACKNOWLEDGEMENTS ..... **xiii**

CHAPTER 1: INTRODUCTION **1**

1.1. OVERVIEW OF MULTIPLE SCLEROSIS 1

1.2. COGNITIVE DEFICITS IN MS 5

1.3. INTRA-INDIVIDUAL VARIABILITY IN PERFORMANCE 10

1.4. RESTING-STATE FUNCTIONAL CONNECTIVITY 14

1.5. RESTING-STATE FUNCTIONAL CONNECTIVITY IN CLINICAL POPULATIONS 18

1.6. SUMMARY AND STUDY AIMS 22

CHAPTER 2: INTRA-INDIVIDUAL VARIABILITY AS A MEASURE OF INFORMATION PROCESSING DIFFICULTIES IN MULTIPLE SCLEROSIS **26**

2.1. OVERVIEW 26

2.2. PUBLICATION STATUS AND AUTHOR CONTRIBUTIONS 27

2.3. ABSTRACT 28

2.3. INTRODUCTION 29

2.4. METHOD 32

2.4.1. PARTICIPANTS *32*

2.4.2. PROCEDURE *33*

2.4.3. MEASURES *33*

2.5 RESULTS 34

2.5.1. DEMOGRAPHICS *34*

2.5.2. MEAN LEVEL PERFORMANCE ON CTIP *34*

2.5.3. VARIABILITY ON CTIP *35*

2.5.4. PREDICTING GROUP MEMBERSHIP *37*

2.6 DISCUSSION 37

2.7 SUMMARY 46

CHAPTER 3: INTRA-INDIVIDUAL VARIABILITY, PROCESSING SPEED, AND ATTENTION NETWORK EFFICIENCY IN MULTIPLE SCLEROSIS 47

3.1. PUBLICATION STATUS AND AUTHOR CONTRIBUTIONS 47

3.2. ABSTRACT 48

3.3 INTRODUCTION 49

3.4 METHOD 51

3.4.1. PARTICIPANTS *51*

3.4.2. CLINICAL MEASURES *52*

3.4.3. ATTENTION NETWORK TEST-INTERACTIONS (ANT-I) *53*

3.4.4. DATA ANALYSIS *54*

3.5 RESULTS 54

3.6 DISCUSSION 57

3.7 SUMMARY 67

CHAPTER 4: STABILITY OF INTRA-INDIVIDUAL VARIABILITY IN RELAPSING REMITTING MULTIPLE SCLEROSIS: A 6-MONTH STUDY 68

4.1. PUBLICATION STATUS AND AUTHOR CONTRIBUTIONS 68

4.2. ABSTRACT 69

4.3. INTRODUCTION 70

4.4 METHOD 72

4.4.1. PARTICIPANTS *72*

4.4.2. ATTENTION NETWORK TEST-INTERACTION (ANT-I) *73*

4.4.3. CLINICAL MEASURES *74*

4.4.4. MAGNETIC RESONANCE IMAGING *75*

4.4.5. PROCEDURE *75*

4.4.6. DATA PREPARATION AND ANALYSIS *76*

4.5. RESULTS 76

4.5.1. DATA PREPARATION AND ANALYSIS *76*

4.5.2. MEAN-LEVEL PERFORMANCE ON THE ANT-I *77*

4.5.2. INTRA-INDIVIDUAL VARIABILITY ON THE ANT-I *78*

4.5.3. CLINICAL MEASURES IN MS GROUP ACROSS SESSIONS *79*

4.6 DISCUSSION 79

4.7 SUMMARY 88

CHAPTER 5: ALTERATIONS IN FUNCTIONAL CONNECTIVITY AND PERFORMANCE VARIABILITY IN MULTIPLE SCLEROSIS 89

5.1. METHODOLGICAL CONSIDERATIONS IN RESTING-STATE FMRI 89

5.1.1. DATA COLLECTION *89*

5.1.2. ACCOUNTING FOR NON-NEURAL NOISE *90*

5.1.2. ANALYSIS APPROACHES TO IDENTIFYING FUNCTIONAL CONNECTIVITY *90*

5.2. PUBLICATION STATUS AND AUTHOR CONTRIBUTIONS 91

5.3. ABSTRACT 92

5.4. INTRODUCTION 93

5.5. METHOD 95

5.5.1. PARTICIPANTS *95*

5.5.2. CLINICAL MEASURES *96*

5.5.3. COMPUTERIZED TEST OF INFORMATION PROCESSING (CTIP) *96*

5.5.4. MRI DATA ACQUISITION *97*

5.5.5. MRI DATA PREPROCESSING AND ANALYSIS *97*

5.5.6. BEHAVIOURAL DATA PREPARATION *99*

5.5.7. PROCEDURE *99*

5.6. RESULTS 100

5.6.1. DEMOGRAPHIC & CLINICAL CHARACTERISTICS *100*

5.6.2. CTIP PERFORMANCE *100*

5.6.3. CTIP PERFORMANCE AND STRUCTURAL MRI *101*

5.6.4. RSFMRI & CTIP PERFORMANCE *101*

5.7. DISCUSSION 102

5.7. SUPPLEMENTAL DATA 116

CHAPTER 6: DISCUSSION 119

6.1. SUMMARY 119

6.2. FURTHER CONSIDERATIONS 120

6.2.2. TASK DEPENDENCE *121*

6.2.3. REPEATED MEASUREMENTS *125*

6.2.4. CLINICAL IMPLICATIONS OF IIV *126*

6.2.4. RESTING STATE FUNCTIONAL CONNECTIVITY AND IIV *127*

6.3. LIMITATIONS AND FUTURE DIRECTIONS 135

REFERENCES 137

APPENDIX 1: FUNCTIONAL CONNECTIVITY BETWEEN THE VMPFC AND FRONTAL POLE ASSOCIATED WITH IIV ON THE ANT-I 168

A.1 PARTICIPANTS 168

A.2 METHOD 168

A.2.1 DATA PREPARATION *168*

A.2.1 NEUROIMAGING ANALYSIS *169*

A.3 RESULTS 169

A.3.1 DEMOGRAPHICS *169*

A.3.2 ANT-I MEAN AND IIV PERFORMANCE *169*

A.3.2 ANT-I IIV AND CTIP IIV *169*

A.3.2 ANT-I RT AND CTIP RT *170*

A.3.3 NEUROIMAGING RESULTS *170*

APPENDIX 2: COPYRIGHT PERMISSIONS 172

LIST OF TABLES

Table 1. Core Regions of the Default Mode Network; adapted from Buckner et al., 2008. ..... **25**

Table 2.1. Descriptive statistics for demographic variables..... **41**

Table 2.2 Standardized coefficients of predictor variables of the discriminant function **42**

Table 3.1 Demographic, disease and neuropsychological characteristics **63**

Table 3.2 Standardized coefficients of predictor variables of logistic regression predicting group membership..... **64**

Table 4.1. Demographic Variables for the MS and Control Groups..... **83**

Table 4.2. Clinical Measures for MS Group Across Session..... **84**

Table 4.2. MRI measures for MS patients across the 6 consecutive monthly sessions ... **85**

Table 5.1 Demographic, Clinical, and MRI Metrics..... **107**

Table 5.2 CTIP performance for both groups. **108**

Table 5.3 Clusters reported as statistically significant (cluster threshold corrected, $z<2.3$, $p<.05$) **109**

LIST OF FIGURES

Figure 2.1 Mean reaction times for MS participants and controls on the three CTIP tests **43**

Figure 2.2 Mean individual standard deviations for MS participants and controls on the three CTIP tests **44**

Figure 2.3 Mean coefficient of variation for MS participants and controls on the three CTIP tests **45**

Figure 3.1 Attention Networks Test (ANT-I). **65**

Figure 3.2 Alerting, Orienting, and Executive Network scores for MS and Control groups from the Attention Network Test (ANT-I). **66**

Figure 4.1. Mean reaction time for MS participants and controls on the ANT-I task across 6 sessions **86**

Figure 4.2. Mean individual standard deviations for MS participants and controls on the ANT-I task across 6 sessions **87**

Figure 5.1. The DMNs across all subjects for the vmPFC (top) and PCC (bottom) seeds. **112**

Figure 5.2. Greater functional connectivity in controls than MS participants using the PCC seed **113**

Figure 5.3. Greater connectivity between the vmPFC seed and left lateral frontal pole associated with greater performance stability on the semantic search reaction time task in the MS group. **114**

Figure 5.4. Lesion burden map for the MS group, displayed with reference to the frontal pole cluster (see Figure 5.3) and the seed regions used in the rsfMRI connectivity analyses **115**

Figure S.1 Diagram of data processing steps **116**

Figure S.2 Correlation scatterplots between lesion load volume and ISD on the CTIP tasks in MS **117**

Figure A.1. Scatterplot of SSRT RT and ANT-I RT in MS patients **171**

ABSTRACT

Cognitive deficits are highly prevalent in multiple sclerosis (MS) and have a negative impact on daily life. Impairments in information processing speed are among the most commonly reported deficits in MS and are generally assessed by evaluating mean-level performance on time-limited tests. However, this approach to assessing performance ignores potential within-subject differences that may be useful for characterizing cognitive difficulties in MS. An alternative method of measuring performance on timed cognitive tasks is to examine the degree of within-subject variability, termed intra-individual variability (IIV). IIV provides information about the characteristics of an individual's performance and may provide novel information about cognitive functioning in MS and other neurodegenerative disorders. The research presented in this dissertation examined IIV in performance as an indicator of cognitive functioning in persons with MS and explored the relations of performance variability to measures of neuronal connectivity derived from resting state functional magnetic resonance imaging (rsfMRI).

Individuals with MS were found to be both slower and more variable on tests of information processing speed and attention. This variability was observed even when controlling for sensorimotor confounds and other systematic variables that may influence variability, such as practice and learning effects. IIV in performance was found to better distinguish MS patients from matched groups of healthy control subjects when compared to common clinical measures of cognitive performance or average response speed. These differences in IIV were also found consistently across six monthly assessments in a group with MS who remained clinically stable over this period. This stability in IIV suggests its feasibility as a measure of changes in longitudinal cognitive or clinical status. Using rsfMRI, greater stability in performance (i.e., lower IIV) was associated with greater functional connectivity between frontal lobe regions (i.e., ventral medial prefrontal cortex and frontal pole) in persons with MS. This increased connectivity appears to represent potential compensatory processes within mildly affected MS individuals. Together the findings demonstrate that IIV is an important characteristic of cognitive performance that may provide new insights into the cognitive deficits present in MS.

LIST OF ABBREVIATIONS USED

ACC	Anterior cingulate cortex
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ANT	Attention Network Test
ANT-I	Attention Network Test-Interactions
BA	Brodmann area
BDI-FS	Beck Depression Index- FastScreen
BOLD	Blood oxygen-level dependent signal
BOLD-SD	Blood oxygen-level dependent signal standard deviation
BPF	Brain parenchymal fraction
CIS	Clinically isolated syndrome
CNS	Central nervous system
COV	Coefficient of variation
CRT	Choice reaction time
CSF	Cerebrospinal fluid
CTIP	Computerized Test of Information Processing
DFIS	Daily Fatigue Impact Scale
DMN	Default mode network
dmPFC	Dorsal medial prefrontal cortex
DMSRU	Dalhousie multiple sclerosis research unit
DTI	Diffusion tensor imaging
EC	Entorhinal cortex

EDSS	Expanded Disability Status Scale
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FP	Frontal pole
FSL	Functional MRI of brain software tool
HF	Hippocampal formation
ICA	Independent component analysis
IIV	Intra-individual variability
pIPL	Posterior inferior parietal lobule
ISD	Individual standard deviation
LST	Lesion segmentation Tool
M	Mean
mPFC	medial PFC
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
PASAT	Paced Auditory Serial Addition Test
PASAT-2	Paced Auditory Serial Addition Test- 2 second
PASAT-3	Paced Auditory Serial Addition Test- 3 second
PCC	Posterior cingulate cortex
PFC	Prefrontal cortex
PH	parahippocampal cortex
PPMS	Primary progressive multiple sclerosis

RRMS	Relapsing remitting multiple sclerosis
rsfMRI	Resting state fMRI
RT	Reaction time
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SPGR	Spoiled gradient recalled
SPM	Statistical Parametric Mapping
SPMS	Secondary progressive multiple sclerosis
SRT	Simple reaction time
SSRT	Semantic search reaction time
T	Tesla
TE	Echo time
TI	Inversion time
TR	Repetition time
VBM	Voxel-based morphometry
vmPFC	Ventral medial prefrontal cortex

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CHAPTER 1: INTRODUCTION

1.1. OVERVIEW OF MULTIPLE SCLEROSIS

Multiple Sclerosis (MS) is an inflammatory neurodegenerative disease of the central nervous system (CNS), which results in inflammation, demyelination, axonal and neural degeneration, and the formation of lesions, termed sclerotic plaques (Compston & Coles, 2008). The widespread nature of this inflammation and degeneration results in a broad range of symptoms, including sensory, motor, neuropsychiatric, and cognitive. Recent prevalence rates in Canada are estimated to be 210-280 per 100,000 (Evans et al., 2013). MS affects approximately three times more females than males and is the most common cause of non-traumatic disability in young adults (Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000; Orton et al., 2006).

The diagnosis of MS requires the dissemination in space (i.e. location) and dissemination in time of CNS white matter lesions, as well as the exclusion of other neurological disorders, which can mimic MS. This can be done through a combination of clinical and paraclinical laboratory assessments, usually involving magnetic resonance imaging (MRI). To receive a diagnosis of clinically definite MS, there must be evidence of at least one lesion in at least two different CNS areas (i.e. dissemination in space), and the simultaneous presence of a new and old lesion or a new lesion compared to a baseline examination (i.e., dissemination in time; Polman et al., 2011). Disease symptoms and severity are commonly assessed in neurology practice using the Expanded Disability Status Scale (EDSS; Kurtzke, 1983). Scores on the EDSS are based on the neurological examination of eight functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral and 'other' (the latter two of which include a non-

specific assessment of cognition, psychological symptoms and sometimes fatigue). Scores on the EDSS range from zero to ten, with zero indicating normal neurological examination for all systems and ten indicating death due to MS (Kurtzke, 1983). An EDSS score of six reflects the inability to walk 100 meters without the use of an ambulatory aid (Kurtzke, 1983).

The clinical course of MS is highly variable, with some patients experiencing few exacerbations in their lifetime and others experiencing frequent and debilitating episodes. In adult onset MS, symptoms emerge between the ages of 18-50 years, with an average age of onset of 30 (Rao, 1990). However, symptom presentation may also occur in children (i.e., younger than age 18), termed pediatric MS (Bigi & Banwell, 2012; Venkateswaran & Banwell, 2010). The presence of an initial acute neurologic episode involving one or more sites in the CNS is termed clinically isolated syndrome (CIS). If this episode is accompanied by white matter abnormalities at clinically unaffected sites, the chance of a second episode occurring in the next two years is 50% and in the next 20 years is 82% (Fisniku et al., 2008). Individuals who have experienced at least two such episodes meet diagnostic criteria for relapsing-remitting MS (RRMS). The rate of relapse is variable across individuals, although the number of new episodes seldom exceeds 1.5 per year (Compston & Coles, 2008). CNS injuries associated with relapses tend to accumulate with time, resulting in incomplete recovery and the presence of persistent symptoms. Approximately 65% of persons with RRMS transition to a secondary progressive phase of MS (SPMS), where the occurrence of relapses and remissions is less evident and disease progression becomes more steady. Twenty percent of persons with MS initially present with a primary progressive course (i.e. PPMS), characterized by a

steady worsening of neurologic functioning without evidence of distinct relapses or symptom exacerbations. Median time of death due to adult onset MS is around 30 years after disease onset, which represents a reduced life expectancy of approximately 5-10 years (Bronnum-Hansen, Koch-Henriksen, & Stenager, 2004). However, recent evidence of a rightward shift in peak age-specific prevalence over the past 20 years in Nova Scotia, suggests improved survival (Marrie et al., In Press).

The precise etiology of MS is unknown but it is thought to involve the combination of environmental exposure and genetic susceptibility. Evidence for environmental contributions stems from the higher prevalence rates of MS in geographic regions furthest away from the equator (e.g. Canada, Northern Europe, Australia and New Zealand). Moreover, migration to and from high risk and low risk regions in childhood has been found to affect risk (Compston & Coles, 2008; Elian, Nightingale, & Dean, 1990). The precise environmental factors involved are unclear, though some have proposed a "hygiene hypothesis", which suggests that individuals who are not exposed to infections in early life (i.e. due to more hygienic environments) develop abnormal responses to infections later in life (Compston & Coles, 2008). Support for this suggestion has come from individuals with MS who report being infected with viruses such as measles, mumps, rubella and Epstein-Barr at later ages than matched controls (Levin et al., 2003). However, there have been numerous other proposed environmental triggers for MS that include sunlight exposure and/or vitamin D deficiency, diet, geomagnetism, pollutants and toxins (Marrie, 2004). Genetic factors also appear to contribute to the risk of developing MS, as first-degree relatives have a 10-25 time greater risk and monozygotic twins have a higher concordance rate (i.e., 20-30%) than

dizygotic twins (i.e., 2-5%; Ramagopalan, Dobson, Meier, & Giovannoni, 2010; Willer et al., 2003).

The pathogenesis of MS is likewise unclear, although it has traditionally been believed to have a primary autoimmune etiology, whereby abnormal T cells in the periphery cross the blood-brain barrier and attack myelin in the CNS. These events are thought to cause the demyelination, degeneration of axons, and eventual cell death observed in MS. This perspective has been termed the "outside-in" model of MS because abnormality of a system in the periphery (i.e. the immune system) targets the CNS (Stys, Zamponi, Van Minnen, & Geurts, 2012). Many laboratory and clinical observations in MS appear consistent with the outside-in model. For example, persons with MS often demonstrate gadolinium-enhancing lesions on MRI, suggestive of inflammation and breakdown of the blood-brain barrier. Pathological examinations of MS brains post-mortem have found inflammatory cells (e.g., T cells and macrophages) in perivascular regions, as well as evidence of myelin breakdown, and axon degeneration (Frohman, Racke, & Raine, 2006; Noseworthy et al., 2000).

Recently an alternative model of MS has been proposed in reaction to laboratory and clinical observations that seem inconsistent with the "outside-in" model. For example, myelin abnormalities have been detected in the inner layers of the myelin sheath that is beyond the target area for inflammation and myelin damage can be observed in areas outside those where there is maximal inflammation (Rodriguez & Scheithauer, 1994). Furthermore, histological examinations have detected diffuse white matter abnormalities in the brain of MS patients independent of inflammation (Seewann, 2009). Most available therapeutic agents for MS are designed to suppress immune and

inflammatory responses and while these are effective at reducing relapses and neuro-inflammation, they are considered ineffective at the later progressive stages of this disease (Stys et al., 2012). Such observations have led to the development of an "inside-out" model of MS which proposes that there is an underlying "cytodegeneration" that occurs years before the presence of overt clinical symptoms (Stys et al., 2012). This model purports that degeneration releases protein/lipid antigens that then promote an inflammatory immune response in an individual already highly primed to react to released antigens. This interaction between cytodegeneration and an aberrant immune system drives further neurodegeneration. There is evidence supporting both the outside-in and inside-out models, and together these highlight the importance of both neuroinflammation and neurodegeneration in the etiology of MS and in the eventual manifestation of motor, sensory, psychiatric, and cognitive symptoms.

1.2. COGNITIVE DEFICITS IN MS

Over a century ago, Jean-Martin Charcot, who is credited with describing and naming MS, also recognized the presence of cognitive difficulties as a feature of this disease. He observed that MS patients had a "marked enfeeblement of the memory" as well as "conceptions [that were] formed slowly" (Charcot, 1877). Current estimates of the prevalence of cognitive deficits in persons with MS are high and in the range of 40-70% (Chiaravalloti & DeLuca, 2008; Langdon, 2011; Rao, Leo, Bernadin, Unverzagt, 1991). Cognitive deficits represent an important symptom in MS as they are associated with reduced health-related quality of life and can negatively affect employment as well as driving abilities (Mitchell, Benito-León, González, & Rivera-Navarro, 2005; Rao, Leo, Ellington, Nauertz, Bernadin, Unverzagt, 1991). Cognitive difficulties have been

demonstrated in all subtypes of MS (i.e., CIS, RRMS, primary progressive MS; PPMS, and secondary progressive MS; SPMS) and at all levels of neurologic disability. However, those with progressive forms of MS often demonstrate more severe levels of cognitive impairments and a more rapid decline in functioning with time (Langdon, 2011). The profile of cognitive deficits typically found in persons with MS can be quite variable, although the most commonly reported difficulties include impairments in memory, information processing speed, attention, and executive functioning (Chiaravalloti & DeLuca, 2008; Langdon, 2011). Problems with visual processing and perceptual abilities are less frequently reported, and language functions are generally considered preserved (Langdon, 2011).

Memory difficulties are common in individuals with MS (Chiaravalloti & DeLuca, 2008; Langdon, 2011). Individuals with MS typically demonstrate poor initial learning and require more repetitions in order to learn a predetermined number of items. However, once the information is learned, recall and recognition performance in persons with MS is often similar to healthy controls (Chiaravalloti & DeLuca, 2008). It is unclear whether these memory deficits reflect pure difficulties in new learning, or the extent to which they are influenced by other cognitive difficulties such as, slowed processing speed, problems with inhibiting distractions, and executive dysfunction (Chiaravalloti & DeLuca, 2008).

Slowing of the speed of information processing has been one of the most commonly reported and studied cognitive impairments in MS (Chiaravalloti & DeLuca, 2008; DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004). MS patients are consistently slower than healthy controls on timed tasks of information processing speed,

and this performance is further impaired with increases in cognitive load (Archibald & Fisk, 2000; Chiaravalloti & DeLuca, 2008; Langdon, 2011; Leavitt, Lengenfelder, Moore, Chiaravalloti, & DeLuca, 2011). Processing speed difficulties correlate with the degree of deficits in memory and slowed processing speed has also been found to predict performance on executive measures (Chiaravalloti & DeLuca, 2008). DeLuca and colleagues (2004) proposed a *Relative Consequence Model* of cognition in MS, which posits that information processing speed is a fundamental deficit in MS and inefficiencies in higher-level cognitive abilities (e.g., working memory, learning, memory) are affected by slowed cognitive processing. Hence abilities, such as learning new information, are affected by the rate at which information can be taken in and processed.

The most commonly used tests of information processing speed in MS research and clinical practice are the Paced Auditory Serial Addition Task (PASAT; Gronwall, 1977) and the Symbol Digit Modalities Test (SDMT; Smith, 1982). However, neither provides a measure of reaction time or an assessment of information processing speed within a specific cognitive domain (Tombaugh, 2006). The PASAT, in particular, has been criticized since poor performance may be attributable to problems with information processing speed, sustained/divided attention, working memory or mathematical abilities (Tombaugh, 2006). The use of adapted versions of the PASAT and SDMT in fMRI studies has demonstrated that these two tests activate somewhat different cortical networks in healthy individuals, with more medial frontal gyri (BA 6) activation found during PASAT performance (Forn et al., 2011).

While deficits in performance on tests of attention are also commonly reported in MS, distinguishing among the constructs of attention, processing speed and working

memory can be difficult (Chiaravalloti & DeLuca, 2008). Interpretation of such findings is also complicated by the variability in how 'attention' is defined. In general, tasks such as forward digit span are typically unaffected in individuals in MS (Benedict et al., 2006) while deficits in sustained attention and divided attention (i.e., attending to two tasks simultaneously) are common (Chiaravalloti & DeLuca, 2008).

Individuals with MS also demonstrate difficulties with executive functioning, although, these have been found to occur less frequently than difficulties in memory and information processing speed. Estimates of the prevalence of executive function deficits in MS range from 15-20% in community-based samples (Benedict et al., 2006; Drew, Tippett, Starkey, & Isler, 2008). Poor performance has been found on tests examining various aspects of executive function including, verbal fluency (phonemic and semantic), abstract reasoning, response inhibition, failure to shift mental sets, and perseveration (Chiaravalloti & DeLuca, 2008; Langdon, 2011). Both attention and executive functions represent cognitive domains that are poorly operationalized and measures created to examine these constructs typically require cognitive abilities that overlap with other cognitive domains.

Attempts have been made to determine the relation between structural neuroimaging (i.e., magnetic resonance imaging; MRI) measures and degree of cognitive impairment in MS. Moderate correlations (r = 0.4-0.5) have been found between lesion burden and cognitive deficits (Benedict & Zivadinov, 2011) while measures of brain atrophy, such as the width of the third ventricle and whole brain or thalamic volumes, appear to have somewhat stronger correlations with cognitive deficits (Benedict & Zivadinov, 2011; Chiaravalloti & DeLuca, 2008; Langdon, 2011). Measures derived

from diffusion tensor imaging (DTI), such as fractional anisotropy, have also been found to have moderate correlations with various cognitive abilities (i.e. processing speed, executive function, verbal and non-verbal memory; Benedict, 2007; Hulst et al., 2013; Rovaris, 2002). However, correlations between neuropsychological measures and structural imaging still vary considerably. Given that MS is a dynamic disease that involves ongoing demyelination, remyelination, axonal loss, and cell death, such variability should be expected. Fluctuations in the appearance of lesions and changes in brain volume metrics associated with the pathophysiology of MS can introduce error in cross-sectional studies investigating relations between structural metrics and cognitive performance. Furthermore, structural imaging does not provide information regarding functional brain changes potentially occurring in MS.

Task-based functional magnetic resonance imaging (fMRI) of cognitive performance in MS patients has demonstrated increased recruitment of cortical networks compared to healthy controls (Langdon, 2011). This increased cortical recruitment has been found in MS patients who demonstrate similar cognitive performance to controls and is thought to represent compensatory mechanisms (Amann et al., 2011; Filippi & Rocca, 2010; Langdon, 2011). Such findings have led to the suggestion that eventual exhaustion or inability to recruit greater cortical activation, with the progression of underlying pathology, is responsible for worsening of cognitive test performance (Loitfelder et al., 2011; Penner & Rausch, 2003).

Of the cognitive domains affected in MS, information processing speed is thought to be especially critical as it is hypothesized to contribute to other deficits in memory, attention, and executive function (DeLuca et al., 2004). However, most clinical studies of

information processing speed use non-specific tests, such as the PASAT and SMDT, and focus primarily on mean-level differences in performance between groups. This emphasis on group-level differences in performance ignores within-person variations in performance that may convey important information regarding the characteristics of cognitive difficulties in MS.

1.3. INTRA-INDIVIDUAL VARIABILITY IN PERFORMANCE

Most cognitive and neuropsychological research has focused on mean-level differences in performance between groups of individuals (MacDonald, Nyberg, & Bäckman, 2006). This provides useful information regarding differences between groups, when variability within individuals is low (MacDonald, Li, & Bäckman, 2009; MacDonald et al., 2006). However, when within-person variability is high and is not due to random sources of error (e.g. extreme response due to external distraction), focusing solely on mean performance can lead to incomplete interpretations of cognition (MacDonald et al., 2009, 2006).

Intra-individual variability (IIV) is a term used to describe within-person fluctuations in performance across a series of trials within a given task (MacDonald et al., 2006). This measure has been found to provide unique predictive information about cognitive performance, such as group membership (e.g., dementia and non-dementia groups), over and above mean performance (Hultsch, Macdonald, Hunter, Levy-bencheton, & Strauss, 2000; MacDonald et al., 2006). IIV has been found to change across the lifespan in healthy individuals, with greater variability in performance found in childhood and adolescent, as well as in late adulthood (i.e. approximately age 60 and onwards) and more stable performance found in young to middle adulthood (Williams,

Hultsch, Strauss, Hunter, & Tannock, 2005). In aging populations, increases in IIV have been associated with cognitive decline and with increased risk of mortality (MacDonald, Hultsch, & Dixon, 2003; Macdonald, Hultsch, & Dixon, 2008; Shipley, Der, Taylor, & Deary, 2006). Greater IIV has also been demonstrated in a variety of neurologic and neurodevelopmental disordered populations, including persons with traumatic brain injury, frontal lobe lesions, dementia, mild cognitive impairment, Parkinson's disease, attention deficit disorder, and schizophrenia (For review see: MacDonald et al., 2009). These observations have led to the hypothesis that IIV may be a behavioural indicator of general CNS integrity (Hultsch et al., 2000; MacDonald et al., 2006).

The source of IIV is unclear, although it has been postulated that IIV may represent momentary lapses of attention (Bunce, Warr, & Cochrane, 1993) and executive control failures (West, Murphy, Armilio, Craik, & Stuss, 2002). Both hypotheses imply that IIV is, in part, related to frontal cortex-mediated processes, a suggestion further supported by studies that demonstrate increased IIV on tasks requiring greater executive demands (e.g., West et al., 2002). Developmental changes in IIV also support involvement of frontal-cortical processes, since IIV is greater in early childhood/adolescence when frontal cortical development is not yet complete, as well as in later adulthood where disruption to frontal cortical functioning is commonly found (MacDonald et al., 2009, 2006). These observations may also be explained by changes in gray matter density or white matter volume across the lifespan (MacDonald et al., 2009; Sowell et al., 2003). For example, in early childhood undifferentiated gray matter may result in neural inefficiency, and hence more IIV. Reductions in gray matter density and

synaptic pruning may result in more stable performance in adolescence and young adulthood, while gray and white matter atrophy in older adults may underlie greater IIV.

Structural MRI imaging findings have supported a relation between IIV and frontal cortex mediated processes. Lesions in frontal gray matter, particularly in the prefrontal cortex, have been associated with greater IIV in performance (Sowell et al., 2003). Individuals with focal frontal lesions have been shown to have greater variability on reaction time tasks than healthy controls and individuals with lesions in other regions (Stuss, Murphy, Binns, & Alexander, 2003). Furthermore, individuals with frontotemporal dementia demonstrate greater performance variability than those with Alzheimer's disease who have a similar level of disease severity (Murtha, Cismaru, Waechter, & Chertkow, 2002). White matter alterations have also been found to relate to IIV in performance. Atrophy of the corpus callosum in individuals with mild cognitive impairment appears to be associated with worse cognitive performance and greater IIV and these associations are greatest for anterior regions of the corpus callosum (Anstey et al., 2007). Moreover, in community dwelling older adults white matter hyperintensities in frontal areas have been found to correlate specifically with increased IIV, but not other measures of cognitive performance (Bunce et al., 2007). These findings suggest that IIV may represent CNS dysfunction in gray and white matter, with a particular concentration in frontal regions.

Investigations into the functional correlates of performance variability using fMRI are sparse. However, Bellgrove and colleagues (2004) demonstrated that greater IIV during "Go" trials of a response-inhibition task (i.e. Go-No Go) in young adults was associated with greater blood oxygen level-dependent (BOLD) activation in bilateral

middle frontal regions (i.e. BA 46) and the left prefrontal gyrus (i.e. BA 44/6) during successful inhibition trials (i.e. No Go). Thus, more frontal medial recruitment likely reflected greater demands for executive control necessary to maintain task performance (Bellgrove et al., 2004). In older adults, more IIV on a word retrieval task was associated with less BOLD activity in the left supramarginal gyrus, a region thought to be involved with sustained attention and deep semantic encoding (MacDonald, Nyberg, Sandblom, Fischer, & Bäckman, 2008). Hence, older adults with less stable performance appeared to recruit less parietal activity during an encoding task. Such findings support the concept that IIV is associated with attentional/executive processes that are mediated by medial frontal regions as well as regions important for attention (e.g. supramarginal gyrus). Thus, observations from functional and structural imaging appear to support the notion that IIV may be a potential behavioural proxy for overall neural efficiency (MacDonald et al., 2009).

In order to build further evidence for the hypothesis that IIV represents a behavioural indicator of CNS integrity investigations into the associations between neural network functioning and IIV are necessary. Kelly and colleagues (2008) investigated the relation between IIV and a functional neural network in the brain known as the 'task negative' or 'default mode network' (DMN). This network involves a set of brain regions (i.e. primarily anterior/posterior cingulate, medial prefrontal cortices, bilateral inferior parietal lobules, and the hippocampal formation) that show coherent BOLD signal fluctuations during stimulus independent thoughts (e.g., self-reflection) and that are consistently found to be deactivated during attention-demanding external tasks (Buckner, Andrews-Hanna, & Schacter, 2008). Kelly and colleagues (2008) found that greater IIV

on a flanker task was associated with less suppression of the DMN in young healthy adults. In healthy older adults, greater IIV on a working memory task predicted greater functional connectivity within the DMN at rest (Grady et al., 2010). This evidence, though limited, suggests that IIV is not only associated with alterations in functioning within specific neural regions but also with overall neural network functioning.

1.4. RESTING-STATE FUNCTIONAL CONNECTIVITY

The brain at rest consumes approximately 20% of our body's energy in order to support ongoing neural signaling (Raichle & Mintun, 2006). Traditional task-based fMRI, used to investigate brain-behaviour relationships, examines increases in metabolic activity that represents only ~5% of the brain's total energy consumption (Raichle & Mintun, 2006). Thus, the majority of our understanding of brain functioning stems from research examining small metabolic changes. Resting-state activity refers to spontaneous fluctuations in BOLD signal that occur in the absence of a stimulus dependent task (i.e., at rest). These fluctuations occur at low frequencies (0.01-0.1 Hz), suggestive of neural activity, and demonstrate temporal correlations across a set of regions, which are organized into networks (Damoiseaux et al., 2006; Fox & Raichle, 2007). These networks have a functional topography (i.e. include regions that are involved in similar functions) and are made up of regions that are structurally related (Damoiseaux et al., 2006; Lowe, Dzemidzic, Lurito, Mathews, & Phillips, 2000). Resting-state functional connectivity refers to the correlations of spontaneous BOLD signal fluctuations between remote brain areas (Fox & Greicius, 2010).

Several functional resting-state networks have been identified including visual (i.e. primary visual and higher order visual), auditory, sensorimotor, "task positive" (i.e.

believed to underlie visual and spatial attention), and "task negative" or default mode networks. These networks have been found consistently across subjects and acquisition sessions, suggesting that they are a reliable occurrence in the brain (Damoiseaux et al., 2006; Fox & Raichle, 2007). Furthermore, regions with apparent opposing function have been found to be anti-correlated in their activity (Fox, 2005). That is, regions consistently found to increase in activity during attention demanding tasks (i.e. "task positive network") are negatively correlated with regions deactivated during externally driven tasks and/or active during spontaneous task-independent thought (i.e. task negative network; DMN; Fox et al., 2005; Toro, Fox, & Paus, 2008). Although these anti-correlations have been criticized because of potential influences of data processing steps (i.e. global normalization of signal) on the magnitude of the correlations, preprocessing does not appear to fully explain this phenomenon (Fox, Zhang, Snyder, & Raichle, 2009; Weissenbacher et al., 2009).

The functional organization of correlated spontaneous BOLD signal fluctuations means that these patterns can be used to predict task-related responses. For example, the degree of left hemisphere lateralization of the somatosensory resting-state network predicts the extent of lateralization of an individual's activation map during a right-finger tapping task paradigm (De Luca, Smith, De Stefano, Federico, & Matthews, 2005). Similar relations have been found in memory, with the degree of functional connectivity between the hippocampus and parietal regions at rest predicting parietal activation during an episodic memory task (Vincent et al., 2006). Resting-state functional connectivity has also been found to correspond to individual differences in performance outside of the MRI machine (e.g., Seeley et al., 2007). For example, individual differences in pre-scan

anxiety and performance on a working memory task are associated with differences in spontaneous network activity (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006; Seeley, 2007). In addition, investigations using resting-state functional connectivity can provide information regarding neuroanatomical models, independent of task design (e.g., Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). Hence, investigating functional connectivity across regions at rest can provide crucial information regarding the response of the brain during cognitive tasks as well as the neuroanatomical relations among brain regions responsible for the relevant behavioural responses.

Currently, the underlying nature of spontaneous BOLD signal fluctuations is unclear. One possibility is that these correlated resting state BOLD signal fluctuations solely reflect neuroanatomical connections. Although there is structural correspondence (e.g., white matter tracts) between regions comprising resting-state networks (Greicius, Supekar, Menon, & Dougherty, 2009; Lowe et al., 2000; van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009), tract tracing in macaque monkeys has also demonstrated evidence of spontaneous BOLD signal correlations between regions in the visual system that do not have direct anatomical connections (Vincent et al., 2007). Similar evidence has been found in the human brain. For example, individuals with complete agenesis of the corpus callosum nonetheless demonstrate bilateral resting-state networks (Tyszka, Kennedy, Adolphs, & Paul, 2011). Studies examining structural connectivity (e.g. through DTI) across functionally correlated regions have demonstrated that direct structural connections are not always present (see Damoiseaux & Greicius, 2009). This suggests that resting state networks are not just a proxy for structural connections, rather, spontaneous BOLD signal correlations likely represent flexible functional connections

that may be mediated by regions with either direct or indirect structural connections (e.g., via a third region; Damoiseaux & Greicius, 2009).

Resting-state activity has also been suggested to only represent activation due to spontaneous mental activity (e.g., mental imagery and reflection) occurring in the scanner. Although spontaneous mental activity likely influences resting state activity, it does not seem to be the primary cause. For example, consistent resting BOLD signal correlations can be observed in a variety of states, including sleep, and anesthesia (See Fox & Raichle, 2007; Heine et al., 2012). Correlated spontaneous BOLD signal fluctuations are also found across a large number of neuroanatomical systems (e.g., visual, auditory, sensorimotor), which seem unlikely to be simultaneously modulated by spontaneous cognition (Fox & Raichle, 2007). Furthermore, resting-state BOLD signal fluctuations are demonstrated in neural networks associated with behaviour (e.g., motor movement) in the absence of overt behaviour (Biswal, Yetkin, Haughton, & Hyde, 1995; Fox, Snyder, Zacks, & Raichle, 2006). Thus, spontaneous BOLD signal fluctuations found in the absence of an instructed task likely do not completely represent spontaneous cognition.

In summary, resting-state functional connectivity likely reflects both structural and functional connections across a series of brain regions that appear to be organized in networks (Damoiseaux & Greicius, 2009; Fox & Greicius, 2010). This method has revealed that regions with similar functional properties (e.g., responsible for somatomotor movements) exhibit consistent spontaneous BOLD fluctuations in the absence of the overt behaviour. Resting-state functional connectivity patterns have also been found to predict an individual's task-response outside of the scanner and have helped refine neuro-

anatomical models of the brain's functional architecture in healthy individuals (see Fox & Raichle, 2007; Fox & Greicius, 2010).

1.5. RESTING-STATE FUNCTIONAL CONNECTIVITY IN CLINICAL POPULATIONS

If resting-state fMRI (rsfMRI) provides information about the functional-structural architecture of the brain in healthy individuals, it may also provide insight into disease processes. Several advantages exist to using rsfMRI techniques to study clinical populations as opposed to traditional task-based fMRI. First, rsfMRI may offer better signal to noise ratios than task-based fMRI. Task-activation studies examine relatively small metabolic changes (i.e. signal) associated with behaviour (Raichle & Mintun, 2006). As a result, several trials, blocks and runs are necessary in order to acquire consistent and reliable activation patterns compared to a 'baseline'. In contrast, spontaneous BOLD activity represents a larger proportion of ongoing neural signaling in the brain (i.e. approximately 60%; Fox et al., 2006). Hence, rsFMRI studies have reported three times the signal to noise compared to task-based studies (Fox & Greicius, 2010). The most direct benefit of this increased signal to noise ratio is that rsfMRI scans can be relatively brief (i.e. approximately 5-10 min in total length).

Another important advantage of rsfMRI is that these spontaneous fluctuations in BOLD signal are task-independent. This is beneficial because interpreting task-based altered activation patterns in clinical populations is confounded by task-demands, task performance, strategy use, effort and specific disease-related changes (Fox & Greicius, 2010; Greicius, 2008). The absence of a task also permits the use of rsfMRI in more severely affected clinical populations. Activation studies often recruit mildly impaired subjects because these subjects are physically and cognitively able to perform the

required task in an MRI environment (Fox & Greicius, 2010; Greicius, 2008). Such selection biases result in limited generalizability of findings to clinical populations and limit our understanding of the disease process. In contrast, rsfMRI can allow for a broader sampling of clinical populations. Furthermore, unlike task-dependent fMRIs that examine functional neurocorrelates associated with performance in a particular cognitive domain, a single rsfMRI dataset can be used to investigate several cortical systems (Fox & Greicius, 2010). Despite the many advantages of rsfMRI, different study designs, data processing techniques and analysis approaches have contributed to inconsistent results across clinical studies. Preliminary guidelines aimed at reducing such inconsistencies have been established (see Fox & Greicius, 2010) and the continual development of processing techniques will help improve the clinical applications of rsfMRI.

At present, applications of rsfMRI to clinical populations have included pre-operative functional mapping for surgical planning as well as examination of associations between clinical variables and various resting state networks (Fox & Greicius, 2010). Many clinical rsfMRI studies have focused on one particular network, the DMN. This network was first observed during traditional activation paradigm fMRI, when a series of brain regions were found to be consistently deactivated during a series of visual tasks (Shulman, 1997). These regions included ventral medial prefrontal cortex (vmPFC; including the anterior cingulate cortex, ACC), dorsal medial PFC, posterior cingulate (PCC)/retrosplenial cortex, posterior inferior parietal lobule (pIPL), hippocampal formation (HF), and lateral temporal cortex (see Table 1.1; Buckner et al., 2008). The precise functional significance of the DMN is presently unclear. It is thought that the DMN may underlie two potential cognitive processes (1) stimulus independent thought

and (2) attention monitoring. Stimulus independent thoughts are thoughts about events other than those directed by the environment or an external task (Buckner et al., 2008). Default regions including the medial PFC and the PCC have been found to be active during stimulus independent thoughts (see Buckner et al., 2008). In particular, the degree of activity in PCC has been positively correlated with frequency of self-reported mindwandering (i.e. "a psychological baseline from which people depart when attention is required elsewhere and to which they return when tasks no longer require conscious supervision"; Mason et al., 2007). DMN regions, especially the medial PFC and hippocampal formation, have been associated with self-reflective thinking (i.e. thinking about oneself on behaviours and/or experiences), theory of mind (i.e. ability to attribute mental states to oneself and others), and autobiographical memory (i.e. the recall of past personal events; see Buckner et al., 2008).

An alternative hypothesis is that the DMN participates in monitoring and mediating the shifts in focus of attention that occur between the internal and external environment (Shulman, 1997; Uddin, Kelly, Biswal, Xavier Castellanos, & Milham, 2009). For example, momentary lapses in externally-focused attention during a task have been associated with decreased activity within the dorsal ACC and PFC, as well as increased activity in the PCC (Weissman, Roberts, Visscher, & Woldorff, 2006). Similarly, during an incidental encoding task, increased activity in the PCC and lateral parietal regions during item presentation has been found to predict the items that would later be forgotten (Otten & Rugg, 2001). Furthermore, successful suppression of the DMN has been found to be associated with better task performance on an N-back task in persons with MS (e.g., Sumowski, Wylie, Deluca, & Chiaravalloti, 2010). These two

hypotheses of DMN functioning (i.e., spontaneous cognition and attention monitoring) are not mutually exclusive and may, in fact, represent different interacting subsystems within the DMN (see Buckner et al., 2008; Uddin et al., 2009).

Altered DMN activity has been reported in a variety of neurologic disorders including Alzheimer's disease, mild cognitive impairment, fronto-temporal dementia, epilepsy, schizophrenia, and autism (see Fox & Greicius, 2010; Greicius, Srivastava, Reiss, & Menon, 2004; Greicius, 2008). Within the MS literature, DMN differences between MS patients and controls have been reported, though findings are inconsistent. In part, this may reflect differences in methodology, data analysis approach, and sample selection characteristics between studies investigating DMN alterations in MS. In early phases of MS, such as with individuals with clinically isolated syndrome, greater 'synchronization' (i.e. greater spatial coherence and amplitude of spontaneous fluctuations) in the PCC of the DMN has been found compared to individuals with RRMS (Roosendaal et al., 2010). Greater deactivation of the PCC has also been reported, during a fMRI-adapted SDMT task, in clinical isolated syndrome patients compared to controls despite equivalent behavioural performance between the two groups (Forn et al., 2013). Such results have been taken to suggest that altered connectivity of the PCC with the DMN may support compensatory processes during early phases of the disease. However, in contradiction to this compensation hypothesis, an 'early' MS sample (i.e. a mixed sample of RRMS and CIS participants) demonstrated that greater functional connectivity between regions of the DMN and the 'task positive network" was associated with poorer cognitive performance on standardized clinical measures (Hawellek, Hipp, Lewis, Corbetta, & Engel, 2011).

Contradictory results regarding DMN functional connectivity have also been found across studies of patients with RRMS. Roosendaal and colleagues (2010) did not find significant differences in DMN functional connectivity between RRMS subjects and controls. However, Bonavita and colleagues (2011) found decreased functional connectivity at the level of the ACC and midline PCC in RRMS individuals, with greater reduction in resting state activity in the PCC associated with greater cognitive impairment (Bonavita et al., 2011). In contrast, Faivre and colleagues (2012) found that *increased* functional connectivity between posterior DMN regions (i.e. PCC and pIPL) was associated with worse cognitive performance in a sample of early RRMS who also demonstrated increased functional connectivity in the DMN (i.e. right middle temporal and occipital gyrus, and left cerebellar hemisphere) relative to controls. In progressive MS (i.e. SPMS and PPMS) reduced DMN functional connectivity, particularly in frontal regions (i.e., left medial PFC, left precentral gyrus, and ACC) has been observed; with reduced ACC functional connectivity associated with worse cognitive performance (Rocca et al., 2010). Thus, to date, it is unclear whether increased DMN functional connectivity in persons with MS represents compensatory or maladaptive processes and the conflicting literature highlights the need for replication with more homogenous and clearly defined clinical samples and analysis approaches.

1.6. SUMMARY AND STUDY AIMS

MS is an inflammatory neurodegenerative disease of the CNS that results in a variety of sensory, motor, neuropsychiatric and cognitive symptoms. Cognitive deficits are highly prevalent in MS and have a large impact on health-related quality of life (Mitchell et al., 2005; Rao et al., 1991). Impairments in information processing speed are the most

commonly found cognitive difficulties in MS (Chiaravalloti & DeLuca, 2008; Langdon, 2011) and are thought to contribute to higher-order cognitive dysfunction such as impaired memory and executive functioning (DeLuca et al., 2004). In clinical settings, processing speed is often assessed using timed paper and pencil tests or computerized tests of reaction time that assess group-level differences in mean performance (i.e. number of accurate items or mean RT differences; MacDonald et al., 2006; Tombaugh & Rees, 2008). An alternative approach is to examine intra-individual variability (IIV) in performance, defined as within-person fluctuations in reaction time performance across a set of trials (MacDonald et al., 2009, 2006). IIV is thought to reflect overall CNS dysfunction and has been shown to be a sensitive marker of impairment in a variety of neurologic, neuropsychiatric and neurodevelopmental disorders (MacDonald et al., 2009, 2006). Understanding the neural underpinnings of IIV may further elucidate the functional significance of this metric. Structural magnetic resonance imaging (MRI) metrics such as, lesion load, whole brain atrophy, and width of the third ventricle, demonstrate moderate correlations with cognitive performance (Benedict & Zivadinov, 2011; Chiaravalloti & DeLuca, 2008; Langdon, 2011) but do not provide information regarding functional brain changes potentially occurring in MS. Resting-state fMRI (rsfMRI) presents a means investigating neural functioning by examining spontaneous BOLD signal fluctuations across regions. This approach has several advantages over traditional task-based fMRI in examining the functional coherence of neural networks in clinical populations as it allows for short scan times, has better 'signal to noise' characteristics, and is task-independent (Fox & Greicius, 2010). Associations between IIV and alterations in the resting-state DMN have been demonstrated in healthy young

(Uddin et al., 2009) and older adults (Grady et al., 2010). Alterations in this network, which is hypothesized to underlie stimulus independent thinking and attention monitoring, may provide insights into the neural processes that underlie IIV in MS.

The specific aims of the dissertation are to: (1) examine whether individuals with MS demonstrate greater IIV on tests of attention and information processing speed compared to healthy controls. (2) Examine relations between IIV and other commonly used clinical neuropsychological tests and assess the potential contribution of IIV to our understanding of cognitive impairments in MS. (3) Examine the stability of IIV across time (i.e. successive sessions) to evaluate its potential utility as a measure of change in disease and clinical status. (4) Explore the neural correlates of IIV in MS by examining its relation to resting-state functional connectivity between regions of the DMN.

Table 1. Core Regions of the Default Mode Network; adapted from Buckner et al., 2008.

Region	Abbreviation	Brodmann Areas included
Ventral medial prefrontal cortex	vmPFC	24, 10, 32ac
Posterior cingulate/ retrosplenial cortex	PCC/Rsp	29/30, 23/31
Posterior inferior parietal lobule	pIPL	39, 40
Dorsal medial prefrontal cortex	dmPFC	24, 32ac, 10p, 9
Lateral temporal cortex	LTC	21
Hippocampal formation	HF	Hippocampus proper; entorhinal cortex (EC) and parahippocampal cortex (PH)

Note: 32ac= dorsal anterior cingulate, 10p= Brodmann 10 polar

CHAPTER 2: INTRA-INDIVIDUAL VARIABILITY AS A MEASURE OF INFORMATION PROCESSING DIFFICULTIES IN MULTIPLE SCLEROSIS

2.1. OVERVIEW

The primary aim of the following chapter was to examine whether individuals with RRMS demonstrate greater IIV on a clinical measure of information processing speed, the Computerized Test of Information Processing (CTIP; Tombaugh & Rees, 2008). The CTIP has been previously used to investigate processing speed in MS (e.g., Tombaugh, Berrigan, Walker, & Freedman, 2010) and provides a precise measure of reaction time across three tasks that increase in cognitive difficulty (i.e. simple reaction time, choice reaction time, and semantic search reaction time). Individuals with neurologic impairments and healthy controls demonstrate perfect to near-perfect accuracy on the CTIP and hence performance on this measure is suggested not to be influenced by individual differences such as intelligence or education (Reicker, Tombaugh, Walker, & Freedman, 2007; Tombaugh, Rees, Stormer, Harrison, & Smith, 2007). The inclusion of tasks of increasing difficulty also allows for the examination of IIV in MS associated with sensorimotor speed (i.e. simple reaction time task), as well as potential increases in IIV associated with increases in cognitive demand (Hultsch et al., 2000).

A secondary aim of the study was to compare two methods of calculating IIV: (a) individual standard deviation (ISD) which accounts for variance due to practice, learning, and group mean-level differences, and (b) coefficient of variation (COV), which accounts for individual mean performance. Finally, IIV was compared to mean-level response speed to determine whether IIV provides unique information regarding MS performance.

2.2. PUBLICATION STATUS AND AUTHOR CONTRIBUTIONS

The following chapter is based on the manuscript: Wojtowicz, M., Berrigan, L., Fisk, J.D. (2012). Intra-individual variability as a measure of information processing speed difficulties in multiple sclerosis. *International Journal of MS Care (IJMSC)*, *14*(2), 77-83. doi: http://dx.doi.org/10.7224/1537-2073-14.2.77

This manuscript does not exactly replicate the final version published in the IJMSC. It is not a copy of the original published article and is not suitable for citation. Magdalena Wojtowicz, the first author, developed the conceptual rationale for the study, collected, analyzed and interpreted the data. She was also the primary contributing author to the manuscript, producing the initial draft and completing all major revisions.

2.3. ABSTRACT

Deficits in information processing speed are among the most commonly reported impairments in multiple sclerosis (MS) and are generally assessed by evaluating mean-level performance on time-limited tests. However, this approach to assessing performance ignores potential within-subject differences in MS patients that may be useful for characterizing cognitive difficulties in MS. An alternative method of measuring performance is by examining the degree of within-subject variability, termed intra-individual variability (IIV). Intra-individual variability provides information about the characteristics of a person's performance over time and may provide novel information about cognitive functioning in MS. This study examined IIV in performance on the Computerized Test of Information Processing (CTIP) using two within-subject variability methods: individual standard deviation and coefficient of variation. Eighteen females with relapsing-remitting MS and 18 healthy female controls completed the CTIP. Consistent with previous research, MS patients demonstrated slower overall mean performance on the CTIP compared with controls, with patients becoming increasingly slower than controls as cognitive demands increased across the tasks. Furthermore, MS patients demonstrated greater IIV as measured by individual standard deviations on all subtests of the CTIP, even with mean-level group differences as well as practice and learning effects controlled. These between-group differences were not found when the coefficient of variation, a more coarse measure of within-subject variability, was used. Intra-individual variability was also found to be a better predictor of neurologic status than mean-level performance. These results suggest that IIV may provide unique insight into cognitive functioning in MS.

2.3. INTRODUCTION

Cognitive impairments are highly prevalent in multiple sclerosis (MS), affecting an estimated 40% to 65% of patients (Benedict et al., 2006; Rao, Leo, Bernardin, & Unverzagt, 1991). Although the type of cognitive difficulties found in MS varies with disease duration and MS disease subtype, one of the most commonly reported impairments is in information processing speed (Chiaravalloti & DeLuca, 2008). Information processing speed is conceptualized as the rate at which elementary cognitive operations can be executed (Salthouse, 1996). A comprehensive understanding of difficulties with information processing speed is critical, as it has been hypothesized that processing speed deficits can contribute to impairments in memory and other higher-order cognitive functions (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004).

In clinical practice and in most clinical research, information processing speed is inferred from the number of test items completed or the accuracy of patients' performance on timed paper-and-pencil tests (e.g., Symbol Digit Modalities Test; SDMT (Smith, 1982) or on tests requiring verbal responses (e.g., Paced Auditory Serial Addition Test; PASAT; Gronwall, 1977). Computerized tests that provide direct measures of reaction time, such as the Computerized Test of Information Processing (CTIP; Tombaugh & Rees, 2008), can provide more precise measurement of processing speed. The CTIP consists of three reaction time tests that become progressively more demanding. Mean-level differences in reaction times between MS patients and healthy controls have been found, with MS patients demonstrating overall slower response times that progressively become slower, compared with healthy controls, as the cognitive demands of the task increase (Tombaugh et al., 2010). Similar findings have been

reported for other reaction time tasks (Archibald & Fisk, 2000). However, such tests have typically been used only to evaluate differences in mean-level performance between groups and have not considered within-subject differences in performance that may be important in characterizing cognitive impairments in clinical populations such as those with MS.

An alternative approach to characterizing cognitive performance is by examining within-subject variability in response speed (i.e., the fluctuation of response performance across serial trials). Within-person fluctuation in response latency on cognitive tasks, termed intra-individual variability (IIV), has been used as a measure of stability in performance (MacDonald et al., 2006). Low variability (i.e., high consistency) indicates better performance, whereas high variability (i.e., low consistency) indicates worse performance (Slifkin & Newell, 1998). Intra-individual variability can be reliably measured and is thought to reflect fairly stable endogenous factors, such as central nervous system (CNS) integrity, as opposed to normal variations in situation-dependent factors such as fluctuations in stress or sleep (Hultsch et al., 2000; Li, Aggen, Nesselroade, & Baltes, 2001).

Intra-individual variability may be a sensitive measure of cognitive functioning in clinical populations and is proposed to be a behavioural marker of overall CNS integrity (MacDonald et al., 2009, 2006). Within-subject variability has been found to relate to cognitive and neurologic status in studies of mild dementia (Hultsch et al., 2000), attention deficit and hyperactivity disorder (Westerberg & Hirvikoski, 2004), Parkinson's disease, and Alzheimer's disease (Burton, Strauss, Hultsch, Moll, & Hunter, 2006). In these studies, greater IIV was associated with worse cognitive performance or greater

neurologic impairment. An association between within-subject variability and neuroimaging indices of anatomical changes in both white and gray matter has also been described for patients with frontotemporal dementia, traumatic brain injury, and mild cognitive impairment (MacDonald et al., 2009). These studies suggest that IIV may provide novel insight into cognitive impairment; however, it has thus far received little attention in the study of MS.

When examining IIV, it is important to dissociate systematic factors that can affect variability (e.g., practice effects, learning, or boredom) and to ensure that differences in variability are not simply a statistical artefact of differences in individual or group mean performance (Hultsch et al., 2000). By controlling for these potential variables, one can begin to examine purer differences in IIV that may provide unique insight into the cognitive functioning of the individual. One method to account for the aforementioned systematic effects is to parcel out these effects using regression and then to calculate individual standard deviations (ISD) using standardized residual scores (Hultsch et al., 2000). A simpler, though potentially less sensitive, method of calculating within-subject variability is to compute the coefficient of variation (COV; the standard deviation divided by the mean) for each individual. Unlike ISD, this latter technique accounts only for differences in variability that may be due to individual mean-level performance. These two approaches may provide different estimates of within-subject variability and thus may have different implications for evaluating cognitive performance in conditions such as MS.

This study aimed to investigate IIV on a computerized clinical test of information processing speed (the CTIP) in a sample of relapsing-remitting MS patients. The CTIP is

a suitable task for measuring trial-by-trial variability, as it includes multiple trials of each task and records exact response times for each trial. We examined IIV on the CTIP using both ISD and COV in order to compare the potential information provided by these two approaches. We hypothesized that MS patients would demonstrate a similar pattern of decreased mean processing speed, as has been seen previously on this task (Tombaugh et al., 2010). However, we also expected that MS patients would be more variable in their performance compared with controls. We anticipated that ISD would be more sensitive to group differences in IIV than COV, as the former method can account for systematic influences (e.g., practice, learning effects, and boredom). Finally, we examined whether IIV could predict neurologic status in our sample.

2.4. METHOD

2.4.1. PARTICIPANTS

Eighteen female patients with MS and 18 healthy female control subjects participated in the study. MS participants were recruited from the Dalhousie MS Research Unit (DMSRU) during regular clinic visits. Seventeen MS participants were right-handed, and all were between 25 and 55 years of age, had been diagnosed with relapsing-remitting MS (Mcdonald et al., 2001), and had Expanded Disability Status Scale (EDSS; Kurtzke, 1983) scores between 0 and 6 (Table 2.1). MS participants were clinically stable at the time of the study; none had experienced a symptom relapse or had been taking corticosteroids within 3 months prior to participation. All MS participants were receiving first-line disease-modifying therapy for treatment of MS at the time of the study. None had comorbid neurodegenerative or psychiatric disorders or a history of substance abuse, learning disability, stroke, head trauma, or seizures. Those with a past history of depression or anxiety disorder were included if this was not an active clinical

problem at the time of the study. Healthy control participants, who met the same inclusion and exclusion criteria except those related to MS, were recruited through local advertisements. All participants reported normal or corrected-to-normal vision at the time of the study.

2.4.2. PROCEDURE

All participants provided written informed consent following procedures approved by the Capital District Health Authority Research Ethics Board. Participants completed the Beck Depression Inventory–Fast Screen (BDI-FS; Beck, Steer, & Brown, 2000) as well as the CTIP in a quiet room with the same administrator and were compensated $20 for completing the study.

2.4.3. MEASURES

Disability was measured with the EDSS (Kurtzke, 1983). EDSS scores were obtained from the medical record of the MS participants' most recent DMSRU clinic visit prior to completing the study (i.e., within 2 weeks of participating in the study).

Depression symptoms were measured using the BDI-FS (Beck et al., 2000). Depression is highly prevalent in MS and can affect performance on cognitive tasks (Demaree, Gaudino, & DeLuca, 2003; Korostil & Feinstein, 2007). The BDI-FS provides a measure of depression not confounded with neurologic symptoms and has been validated for use with individuals with MS (Benedict, Fishman, McClellan, Bakshi, & Weinstock-Guttman, 2003).

The CTIP (Tombaugh & Rees, 2008) was used to measure information processing speed. The CTIP includes three reaction time subtests that become progressively more demanding: 1) a simple reaction time (SRT) task in which participants are asked to press

the spacebar as soon as a single "X" appears on the screen, 2) a choice reaction time (CRT) task in which participants are presented with either the word "DUCK" or the word "KITE" and are asked to press the right key (i.e., "/") for the former and the left key (ie, "z") for the latter, and 3) a semantic search reaction time (SSRT) task in which participants are asked to decide if a specific word belongs to a category. On each trial, one of four semantic categories is presented at random (Weapon, Furniture, Bird, or Fruit), and 2 seconds later a word appears below the category. The participants are asked to press the right key (i.e., "/") if the word belongs to the category and the left key (i.e., "z") if it does not belong to the category. Each task includes 10 practice trials and 30 test trials (total CTIP duration of 10–15 minutes).

2.5 RESULTS

2.5.1. DEMOGRAPHICS

Demographic variables for the MS and control groups are presented in Table 2.1. The two groups were matched on age ($F(1,34) = 0.326$, $p = .572$) and years of education ($F(1,34) = 2.511$, $p = .122$) and did not differ on their self-reported symptoms of depression ($F(1,34) = 0.01$, $p = .921$). Because no differences in depressive symptoms between the two groups were found, this variable was excluded from further analyses. For MS participants, the median EDSS score was 2.0 (range, 1–3.5), and the median duration of disease as measured in years since onset of reported MS symptoms was 6.5 (range, 0–28).

2.5.2. MEAN LEVEL PERFORMANCE ON CTIP

Accuracy information is not available for the SRT. The groups did not differ on number of errors on the CRT ($F(1,34) = 0.168$, $p = .684$) or the SSRT ($F(1,34) = 0.373$, $p = .546$). On the CRT, mean (SD) number of errors was 0.44 (0.86) for the MS group and

0.33 (0.77) for the control group. On the SSRT, mean (SD) number of errors was 0.94 (1.30) for the MS group and 0.72 (0.83) for the control group.

Group mean reaction time scores on each CTIP subtest are shown in Figure 2.1. A repeated-measures analysis of variance (ANOVA) with CTIP subtest as the within-subject variable and Group as the between-subject variable was used to analyze the mean reaction time scores; the Greenhouse-Geiser correction was applied. This analysis revealed that reaction times increased as the tasks became more cognitively demanding (Test: $F(1.5, 50.5) = 289.77$, $p < .001$) and that the MS group had significantly longer reaction times than controls (Group: $F(1,34)= 16.01$, $p < .001$). In addition, the reaction times of the MS participants diverged increasingly from those of controls as the subtests became more difficult (Test × Group: $F(1.5, 50.5)= 4.03$, $p = .035$). A series of one-way ANOVAs revealed that MS participants had significantly longer reaction times than controls on each subtest of the CTIP (CRT: $F(1,34) = 11.31$, $p = .002$; SRT: $F(1,34) = 12.78$, $p = .001$; SSRT: $F(1,34) = 10.93$, $p = .002$). MS participants demonstrated slower reaction times even when the potential influences of motor abilities on processing speed were controlled (i.e., mean reaction times from the SRT were subtracted from CRT and SSRT; CRT: $F(1,34) = 6.63$, $p = .015$; SSRT: $F(1,34) = 9.63$, $p = .004$).

2.5.3. VARIABILITY ON CTIP

Intra-individual variability was measured by calculating ISDs for all participants. Only correct trials were used for this calculation, and extreme values (i.e., 3 SDs from the mean of each group) were removed.). This represents a conservative approach to calculating IIV, as removing extreme values will likely reduce the amount of within-subject variability (Burton et al., 2006; Hultsch et al., 2000). To avoid statistical issues

associated with unequal and missing trials, group-level mean values were imputed for missing data (<5% of the total data). Systematic differences in reaction time due to trial as well as mean-level differences in reaction time associated with group membership were parceled from the data using a regression with group and trial information entered as independent variables (Hultsch et al., 2000). Then, standardized residual scores were converted to T scores to allow for comparisons across tasks, and an ISD score was calculated for each participant. In addition to ISD, COVs (standard deviation of reaction time divided by mean reaction time and multiplied by 100) were calculated for correct trials for each participant. This approach eliminates the impact of the individuals' mean-level differences on standard deviation and provides an alternative measure of within-person variability. Both ISDs and COVs were compared using a series of ANOVAs.

Group ISDs on each CTIP test are shown in Figure 2.2. A repeated-measures ANOVA revealed that overall IIV increased with subtest difficulty (Test: $F(2,68) = 5.3$, $p = .007$) and that MS participants were more variable in their performance (Group: $F(1,34)= 20.02$, $p < .001$). However, no significant group by test interaction was found (Test × Group: $F(2,68)= 0.340$, $p = .71$). A series of one-way ANOVAs revealed that MS participants were significantly more variable than controls on each subtest of the CTIP (CRT: $F(1,34)= 14.16$, $p = .001$; SRT: $F(1,34) = 9.70$, $p = .004$; SSRT: $F(1,34) = .26$, $p = .001$). MS participants had greater variability even when the potential influences of motor abilities on processing speed were controlled (i.e., SRT performance was regressed from CRT and SSRT ISD scores; CRT: $F(1,34)= 10.48$, $p = .003$; SSRT: $F(1,34) = 14.01$, $p = .001$).

Group COVs on each test are shown in Figure 2.3. A repeated-measures ANOVA revealed that COVs also increased with test difficulty (Test: $F(2,68) = 13.38$, $p < .001$). However, MS participants were not found to be more variable in their performance (Group: $F(1,34)= 3.20$, $p = .08$), nor was there a significant group by test interaction (Test × Group: $F(2,68)= 1.146$, $p = .324$) when COV was examined. A series of one-way ANOVAs revealed that MS participants did not have greater COVs compared with controls on any of the CTIP subtests (SRT: $F(1,34)= 3.53$, $p = .069$; CRT: $F(1,34) = 0.01$, $p = .921$; SSRT: $F(1,34) = 2.54$, $p = .120$).

2.5.4. PREDICTING GROUP MEMBERSHIP

We examined the unique contributions of mean performance and IIV on predicting group membership using a discriminant function analysis. Mean reaction time and ISD scores for each CTIP task were included simultaneously in the analysis to determine which of these variables could best predict whether a participant belonged to the MS group or the control group. We did not include COVs of each CTIP subtest given that no significant differences between groups were found. The combined information about mean-level performance and IIV successfully predicted group membership (Wilks $\Lambda = 0.54$, χ^2_6 [N = 36] = 19.138, $p = .004$) and correctly classified 83.3% of all cases. Table 2.2 presents the standardized weights of each predictor. These results indicate that ISD scores on the SSRT ($\beta = 0.83$) and the SRT ($\beta = 0.60$) were the best predictors for identifying whether a subject belonged to the MS group or the control group.

2.6 DISCUSSION

Deficits in information processing speed are among the most commonly reported cognitive difficulties in MS (Chiaravalloti & DeLuca, 2008). This study examined an

alternative approach to characterizing information processing speed by measuring IIV in response speed on the CTIP in a sample of MS patients and healthy controls. To our knowledge, this study represents the first investigation of within-subject variability on the CTIP in MS.

As shown previously by Tombaugh and colleagues (2010) we found that MS patients demonstrated slowing in mean response time on all three CTIP subtests compared with healthy controls, despite being equally accurate in their performance. In addition, we found that MS patients' response speed became increasingly slower than that of controls on the more cognitively demanding subtest (i.e., SSRT; Figure 2.1). The consistency of these findings with previous reports in MS suggests that the CTIP may be a reliable clinical measure of processing speed deficits in this disease.

In addition to slowed information processing, the MS patients also demonstrated greater IIV in their response speed when ISDs were examined. A significant difference in variability emerged even though mean-level group differences in response time and effects of practice, learning, and boredom were controlled. Differences in variability between groups were not found when within-subject variability was calculated using COVs. This likely occurred because COVs solely account for differences in variability due to individual mean-level performance. Other factors that may influence variability such as practice effects, learning, boredom, and group differences in mean reaction time are not accounted for and can artificially mask or inflate true within-subject variability. Calculation of ISD as described in this study helps eliminate systematic variability caused by the aforementioned factors and produces a purer measure of variability that cannot be explained away by extraneous factors. When studied in this way, within-subject

variability appears to represent a unique intrinsic characteristic of the individual that may be affected by endogenous changes in the individual's CNS integrity (Hultsch et al., 2000).

We also sought to determine whether IIV on the CTIP contributed distinct information about cognitive performance in our sample, as compared to mean-level differences in reaction time alone. Our analysis revealed that IIV on the SSRT and SRT subtests, as measured by ISD, best predicted group membership. Mean-level differences in reaction time were not as useful in predicting neurologic status. It is noteworthy that IIV on the CRT also contributed little to the discrimination of group membership in this analysis and that MS patients showed the greatest variance in ISD on this task (Figure 2.2). Perhaps the greater difficulty in performing consistently on this task shown by some MS patients reflects the considerable change in task demands for this subtest. Specifically, this requires shifting from the SRT subtest, involving a unimanual response to a single target stimulus, to the CRT subtest, which requires bimanual responding based on a decision between two responses. Because the standard CTIP presents the three subtests in a set order of increasing difficulty, randomization of the subtest order was not attempted in the current study. Nevertheless, the findings do suggest that IIV, as measured by ISD, provides unique information about the neurologic status of MS patients and may provide a better indicator of cognitive functioning than mean-level response latency in relatively mildly affected patients.

Our findings of greater IIV in MS patients compared with controls is consistent with findings of greater variability in performance on reaction time tasks in other neurologic populations, such as those with traumatic brain injury, dementia, and

Parkinson's disease (Burton et al., 2006; Hultsch et al., 2000; MacDonald et al., 2009). Recently in a sample of relapsing-remitting and secondary progressive MS patients, standard deviation in response time on a timed digit recognition task was also associated with greater self-reported fatigue (Bruce, Bruce, & Arnett, 2010). Our findings add to the accumulating literature suggesting that within-subject variability is an important component of cognitive performance and that variability may provide additional insight into the difficulties experienced in neurologic conditions, including MS. Although this study included only a relatively small sample of mildly affected relapsing-remitting MS patients, our findings clearly demonstrate the need for future research on IIV with a broader range of MS disease subtypes and disability severity. Future research examining individual response variability in other cognitive domains would also help further elucidate the function of response variability as a measure of the MS disease process.

Table 2.1. Descriptive statistics for demographic variables

Variable	MS group (n = 18)	Control group (n = 18)
Age, mean (SD), y	42.33 (7.30)	40.83 (8.42)
Education, mean (SD), y	14.56 (1.91)	15.67 (2.28)
BDI-FS, mean (SD)	1.22 (1.77)	1.17 (1.58)
Disease duration,[a] median (range), y	6.5 (0–28)	—
EDSS score, median (range)	2.0 (1–3.5)	—

Abbreviations: BDI-FS, Beck Depression Inventory–Fast Screen; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; y, years.

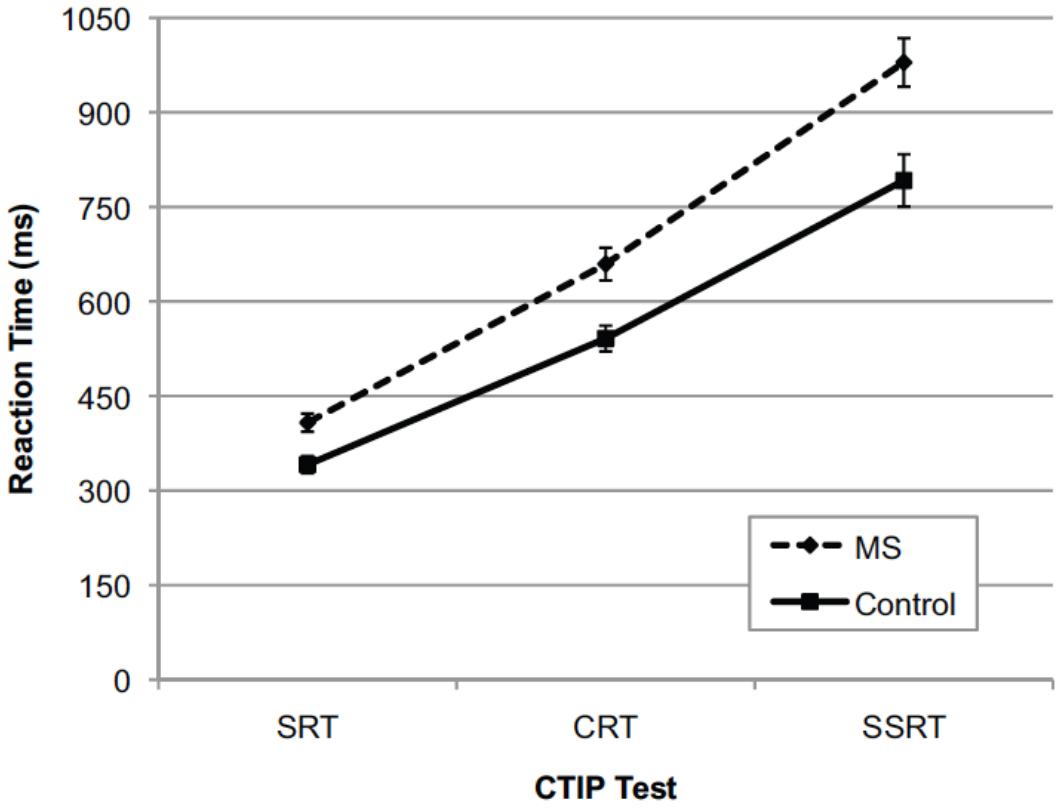
[a]Time since onset of reported MS symptoms.

Table 2.2 Standardized coefficients of predictor variables of the discriminant function

Predictor	Standardized coefficient
ISD for SRT	0.601
ISD for CRT	−0.229
ISD for SSRT	0.828
Mean for SRT	0.243
Mean for CRT	0.264
Mean for SSRT	−0.316

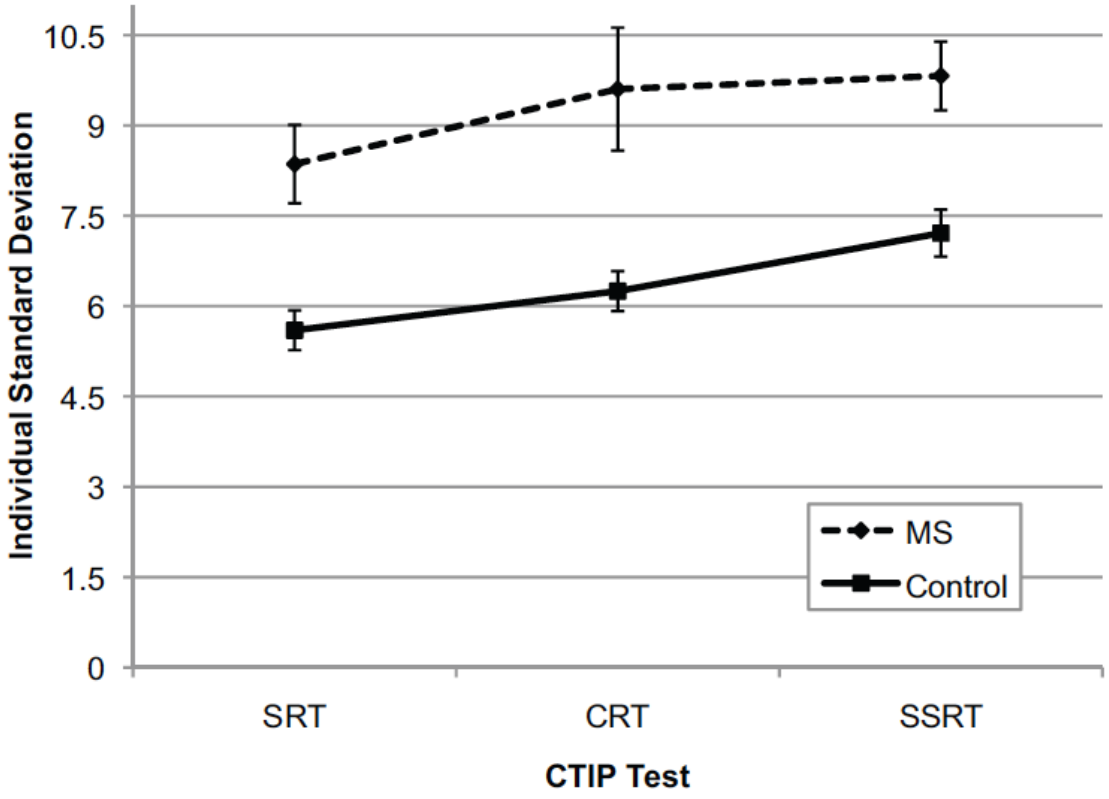
Abbreviations: CRT, choice reaction time; ISD, individual standard deviation; SSRT, semantic search reaction time; SRT, simple reaction time.

Figure 2.1 Mean reaction times for MS participants and controls on the three CTIP tests



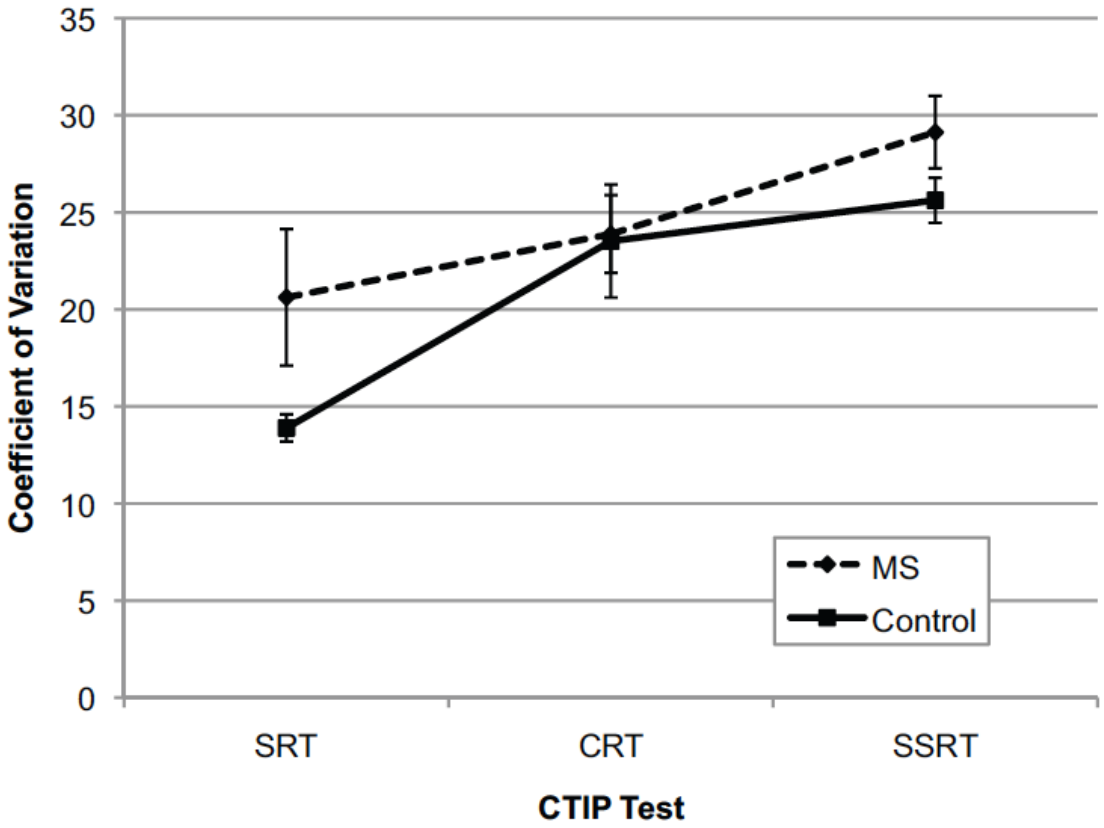
Error bars represent standard error. CRT, choice reaction time; CTIP, Computerized Test of Information Processing; SRT, simple reaction time; SSRT, semantic search reaction time.

Figure 2.2 Mean individual standard deviations for MS participants and controls on the three CTIP tests



Error bars represent standard error. CRT, choice reaction time; CTIP, Computerized Test of Information Processing; SRT, simple reaction time; SSRT, semantic search reaction time.

Figure 2.3 Mean coefficient of variation for MS participants and controls on the three CTIP tests



Error bars represent standard error. CRT, choice reaction time; CTIP, Computerized Test of Information Processing; SRT, simple reaction time; SSRT, semantic search reaction time.

2.7 SUMMARY

Chapter 2 revealed that individuals with RRMS demonstrate greater IIV compared to healthy controls on a clinical measure of information processing (i.e. CTIP). These differences were apparent using the ISD approach, which accounts for systematic influences on variance associated with practice, learning and group mean-level performance. Individuals with RRMS demonstrated greater variability even when potential sensorimotor confounds were accounted for (i.e., performance on the simple reaction time task). Consistent with previous findings of IIV (e.g., Hultsch et al., 2000), IIV increased with subtest difficulty for both groups. Furthermore, IIV was also found to be a better predictor of group membership compared with mean-level performance. Together these findings suggest that IIV may be an important component of cognitive performance in MS.

In Chapter 3, IIV in MS will be further examined using a computerized experimental task of attention and executive function, the Attention Network Test-Interaction (ANT-I; Callejas, Lupiàñez, Funes, & Tudela, 2005). Since IIV is suggested to reflect momentary lapses of attention (Bunce, Warr, & Cochrane, 1993) and executive control failures, the relations between IIV, ANT-I attention networks (i.e. alerting, orienting, and executive function), as well as performance on a clinical measure of information processing speed (i.e. PASAT) will be explored. Finally, the relative utility of IIV in distinguishing patients with MS from matched healthy controls compared with other cognitive indicators will be examined.

CHAPTER 3: INTRA-INDIVIDUAL VARIABILITY, PROCESSING SPEED, AND ATTENTION NETWORK EFFICIENCY IN MULTIPLE SCLEROSIS

3.1. PUBLICATION STATUS AND AUTHOR CONTRIBUTIONS

The following chapter is based on the manuscript: Wojtowicz, M., Omisade, A., Fisk, J.D. (2013). Indices of Cognitive Dysfunction in Relapsing-Remitting Multiple Sclerosis: Intra-individual Variability, Processing Speed and Attention Network Efficiency. *Journal of the International Neuropsychological Society (JINS)*, *14*(2), 77-83. doi:10.1017/S1355617713000027.

This manuscript does not exactly replicate the final version published in the JINS. It is not a copy of the original published article and is not suitable for citation. Magdalena Wojtowicz, the first author, developed the conceptual rationale for the study, collected 50% of the data and then analyzed and interpreted the data. She was also the primary contributing author to the manuscript; producing the initial draft and completing all major revisions.

3.2. ABSTRACT

Background: Impairments in attention and information processing speed are common in Multiple Sclerosis (MS) and may contribute to impairments of other cognitive abilities. This study examined attentional efficiency, information processing speed and intra-individual variability in response speed using the Attention Network Test-Interactions (ANT-I) in mildy-affected patients with MS. Methods: Thirty-one patients with relapsing remitting MS and 30 age, sex, and education-matched controls completed the ANT-I, as well as the Paced Auditory Serial Attention Test (PASAT), as a standard clinical measure of information processing efficiency. Results: As expected, patients with MS were slower in reaction time performance on the ANT-I and had poorer performance on the PASAT compared to controls. Patients with MS also demonstrated poorer efficiency in their executive control of attention on the ANT-I, suggesting difficulties with top-down allocation of attention. In addition, the MS group demonstrated greater intra-individual variability in the responses to the ANT-I even when their slower overall response time and other factors such as practice were accounted for. Intra-individual variability was found to best predict group membership compared to PASAT scores and other ANT-I scores. Conclusions: These results suggest that intra-individual variability may provide sensitive, unique and important information regarding cognitive functioning in early MS.

3.3 INTRODUCTION

Cognitive impairments are common in multiple sclerosis (MS), with approximately 45-70% reporting cognitive difficulties (Bobholz & Rao, 2003; Heaton, Nelson, Thompson, Burks, & Franklin, 1985; Jønsson et al., 2006; Rao, Leo, Ellington, Nauertz, Bernadin, & Unverzagt, 1991). Though the type of impairment varies with disease duration and subtype (e.g., relapsing-remitting; primary progressive, etc), the most common deficits are in information processing speed and attention (Chiaravolloti & Deluca, 2008). Understanding the core cognitive deficits affecting individuals with MS is critical because problems with attention and information processing speed can contribute to impairments in higher-order cognitive functions such as memory (DeLuca et al., 2004). While there is a growing interest in assessing attention processes in MS, measuring attention is dependent on the way in which attention is defined. Posner's model proposes three attention networks, including: (i) an alerting network that is involved in achieving and maintaining vigilance, (ii) an orienting network that involves selecting and attending to specific spatial information, and (iii) an executive network that is involved in goal-directed control of attention and decision-making (Posner & Petersen, 1990; Posner, 1994). The Attention Network Test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002) and its variant the Attention Network Test-Interaction (ANT-I; Callejas et al., 2005; Callejas, Lupiáñez, & Tudela, 2004) are designed to assess the efficiency of these three networks using a combined cued reaction time (Posner, 1980) and flanker task (Eriksen & Eriksen, 1974).

Both the ANT and ANT-I have been used to assess attention network efficiencies in MS. Deficits in the alerting network of individuals with MS have been found using the ANT (Crivelli et al., 2012; Urbanek et al., 2010). Interactions between the alerting and

executive networks have also been found using the ANT and the ANT-I, suggesting that the presence of alerting cues alter executive control in patients with MS (Crivelli et al., 2012; Omisade et al., 2012). Furthermore, patients with MS with greater pathology on structural MRI scans have been found to have greater disturbances in the executive network while in an alerted state (Omisade et al., 2012). In addition to providing information regarding attention network performance, the ANT and ANT-I can also be used to examine speed and stability of information processing as both require participants to remain vigilant and perform a complex reaction time task for approximately 20 minutes.

Understanding performance characteristics of individuals with MS within a task is particularly important given that they not only demonstrate slowed processing speed (DeLuca et al., 2004; Archibald and Fisk, 2001) but also more performance variability (Bodling, Denney, & Lynch, 2012; Bruce, Bruce, & Arnett, 2010; Wojtowicz, Berrigan, & Fisk, 2012). This intra-individual performance variability reflects fluctuations in reaction time across a series of trials and is considered to be a marker of overall central nervous system integrity (MacDonald, Nyberg, & Bäckman, 2006). Low variability (i.e. high consistency) is thought to reflect better neurocognitive functioning (MacDonald et al., 2006) whereas increased intra-individual variability has been associated with cognitive dysfunction of varying severity in clinical populations, including mild dementia (Hultsch et al., 2000), Parkinson's disease, Alzheimer's disease (Burton et al., 2006), and attention deficit and hyperactivity disorder (Westerberg, Hirvikoski, Forssberg & Klingberg, 2004).

There is increasing evidence that intra-individual variability may provide information about cognitive difficulties in MS. Patients with MS have been found to be more variable than healthy controls on reaction time tasks, even when controlling for potential sensorimotor confounds (Wojtowicz et al., 2012). This variability is increased in patients with MS on tasks with greater cognitive demands (Bodling et al., 2012; Wojtowicz et al., 2012) and is associated with greater self-reported fatigue (Bruce et al., 2010). Together these findings suggest that intra-individual variability may be a sensitive indicator of changes in cognitive functioning for mildly affected patients with MS who otherwise may not demonstrate deficits on commonly used clinical tests.

The present study investigated intra-individual variability in information processing speed and attention network efficiency in a sample of patients with mildly affected, relapsing-remitting MS using the ANT-I. We examined the utility of intra-individual variability in distinguishing patients with MS from matched healthy controls. We also explored the associations between intra-individual variability and attention network scores on the ANT-I, as well as scores on another common clinical test of cognition, within our sample of patients with MS.

3.4 METHOD

3.4.1. PARTICIPANTS

All participants provided informed consent following procedures approved by the Capital District Health Authority Research Ethics Board. Thirty-one females with MS and 30 healthy female control subjects participated. We recruited females with relapsing-remitting MS (RRMS) to maximize the homogeneity of our sample and because of their predominance among clinic-attending patients (Koch-Henriksen & Sørensen, 2010). All

participants with MS were recruited from the Dalhousie MS Research Unit (DMSRU), Halifax, Nova Scotia. Patients with MS were between 25 and 55 years of age, diagnosed with clinically definite RRMS according to the McDonald criteria (Mcdonald et al., 2001), with Expanded Disability Status Scale (EDSS; Kurtzke, 1983) scores between 0 and 6. All were stable at the time of the study; none had experienced a symptom relapse or had been taking corticosteroids within three months prior to participation. Twenty-four were receiving first-line disease-modifying drug therapy, two were taking immunosuppressive medications, and the remaining participants were not using disease-modifying therapies (O'Connor & Devonshire, 2008). Based on their self-report and a review of their health records, none of the patients had co-morbid neurodegenerative or psychiatric disorders or a history of: substance abuse, learning disability, stroke, head trauma, or seizures. Those with a history of depression or anxiety disorders were included if clinical symptoms were not interfering with daily functioning at the time of the study as determined by self-report to DMSRU clinic staff. Healthy control participants, who met the same inclusion and exclusion criteria except those related to MS, were recruited through local advertisements. All participants reported normal or corrected-to-normal vision at the time of the study.

3.4.2. CLINICAL MEASURES

EDSS scores for all patients with MS were obtained from the medical record of their most recent DMSRU clinic visit, which was within 2 weeks of their participation. At the time of the study, participants completed the Beck Depression Inventory-Fast Screen (BDI-FS; Beck et al., 2000) to assess presence and severity of symptoms associated with depression. All participants also completed the 3-second and 2-second versions of the

PASAT included in the Multiple Sclerosis Functional Composite battery (Fischer, Rudick, Cutter, & Reingold, 1999) as clinical measures of information processing speed.

3.4.3. ATTENTION NETWORK TEST-INTERACTIONS (ANT-I)

The ANT-I employs a 2 (alerting) x 3 (orienting) x 2 (executive) design (See Figure 3.1). Twenty-five practice trials (with visual feedback for correct and incorrect responses) are followed by 288 test trials (without feedback) in which stimuli are presented at intervals varying from 400 to 1600 ms. Participants are presented with a fixation cross in the middle of a computer screen on each trial. The alerting stimulus is a 50 ms, 2000 Hz tone that follows the inter-stimulus interval on half of the trials. The orienting cue is an asterisk that is presented on the screen for 50 ms, on 2/3 of the trials. This occurs 100 ms after the alerting tone or the period when the tone would have been presented. Ninety-six of the trials are preceded by a "valid" spatial cue in which the asterisk appears in the location where the target stimulus will subsequently appear. Another 96 trials are preceded by an "invalid" cue, in which the asterisk is presented at the same distance from the central fixation cross, but in the opposite direction as the eventual target location (i.e. above rather than below the fixation cross). No cue is presented on the remaining 96 "no cue" trials. The target stimulus on every trial is an arrow that appears either above or below the fixation cross. The participant's task is to identify its direction by pressing either the "/" key for a right-pointing arrow or the "z" key for a left-pointing arrow on the computer keyboard. The executive (or "congruency") condition is manipulated by surrounding the target arrow with two arrows of equal size on each side. These "flanker" arrows point either in the same (congruent) or the opposite (incongruent) direction as the target. Half of the trials present congruent flankers while on the other half the flankers are

incongruent with the target direction.

3.4.4. DATA ANALYSIS

The efficiencies of the three attention networks were calculated from the ANT-I as follows: Alerting efficiency (Network Score) was evaluated by subtracting the subject's mean reaction time (RT) in conditions when the alerting tone was present from their mean RT when the alerting tone was absent. Orienting Network Score was evaluated by subtracting mean RT in the valid cue conditions from the mean RT in the invalid cue conditions. Executive control Network Score was measured by subtracting the mean RT for congruent flanker trials from the mean RT for incongruent flanker trials (Callejas et al., 2005; Callejas et al., 2004; Fan et al., 2002). Only correct trials were included in these analyses. Interactions among network scores and group were determined using a group (2) x alerting (2) x orienting (3) x executive (2) mixed model ANOVAs for RT.

Intra-individual variability was measured by calculating individual standard deviations (ISDs) for all participants. This method of estimating intra-individual variability has been found to be more sensitive than alternative measures, like coefficient of variation (CoV; Wojtowicz et al., 2012). Only correct trials were used. Data were screened for outliers (i.e. > than 3 SD from the group means) with mean group RTs imputed for missing values, representing a conservative approach to estimating individual variability (Hultsch et al., 2000). To avoid confounding with within-person variability, systematic differences in RT due to trial and block as well as mean level differences in RT associated with group membership were removed (Hultsch et al., 2000). Residual scores were converted to T-scores and an ISD score was calculated for each participant.

3.5 RESULTS

Demographic and clinical data for the participants can be found in Table 3.1. The groups

were matched on age ($t(59)= .819$, p= .42; Cohen's $d= 0.21$) and education ($t(59)= -1.34$, p= .19; Cohen's $d= 0.34$). Patients with MS endorsed more depressive symptoms on the BDI-FS ($t(56.05)= 2.11$, $p= .04$; Cohen's $d= 0.56$); six scored within the clinical range (i.e. >4). Patients with MS made fewer correct responses on both the 3-second ($t(59)= -2.89$, p= .005; Cohen's $d= 0.75$) and 2-second PASAT ($t(53.96)= -3.94$, p <.001; Cohen's $d= 1.07$). Using normative values published by Boringa et al. (2001), individual PASAT scores were converted into z-scores and a 1.5 standard deviation cut-off was used to determine impairment on the PASAT-3 and PASAT-2. Two patients with MS met this criterion for impairment on the PASAT-3 while 8 were impaired on the PASAT-2. One control was impaired on the PASAT-3 and 2 controls were impaired on the PASAT-2. This represents the expected variation of performance found in a normally distributed healthy sample.

Patients with MS and controls did not differ in response accuracy on the ANT-I ($t(59)= -.89$, $p= .38$; Cohen's $d= .23$; Correct trials: $M_{MS}= 282.4$, $SD_{MS}= 5.79$, Accuracy $\%_{MS}= 98.0\%$; Correct trials: $M_{Control}= 283.4$ $SD_{Control}= 4.06$, Accuracy $\%_{MS}= 98.4$). A group (2) x alerting (2) x orienting (3) x executive (2) mixed model ANOVA of mean RT was used to examine interactions between networks and group (Callejas et al., 2005; Callejas et al., 2004). This revealed a main effect of group, with patients with MS demonstrating slower overall performance ($F(1,59)= 16.24$, $p< .001$; $M_{MS}= 743.40$, SD_{MS} =1 17.87, $M_{Control}= 630.511$ $SD_{Control}= 100.52$; Cohen's $f= 0.52$), as well as main effects of alerting ($F(1,59)= 33.00$, $p< .001$; Cohen's $f= .748$), orienting ($F(1,59)= 74.42$, p<.001; Cohen's $f= 1.12$), and executive control ($F(1,59)=449.98$, $p<.001$; Cohen's $f= 2.76$). Both patients with MS and controls performed faster when presented with alerting

tones and valid spatial cues, and when target flankers were congruent. A group x executive interaction ($F(1,49)= 4.05$, $p< .05$; Cohen's $f= 0.26$) was examined further using planned pairwise comparisons, which demonstrated that patients with MS had particularly slowed performance on trials with incongruent flankers (M_{MS}=808.26, SD_{MS}= 132.43; $M_{Control}$= 684.12, $SD_{Control}$= 109.91). Figure 3.2 displays between group differences for individual alerting, orienting and executive network scores as determined by the subtraction of RTs described in the Methods section. A series of t-tests revealed no difference between patients with MS and controls for the alerting ($t(59)= -.479$ $p= .63$) and orienting networks ($t(59)= .869$, $p= .39$), though a difference in the executive network was evident for the MS group ($t(59)= 2.00$, $p= .05$; Cohen's $d= .52$).

A t-test was used to compare ISD scores across groups. Patients with MS had greater variability across all trials of the ANT-I ($t(59)= 5.92$, $p< .001$; $M_{MS}= 9.37$, $SD_{MS} = 1.71$, $M_{Control} = 6.99$ $SD_{Control}= 1.42$; Cohen's $d= 1.5$). Pearson correlations were then calculated to examine potential relations between ISD, attention network scores, performance on the PASAT, and disease characteristics within the MS group. PASAT data from one patient were removed due to the participant's inability to follow the test instructions. ISD scores did not correlate significantly with ANT-I Network scores (Alerting Network, $r= .10$, $p= .61$; Orienting Network, $r= .26$, $p= .15$; Executive Network, $r= .12$, $p= .53$), or PASAT scores (PASAT-2, $r= -.22$, $p= .23$; PASAT-3, $r= -.33$, $p= .08$); or with disease characteristics (EDSS, $r= .17$, $p= .37$), years since symptom onset, $r= .17$, $p= .46$), or depressive symptoms (BDI-FS, $r= .09$, $p= .65$).

Next, we used logistic regression to examine the unique contributions of ISD, Executive Network scores, and PASAT scores to predicting group membership (MS vs.

control). Alerting and Orienting Network scores were not entered into the analysis as they did not differ between groups. The combined information significantly predicted group membership ($\chi^2(4,N= 59)= 37.49$, $p< .001$; Cox & Snell R square= .47; Nagelkerke R square= .63) and correctly classified 86.4% of all cases (24 of 29 MS patients; 27 of 30 controls). Table 3.2 presents the standardized weights of each predictor. Individual variability was the best predictor of group membership (i.e. ISD scores; $p= .001$) followed by PASAT 2 scores ($p= .014$).

3.6 DISCUSSION

Deficits in information processing speed and attention are two of the most commonly reported cognitive impairments in MS (Chiaravolloti & Deluca, 2008;Arnett & Strober, 2011). This study sought to investigate response speed, attention network efficiency and intra-individual variability in information processing speed in a sample of mildly affected patients with MS using the ANT-I. The ANT-I examines separate attention networks (i.e. alerting, orienting, and executive), provides information regarding general information processing efficiency, and can be used to examine the stability of a participant's performance over time through calculating intra-individual variability. We also examined the relative utility of intra-individual variability, attention network efficiency and performance on a standard cognitive test (i.e. PASAT-3; PASAT-2) in distinguishing patients with MS from matched healthy controls.

Inefficiency in PASAT performance is commonly found among patients with MS (Fisk & Archibald, 2001; Tombaugh, 2006) and our sample of mildly affected patients with MS performed worse than controls on both the 3-second and 2-second PASATs. Despite these mean-level group differences, however, relatively few individuals with MS were cognitively impaired. While PASAT scores have been found to correlate with other

cognitive tasks, disease severity, and neuroimaging indices of neurological impairment (Bellmann-Strobl et al., 2009; Hayton et al., 2012; Snyder & CappelJeri, 2001) it is unclear whether this is due to slowed processing speed, impaired sustained or divided attention, or poor working memory (Tombaugh, 2006). Thus, the ability of the PASAT to provide insight into specific cognitive and neurological functioning is limited. As a result, a current debate exists whether the PASAT should be replaced by the Symbol Digit Modalities Test (Smith, 1982) for the assessment of information processing speed in MS (Brochet et al., 2008; Drake et al., 2010). However, neither of these assessment methods provide a precise measure of reaction time nor do they allow for the assessment of information processing speed within specific cognitive domains. In contrast, the ANT-I allows for evaluation of information processing efficiency in individuals with MS across isolable attention networks (Ishigami & Klein, 2009). Response accuracy did not differ between the groups and all subjects demonstrated the expected facilitatory effects of alerting tones, valid spatial cues and congruent flankers (Callejas et al., 2005; Callejas et al., 2004). However, patients with MS demonstrated evidence of executive network impairment in their prolonged responses when required to ignore conflicting flanking stimuli. In the MS group, inefficiencies in performance became most evident under situations requiring the resolution of conflicting input to determine response options.

Our findings that patients with MS have problems allocating attentional resources necessary for response inhibition differ somewhat from previous studies using the original version of the ANT in individuals with MS (Crivelli et al., 2012; Urbanek et al., 2010). These investigators found deficiencies in the alerting network of patients with MS and differences in response inhibition only in the context of an alerting cue (i.e. patients

with MS were slower on incongruent trials after the presence of an "alerting" cue). This may be attributable to methodological differences between the ANT and the ANT-I since the alerting and orienting networks in the ANT are confounded (Ishigami & Klein, 2009; Ishigami & Klein, 2010) with both being defined by similar visual cues (i.e. a double asterisk as an alerting cue and a single asterisk as a spatial orienting cue). The ANT-I uses separate sensory modalities for alerting and orienting, with an auditory cue for the former and a visual cue for the latter, and this difference in sensory modalities for the alerting network may account for the discrepant findings. Consistent with our results, Omisade et al. (2012) did not find differences in the alerting network in patients with MS using the ANT-I, although they did find executive network inefficiency when patients were in the alerted state. While our findings confirm the presence of executive network inefficiency among the patients with MS, we did not find that this was dependent on the alertness of patients. The differences between our findings and those of Omisade and colleagues (2012) may be attributable to the differences in disease severity, with the patients in the current sample being more mildly affected. Since Omisade et al. (2012) demonstrated that the strength of the alerting x executive interaction increases with greater structural MRI damage; it is possible that the patients in our sample were too mildly affected for this interaction to emerge. Despite some discrepancies in ANT and ANT-I performance among patients with MS in the studies to date, all have demonstrated some degree of inefficiency in the executive control in MS.

Our findings are consistent with previous suggestions of impaired "top-down attentional control" among patients with MS (McCarthy, Beaumont, Thompson, & Peacock, 2005; Nebel et al., 2007; Paul, Beatty, Schneider, Blanco, & Hames, 1998).

Decline in the executive control of attention in our patient sample did not reflect generalized slowing or inefficiency of attention networks. Thus, these results are consistent with DeLuca et al.'s (2004) Independent Consequence model of cognitive dysfunction, which proposes that impairments in some higher-order cognitive abilities in individuals with MS, such as executive functions, may be independent of a generalized slowing of information processing.

Importantly, we also found that patients with MS demonstrated greater intra-individual response variability on the ANT-I, regardless of any cognitive slowing or difficulties with executive control of attention. This is consistent with other studies that have demonstrated greater intra-individual variability in RT performance in MS (Bodling et al., 2012; Bruce et al., 2010; Wojtowicz et al., 2012) as well as other neurodegenerative disorders (Burton et al., 2006; Hultsch et al., 2000). Greater intra-individual variability in our sample of patients with MS was not associated with disease duration or EDSS. Poor associations between EDSS and cognitive test performance are common (Arnett & Strober, 2011). Although the range of EDSS scores in our sample was constrained by our selection criteria, Bodling et al. (2012) also failed to find an association between intra-individual response time variability and EDSS, or disease duration within a more diverse sample of patients.

The absence of significant associations between intra-individual variability, attention network scores and PASAT scores in our sample suggests that intra-individual variability provides a distinct isolable measure of cognitive function. Supporting this suggestion, we were able to demonstrate that intra-individual variability contributed the most to a model predicting group membership for patients with MS and controls. Prior

studies have demonstrated an association between within-subject variability and degradation in both white and gray matter for other neurological populations including frontotemporal dementia, traumatic brain injury and mild cognitive impairment (MacDonald, Li, Backman, 2009). MS involves both white matter (Ludwin, 2006) and gray matter pathology (Geurts & Barkhof, 2008; Vercellino et al., 2005) that affects widespread brain regions. As such, intra-individual variability in cognitive tasks like the ANT-I, that require the integrity of multiple neuronal networks (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005) may be a sensitive means of capturing the behavioural consequences of the pathophysiological changes affecting patients with MS. Future research integrating neuroimaging methods may reveal more direct relations between specific pathological changes, intra-individual variability and attentional network integrity in MS.

One limitation of our study was our enrollment of only female relapsing-remitting patients with a relatively limited range of disability, which in turn limits our ability to generalize to the larger MS population. Also, among individuals with MS, self-reported fatigue has been found to influence information processing speed (Andreasen, Spliid, Andersen, & Jakobsen, 2010; Weinges-Evers et al., 2010) as well as performance variability (Bruce et al., 2010). We were unable to directly investigate the role of fatigue in our study and future work is necessary to determine the relation of fatigue and intra-individual variability in attention performance for individuals with MS. Our findings do identify the need for further research into intra-individual variability, with a broader range of individuals with MS and a greater variety of cognitive tasks. This study also contributes to the growing evidence of attentional network deficits in MS and

demonstrates the need for further research investigating the use of measures such as the ANT-I to identify the core features of cognitive dysfunction in this disease.

Table 3.1 Demographic, disease and neuropsychological characteristics

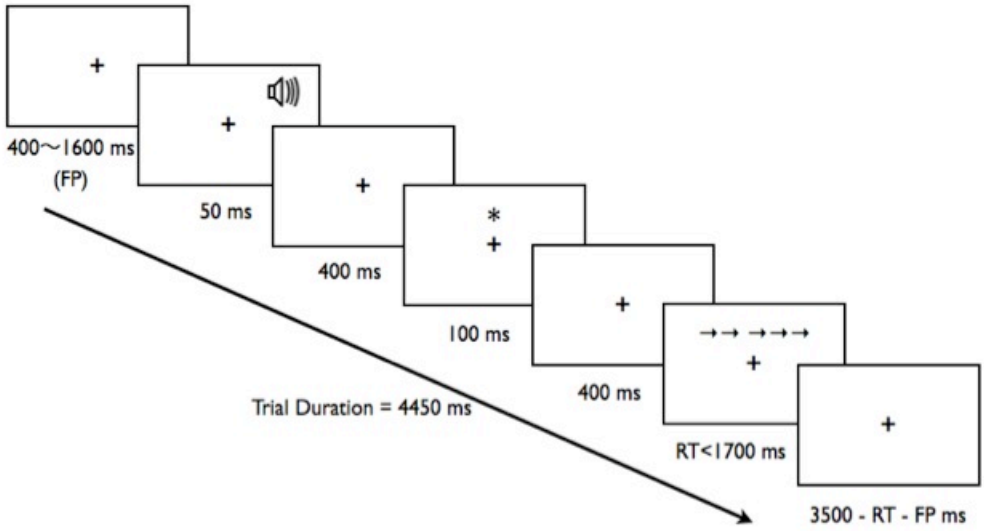
	MS Group (n=31)	**Control Group (n=30)**
Age M (SD)	42.13(7.29)	40.50(8.23)
Education in Yrs, M(SD)	14.87 (2.38)	15.73(2.63)
BDI-FS M(SD)	1.87(2.01)[a]	.90(1.53)
Yrs Onset[c] Median (SD)	8(7.46)	____
EDSS Median (Range)	2.5(0-6)	____
3-second PASAT M(SD)	43.03(10.76)[b]	50.13(8.20)
2-second PASAT M(SD)	26.74(13.71)[b]	38.60(9.31)

Note. [a]p<.05; [b] p<.01; [c] Years since onset of reported MS symptoms

Table 3.2 Standardized coefficients of predictor variables of logistic regression predicting group membership

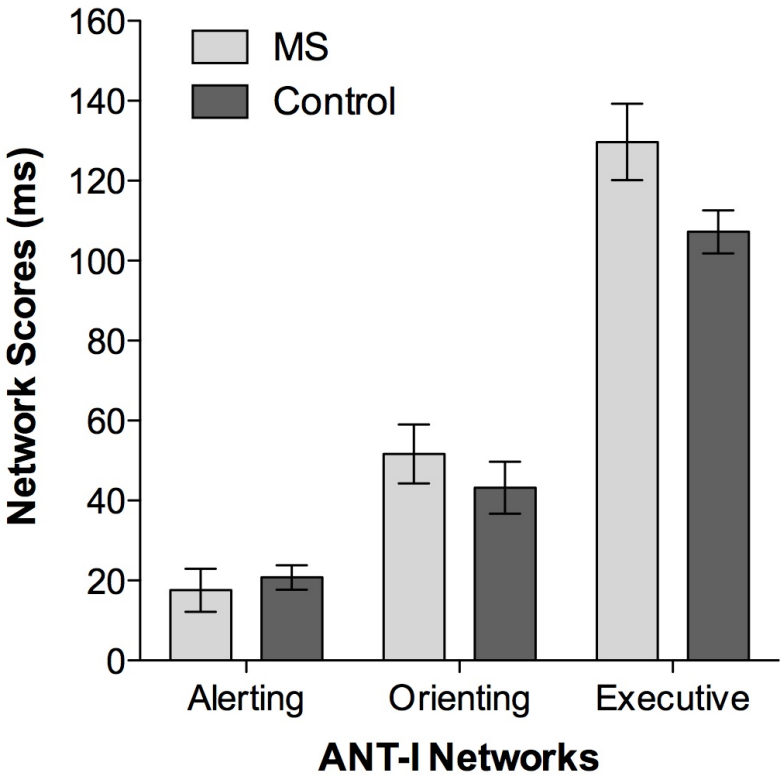
	***B*(SE)**	***Wald***	***p***
ISD	-1.64(.492)	11.07	.001
Executive network	.021(.014)	2.10	.147
PASAT-3	-.098 (.068)	2.06	.151
PASAT-2	.138(.056)	6.04	.014

Figure 3.1 Attention Networks Test (ANT-I)



Following a 400-1600 ms inter-trial period, the stimulus is preceded by an alerting tone (second panel from the top), and a valid orienting cue (fourth panel from the top). The target arrow is surrounded by congruent flankers (second panel from the bottom).

Figure 3.2 Alerting, Orienting, and Executive Network scores for MS and Control groups from the Attention Network Test (ANT-I)



Error bars represent standard deviations

3.7 SUMMARY

In Chapter 3, it was found that individuals with MS performed slower than healthy controls on the ANT-I and demonstrated even slower responses when presented with conflicting information (i.e. a greater executive network score). Moreover, the MS group was more variable in their performance than healthy controls, even when controlling for factors such as practice, learning effects, and group level differences in mean performance. This IIV in performance was not related to performance on a clinical test of information processing speed (i.e. PASAT) nor was IIV related to attention network scores. Furthermore, IIV and PASAT-2 scores were the best predictors of group membership.

IIV in MS performance appears to be a consistent phenomenon, which thus far, has been demonstrated cross-sectionally across two separate cognitive tasks. Furthermore, IIV appears to be a sensitive indicator of neurologic status (i.e. group membership) and likely reflects a distinct isolable measure of cognitive function. These findings suggest that IIV is an important indictor of cognitive performance in MS and may provide novel insights into deficits in information processing speed. However, MS is a progressive illness and an understanding of the stability of IIV in this population is required. The following chapter examines the short-term stability of IIV in a group of individuals with MS and healthy controls across six consecutive monthly sessions.

CHAPTER 4: STABILITY OF INTRA-INDIVIDUAL VARIABILITY IN RELAPSING REMITTING MULTIPLE SCLEROSIS: A 6-MONTH STUDY

4.1. PUBLICATION STATUS AND AUTHOR CONTRIBUTIONS

The following chapter is based on the manuscript: Wojtowicz, M., Ishigami, Y., Mazerolle, E.L., Fisk, J.D. (Under Review). Stability of Intra-Individual Variability as a Marker of Neurologic Dysfunction in Relapsing Remitting Multiple Sclerosis. *Journal of Clinical and Experimental Neuropsychology (JCEN)*. Manuscript Number 13-110.

Magdalena Wojtowicz, the first author, developed the conceptual rationale for the study, collected the MS patient data and then analyzed and interpreted the data. She was also the primary contributing author to the manuscript; producing the initial draft.

4.2. ABSTRACT

Background: Impairments in information processing speed are common in multiple sclerosis (MS), with affected individuals demonstrating slower responses and more intra-individual variability (IIV) in their performance on timed tasks. Evidence suggesting that IIV provides novel information about cognitive deficits in MS is accumulating, however little is known about the stability of IIV across multiple assessments. In this study, we investigated IIV in response speed in persons with MS across six monthly sessions using the Attention Network Test-Interaction (ANT-I). Method: Individuals with relatively mild relapsing remitting MS and healthy controls completed the ANT-I at 6 monthly intervals. Clinical assessments (Sessions 1 & 6) and conventional MRI studies (Sessions 1-6) were examined for individuals with MS. Results: The MS group's clinical and neuroimaging measures were stable during the six month period. Individuals with MS were slower and more variable in reaction time performance on the ANT-I compared to controls. Differences in IIV between groups were maintained across the six sessions, with IIV demonstrating less susceptibility to across-session practice effects than mean latency scores. Conclusions: IIV provides a stable measure of cognitive performance in mildly affected persons with MS who are clinically and radiologically stable. Further studies exploring its utility as a clinical outcome are warranted.

4.3. INTRODUCTION

Multiple Sclerosis (MS) causes progressive damage to the central nervous system (Polman et al., 2011) and has wide ranging effects that frequently include impairments of cognition (Chiaravalloti & DeLuca, 2008). Deficits in information processing speed are among the most commonly reported impairments (Chiaravalloti & DeLuca, 2008), although persons with MS have also been found to display more performance variability in their responses on timed tests (Bodling, Denney, & Lynch, 2012; Bruce, Bruce, & Arnett, 2010; Wojtowicz, Berrigan, & Fisk, 2012; Wojtowicz, Omisade, & Fisk, 2013). These recent findings of greater intra-individual variability (IIV) in response speed among persons with MS are consistent with prior studies, which have demonstrated increased IIV on timed cognitive tasks by persons with various other neurological disorders including dementia, attention deficit and hyperactivity disorder, Parkinson's disease and Schizophrenia (Burton, Strauss, Hultsch, Moll, & Hunter, 2006; Hultsch, Macdonald, Hunter, Levy-bencheton, & Strauss, 2000; MacDonald, Li, & Bäckman, 2009). Such studies have typically found greater IIV to be associated with poorer overall cognitive performance as well as with greater neurologic impairment (see MacDonald et al., 2009).

IIV has been associated with central nervous system integrity (e.g., white matter hyperintensities and lesions in grey matter) in community dwelling adults and persons with dementia, as well as in persons with MS (Bunce et al., 2013; MacDonald et al., 2009; Mazerolle, Wojtowicz, Omisade, Fisk, 2013). IIV in cognitive test performance has been examined across consecutive weekly assessments in patients with arthritis, mild dementia, Parkinson's disease and Alzheimer's disease (Burton et al., 2006; Hultsch et al., 2000). These studies have found that IIV decreases across sessions, presumably due

to repeated exposure and practice with the study tasks. Nonetheless, those individuals who demonstrate greater IIV within the first session typically continue to do so across sessions; suggesting that within specific populations, IIV may be a relatively stable measure (Burton et al., 2006; Hultsch et al., 2000).

Evidence suggesting that IIV may provide novel information about cognitive deficits in MS is accumulating. Individuals with MS appear more variable than healthy controls on tasks of information processing speed, even when potential sensorimotor difficulties are accounted for (Bodling et al., 2012; Wojtowicz et al., 2012; Wojtowicz et al., 2013). IIV in persons with MS has also been found to increase with greater cognitive demands (Bodling et al., 2012; Wojtowicz et al., 2012) and has been found to be associated with self-reported cognitive fatigue (Bruce et al., 2010). Furthermore, IIV in performance has been demonstrated to be a better predictor of neurological status compared with mean-level response speed and performance on clinical cognitive measures (Bodling et al., 2012; Wojtowicz et al., 2013). Such findings suggest that IIV has the potential to be an important clinical indicator of cognitive impairment in MS. However, MS is a progressive illness and before IIV can be considered as having potential clinical utility as a measure of cognitive functioning for those with MS, a better understanding of the short-term stability of IIV in this population is required. To date, no studies have examined repeated measurement of IIV on tests information processing speed and attention in persons with MS.

We aimed to evaluate the stability of IIV as determined by performance of the Attention Network Test-Interactions (ANT-I; Callejas, Lupiàñez, Funes, & Tudela, 2005) on six repeated assessments at monthly intervals in a sample of clinically stable persons

with MS. We hypothesized that persons with MS would demonstrate greater IIV compared to healthy controls and that this between-group differences would remain stable across sessions for both groups.

4.4 METHOD

4.4.1. PARTICIPANTS

All participants provided informed consent following procedures approved by the Capital District Health Authority Research Ethics Board. A total of 22 subjects were enrolled in this 6-month study (i.e. a total 132 data points). This included a group of 11 female participants with relapsing remitting MS (RRMS; Polman et al., 2011) and 11 healthy female control participants. Similar sample sizes have previously been used in studies investigating repeated measurements of IIV in other clinical samples (Burton et al., 2006; Hultsch et al., 2000; N=10 in each group and approximately N=15 in each group, respectively). The MS sample was restricted to females because of their predominance in clinic attending samples (Koch-Henriksen & Sørensen, 2010). MS participants were recruited from the Dalhousie MS Research Unit (DMSRU), the only specialty clinic for MS care within its region. MS patients who were between 25 and 55 years of age and who had an Expanded Disability Status Scale (EDSS; Kurtzke, 1983) score between 0 and 6 were invited to participate. See Table 1 for the demographics of the enrolled participants. All MS patients had a relapsing remitting disease course but were clinically stable at the time of the study (i.e., had not experienced a symptom relapse or taken corticosteroids within three months prior to participation) and were taking first-line disease-modifying therapies at the time of the study. Exclusion criteria were co-morbid neurologic or psychiatric disorders or a history of substance abuse, learning disability, head trauma, or seizures. Those with a history of depression or

anxiety disorder were included only if this was not considered an active clinical problem by DMSRU staff at the time of enrolment. Healthy controls, who met the same inclusion and exclusion criteria, and who lacked a family history of any autoimmune disorder, were recruited via local advertisements. All participants reported normal or corrected-to-normal vision at the time of the study.

4.4.2. ATTENTION NETWORK TEST-INTERACTION (ANT-I)

The ANT-I is a variation on the Attention Network Test (ANT) and has been described in detail elsewhere (Callejas et al., 2005; Ishigami, Fisk, Wojtowicz, & Klein, 2013). Briefly, the ANT-I contains one block of 24 practice trials followed by 6 experimental blocks of 48 trials each, for a total of 288 trials. Feedback on performance accuracy is given only during the practice block. A fixation cross (+) appears in the center of the screen at the beginning of each block. During half of the trials an auditory tone (2000 Hz) is presented for 50 msec. A visual cue (i.e. asterisk) is then presented either above or below the fixation cross for 100 msec on two thirds of the trials. One third of the trials include a "valid" visual cue in which the asterisk appears in the location where the target stimulus will subsequently appear. Another third of the trials include an "invalid" cue, in which the asterisk is presented in the opposite location of where the target stimulus will subsequently appear. No visual cue is presented for the remaining trials. Participants are required to indicate the direction of a center (i.e. target) arrow, which is surrounded by two "flanker" arrows on each side that either point in the same or the opposite direction as the target arrow. The participants identify direction of the central arrow by pressing either the "/" key for a right-pointing arrow or the "z" key for a left-pointing arrow on the computer keyboard. The design of the ANT allows for the examination of three attention

networks (i.e. alerting, orienting and executive). The alerting network is evaluated by examining reaction time differences between trials where the alerting tone compared to trials where the alerting tone was present. The orienting network is evaluated comparing reaction times in the valid cue conditions with reaction times in the invalid cue conditions. Finally, the executive network is measured by comparing reaction times for congruent flanker trials with reaction times from incongruent flanker trials. The stability, isolability, robustness and reliability of the three ANT-I attention networks across sessions have been described previously for MS patients (Ishigami et al., 2013) and for healthy persons of various ages (Ishigami and Klein, 2010; 2011). However, the ANT-I can also be used as a measure of continuous attention (Callejas et al., 2005; Wojtowicz et al., 2013), as was the case in the current study. To do this, mean RT and IIV are examined across all trials of the ANT-I. The stability of IIV between groups on this test has not yet been examined. The total duration of the ANT-I is approximately 20 minutes.

4.4.3. CLINICAL MEASURES

Neurologic disability was assessed via the Expanded Disability Status Scale (Kurtzke, 1983). Scores on the EDSS range from zero to ten, with zero indicating normal neurological examination for all functional systems and ten indicating death due to MS. An EDSS score of six reflects the need for an ambulatory aid to walk 100 meters (Kurtzke, 1983) and thus all subjects enrolled this study were fully ambulatory (Table 4.1). Self-reported symptoms of depression and fatigue were assessed using the Beck Depression Inventory-Fast Screen (BDI-FS; Beck, Steer, & Brown, 2000) and the Daily Fatigue Impact Scale (D-FIS; Fisk & Doble, 2002), respectively. The 2 and 3-second versions of the Paced Auditory Serial addition Test (PASAT) included in the Multiple

Sclerosis Functional Composite battery (Fischer, Rudick, Cutter, & Reingold, 1999) as well as the oral version of the Symbol Digit Modalities Test (SDMT; Smith, 1982) were administered as standard clinical assessments of information processing speed and attention. All clinical measures were collected at Session 1 and again at Session 6 (i.e. 6 months later) and were used to assess for changes in neurological, psychological, and cognitive status of participants with MS.

4.4.4. MAGNETIC RESONANCE IMAGING

MRI data were collected for participants with MS during each assessment sessions (i.e. sessions 1 through 6) using a 1.5T General Electric MRI with the standard eight channel head coil. A T1-weighted anatomical image was acquired with a spoiled gradient recalled (SPGR) sequence (TR/TE = 25/5 msec, 40 degree flip angle, FOV = 240 mm2, 256 x 256 matrix, 124 1.5 mm axial slices). A T2-weighted fluid-attenuated inversion recovery (FLAIR) image was acquired with TR/TE/TI = 8000/120/2000 msec, two averages, FOV = 240 mm2, 256 x 224 matrix, and 56 3-mm axial slices. Of the 66 scans collected, two were excluded from analyses due to loss of data during file transfer (i.e. session 5 scans for two subjects).

4.4.5. PROCEDURE

All participants performed the ANT-I during 6 sessions at approximately monthly intervals (M_{days}(SD) = 33.68(3.53)). MRI scans were acquired at these monthly assessments for MS participants. Participants with MS also completed the BDI-FS, D-FIS, PASAT, and SDMT on the same day as their first and last sessions of the study. EDSS scores, as documented by clinic staff within two weeks of Session 1 and Session 6, were obtained from the medical records of the DMSRU.

4.4.6. DATA PREPARATION AND ANALYSIS

For the analyses of the ANT-I, only correct trials were used in all reaction time (RT) analyses. Data were screened for extreme values (i.e. 3 SDs from the mean of each group) and group-level mean values were imputed for missing data (<5% of the total data). IIV was measured by calculating individual standard deviation (ISD) scores. Systematic differences in RT due to trial and group membership were parceled from the data using regression (Hultsch et al., 2000). Standardized residual scores were converted to T-scores and ISD was calculated for each individual at each session. Errors, mean RT, and ISD scores were analyzed using separate repeated measures ANCOVAs that included age and education as covariates. Session 1 and session 6 clinical data were compared using a series of paired t-tests.

For the MS participants' MRI data, the Lesion Segmentation Toolbox (LST; Schmidt et al., 2012) was used to segment T1-weighted anatomic images into grey matter, white matter, and CSF tissue classes using Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm/) and its Voxel-Based Morphometry toolbox (VBM8; http://dbm.neuro.uni-jena.de/vbm). LST was also used to identify T2 hyperintense MS lesions and total lesion load was calculated for each MS participant. To provide an indicator of global brain atrophy, brain parenchymal fraction (BPF, i.e. grey matter+white matter /grey matter+white matter+ crebrospinal fluid; Phillips et al., 1998) was calculated after lesion filling in LST (De Stefano, Battaglini, & Smith, 2007). A repeated measure ANOVA was used to examine changes in neuroimaging measures across the 6 sessions.

4.5. RESULTS

4.5.1. DATA PREPARATION AND ANALYSIS

For participants with MS, the median EDSS score was 2.3 (Range, 1.5–3.5), and the median duration of disease as measured in years since onset of reported MS symptoms was 7.3 (range, 0–28); representing a group of individuals with relatively mild neurologic disability. The healthy control group was somewhat younger ($M_{Control}(SD)$ = 37.12(6.34); $M_{MS}(SD)$ = 44.00(6.81); t (20) = 2.451, p = .02) and had more years of education ($M_{Control}(SD)$ = 16.82(1.54); $M_{MS}(SD)$ = 14.45(2.21); t (16.2)= -3.178, p =.006) than the MS group (See Table 4.1). Given these differences, age and education were used as covariates in all remaining analyses.

4.5.2. MEAN-LEVEL PERFORMANCE ON THE ANT-I

The MS and control groups did not differ on the number of errors on the ANT-I (F (1, 20) = 2.07, p = .166). Mean error (95% CI) across sessions was 1.9 (.36-3.4) for the MS group and 3.4 (1.86-4.93) for healthy controls. A 2(Group) x 6(Session) repeated measures ANCOVA using mean latency scores was conducted, with age and education as covariates. The assumption of homogeneity of regression slopes was met; Levine's tests of equality of error variances were not significant (p > .05). Age and education were not significant covariates (i.e. F (1, 18)= .196, p = .66, η_p^2 = .01; F (1, 18) = .025, p = .88, η_p^2 = .001, respectively). A main effect of Group was found (F (1, 18) = 9.28; p = .007; η_p^2 = .34), with MS participants demonstrating slower responses (M_{MS} = 667.87 ms; 95%CI_{MS} = (619.24-716.48 ms)) than healthy controls ($M_{Controls}$= 557.04 ms; 95%CI_{MS} = (508.42-605.66 ms)). A main effect of sessions was also found; Greenhouse Geisser correction applied (F (3.21, 90) = 37.11, p <.001; η_p^2 = .67). Post-hoc analyses, adjusted for multiple comparisons, indicated that response latency decreased across sessions (F (5, 14) = 23.30, p <.001; η_p^2 = .34). Finally, a significant Group x Session interaction was

found (F (3.21, 90) = 4.28; p = .007; η_p^2 = .19) indicating that MS participants demonstrated a greater overall decrease in latencies (M_{MS} = 103.17 ms; $M_{Controls}$ = 53.83 ms) across sessions compared to healthy controls (Figure 4.1). Post-hoc analyses, adjusted for multiple comparisons, indicated that within the MS group response latencies continued to decrease across the first four sessions (i.e. the first three months of testing; p < .05) and then stabilized between session 4-6 (p > .05; Figure 4.1). In healthy controls, latencies remained relatively stable across sessions with significant differences found between session 1 and 6 (p <. 001) and when comparing session 3 to session 5 (p < .001) due to a slight increase in mean RT for the control group in session 3 (see Figure 4.1). Given that age and education were not significant covariates, the analysis was rerun using a 2(Group) x 6(Session) repeated measures ANOVA, which rendered similar results.

4.5.2. INTRA-INDIVIDUAL VARIABILITY ON THE ANT-I

A 2 (Group) x 6 (Session) repeated measures ANCOVA using ISD scores was conducted, with age and education as covariates. The assumption of homogeneity of regression slopes was met; Levine's tests of equality of error variances were not significant (p > .05). Again, age and education were not significant covariates (i.e. F (1, 18) = .019; p = .89; η_p^2 = .001; F (1, 18) = .491; p = .49, η_p^2 = .03, respectively). The MS group demonstrated greater intra-individual variability on the ANT-I across sessions (F (1, 18) = 10.607, p = .004; η_p^2 = .37). A significant main effect of session was also found (F (2.94, 90) = 15.68, p < .001; η_p^2 = .47). No significant Group x Session interaction was found. Nonetheless, post-hoc analyses, adjusted for multiple comparisons, were conducted to examine within group changes in ISD across sessions. Within the MS group ISD decreased across the first three sessions (i.e. the first two months of testing; p < .05)

and then stabilized across session 3-6 (p >. 05; Figure 4.2). In healthy controls, ISD scores remained relatively stable across sessions with significant differences found only between session 1 and 6 ($p < .001$) as well as between 3 and 5 ($p < .01$) due to a slight increase in ISD in session 3 (see Figure 4.2). Given that age and education were not significant covariates, the analysis was rerun using a 2(Group) x 6(Session) repeated measures ANOVA, which rendered similar results.

4.5.3. CLINICAL MEASURES IN MS GROUP ACROSS SESSIONS

Data for the clinical and neuroimaging measures at Session 1 and 6 are presented in Table 4.2. A series of paired t-tests for these measures revealed no significant differences (p>.05; see Table 4.2). Likewise, a repeated measure ANOVA examining changes in neuroimaging measures across all six sessions revealed no significant differences (p>.05; for all measures; see Table 4.3). These data suggest that the radiological, neurological and cognitive status of the MS participant sample remained stable across the 6-month period during which the study was conducted.

4.6 DISCUSSION

To our knowledge, this is the first study to demonstrate short-term stability of group-level differences in IIV on a task of complex attention for individuals with MS. Consistent with previous cross-sectional literature, participants with MS demonstrated slower and more variable performance on a test of complex attention in comparison to healthy controls (Bodling et al., 2012; Bruce et al., 2010; Wojtowicz et al., 2012, 2013). Importantly, these between-group differences in IIV were maintained over 6 assessments at monthly intervals in a sample of MS participants who were stable on standard clinical, cognitive and radiological measures. These results suggest that greater IIV in response speed on tests of complex attention is a consistent phenomenon in clinically stable

persons with MS and that it may reflect central nervous system integrity, similar to that suggested for other neurologic disorders (MacDonald et al., 2009, 2006).

Decreased IIV across four consecutive weekly sessions has been reported in studies of both healthy and neurologically impaired populations, including individuals with Alzheimer's disease, Parkinson's disease, and mild dementia (Burton et al., 2006; Hultsch et al., 2000). We also found decreased IIV across the monthly sessions for both healthy controls and MS groups, suggesting that IIV is indeed affected by previous exposures to the task. However, despite this decrease, the MS group consistently demonstrated greater variability than healthy controls and by the third monthly test session the differences between groups were stable in magnitude. Thus, it appears as though IIV has the potential to consistently demonstrate group-level performance differences between healthy control subjects and clinically stable MS patients across multiple sessions.

The pattern of results was somewhat similar for mean response latency in that RT differed between groups and both groups demonstrated decreased latencies across sessions. However, a group by session interaction was found with RT scores that indicated greater overall decreases in mean RT for the MS group compared to healthy controls; a finding not present for IIV. Furthermore, while mean RTs within the MS group did stabilize, this was not until the fourth monthly session. Furthermore, while mean RTs within the MS group did stabilize, this was not until the fourth monthly session. Given that clinical measures (e.g., EDSS, MRI) remained relatively stable over the six month period, we speculate that the group by session interaction for mean RT reflects larger practice effects in the MS group, rather than sensitivity to clinical

phenomena. Specifically, our results suggest that previous task exposures affected both mean RT and IIV but this effect appeared to diminish after fewer sessions for IIV. Such findings could have implications for the requirements of "run-in" phases of studies hoping to use timed cognitive tests as outcome measures of treatment efficacy. Although, a "run-in" period would still be required when examining variability in reaction time performance, a measure such as IIV that appears to stabilize after fewer sessions may be a more efficient indicator of responsiveness to treatment.

By design, this study included a group of mildly affected individuals with relapsing remitting MS, for whom cognitive deficits were expected to be subtle. The sensitivity of IIV in such individuals suggests that it may be a particularly useful measure of cognitive functioning in those with relatively mild neurologic disability. Moreover, we were able to demonstrate consistent IIV group differences on repeated monthly assessments between healthy controls and individuals with MS who had stable measures of neurologic status (EDSS scores), structural MRI measures (lesion load and brain volume parameters), psychological status (self-reported depression and fatigue symptoms) and cognitive status (PASAT and SDMT scores) over the 6-month period. Such demonstrations of sensitivity to clinical status and short-term stability in relation to other clinical measures are important steps in establishing the validity of ISD as a potential outcome measure for studies of cognitive changes in persons with MS. In aging populations, IIV has been demonstrated to be a unique predictor of cognitive decline as well as terminal decline (i.e. accelerated cognitive deterioration occurring close to death) above and beyond demographic factors and cardiovascular health (Dixon et al., 2007; MacDonald, Hultsch, & Dixon, 2003; Macdonald, Hultsch, & Dixon, 2008). Further research examining the

responsiveness of IIV to changes in clinical and cognitive status in persons with MS are necessary to determine if IIV can provide a measure of clinically meaningful change.

Important limitations of our study include small group sizes and select sampling criteria for MS participants. Nonetheless, studies of similar sample sizes have effectively demonstrated stability of IIV measures across multiple test sessions in other clinical populations (Burton et al., 2006; Hultsch et al., 2000). Additionally, the multiple assessments performed during our study yielded a large data set for analyses (e.g. 132 data points for RT and ISD; 66 data points for MRI measures). While we examined the most commonly used screening tests of cognitive functioning for persons with MS, further studies examining should compare IIV to additional neuropsychological tests in a more representative sample of persons with MS. Despite these limitations, and the need to examine larger and more diverse MS samples, our findings demonstrate the potential of IIV as a measure of the cognitive performance in longitudinal studies of clinically stable persons with MS. Additional studies exploring the potential of IIV as a clinical outcome in larger and more diverse MS samples are warranted. Doing so will establish whether IIV is indeed responsive to meaningful changes in cognitive and neurologic functioning in this population.

Table 4.1. Demographic Variables for the MS and Control Groups

Variable	MS Group (N=11)	Control Group (N=11)	Sign (p-value)
Age, mean (Range)	44.00 (35-54)	37.18 (29-50)	.02
Education, mean (Range)	14.45 (12-18)	16.63 (14-18)	.01
EDSS score, median (range)	2.27 (1.5-3.5)	__	
Years since symptom onset, mean (range)	7.3 (0-20)	__	

Abbreviations: EDSS, Expanded Disability Status Scale.

Table 4.2. Clinical Measures for MS Group Across Session

Variable	MS Group (N=11)		Sign (p-value)
	Session 1 (N=11)	Session 6 (N=11)	
EDSS score, median (range)	2.27 (1.5–3.5)	2.18 (1.5-3.5)	.44
BDI-FS, mean (SD)	1.54 (1.92)	1.18(1.60)	.40
DFIS, mean (SD)	10.2	11.3[a]	.49
PASAT 3, mean, (SD)	48.36 (7.63)	52.73 (10.24)	.08
PASAT 2, mean, (SD)	38.45 (10.13)	39.64(10.30)	.43
SDMT, mean, (SD)	60.45 (7.89)	61.91 (8.99)	.48
Lesion Volume (mL)	9.46(9.10)	10.00(10.03)	.24
Grey Matter Volume (mL)	572.71(27.92)	570.97(33.67)	.63
White Matter Volume (mL)	484.33(32.80)	481.72(31.34)	.10
CSF Volume (mL)	222.72(26.98)	225.81(27.49)	.23
BPF	.83(.020)	.82(.021)	.25

Abbreviations: BDI-FS, Beck Depression Inventory–Fast Screen; BPF, Brain Parenchymal Fraction; D-FIS, Daily Fatigue Impact Scale; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modalities Test. [a]N=10.

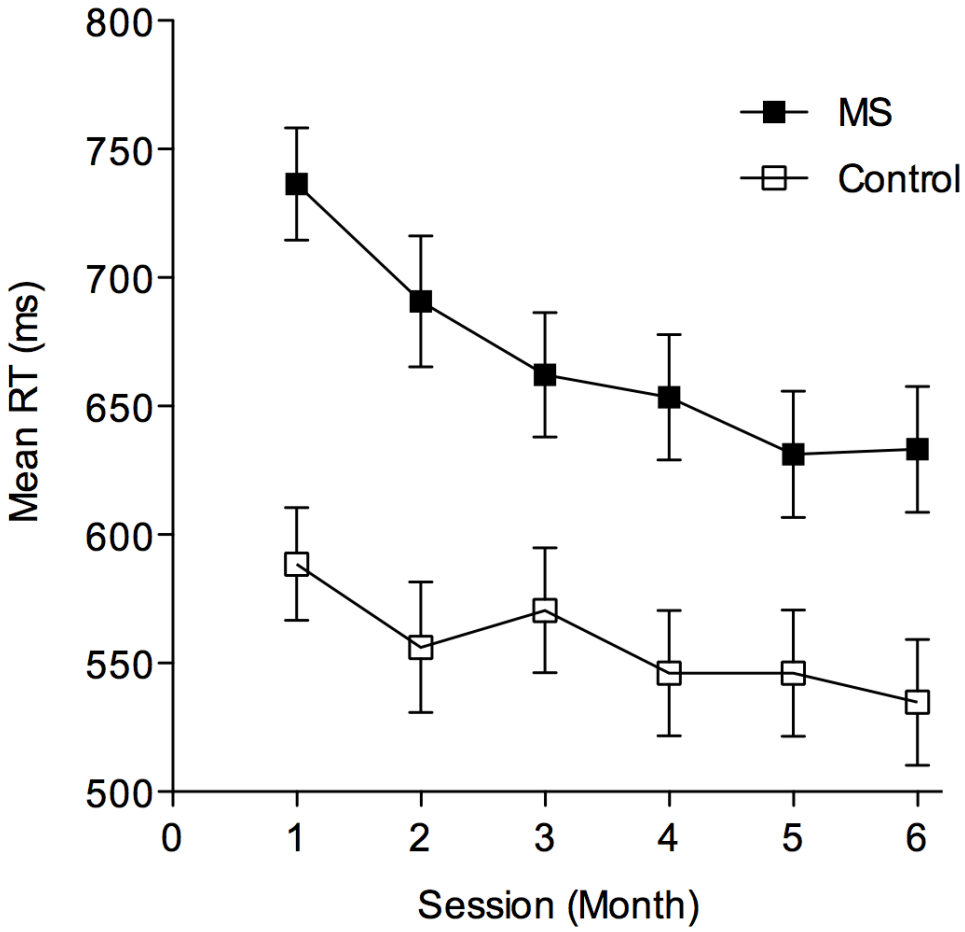
Table 4.2. MRI measures for MS patients across the 6 consecutive monthly sessions

	Session 1		Session 2		Session3		Session 4		Session 5[a]		Session 6		Sig.
MRI measure	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	***p***
Lesion mL	9.46	9.51	9.57	9.72	10.42	10.01	9.10	9.35	9.34	9.24	10.08	10.03	.50
GM mL	572.71	27.92	570.52	34.19	574.92	30.47	570.74	34.53	566.29	31.94	570.97	33.67	.13
WM mL	484.33	32.8	481.23	30.35	480.53	33.08	481.81	29.43	484.18	32.84	479.37	33.81	.11
CSF mL	222.72	26.98	224.45	24.24	222.87	30.03	225.66	26.42	224.82	28.69	225.81	27.49	.24
BPF	0.83	0.02	0.83	0.02	0.83	0.02	0.82	0.02	0.82	0.02	0.82	0.02	.21

Abbreviations: GM, Gray matter; WM, White matter; CSF, Cerebrospinal fluid; BPF, Brain Parenchymal Fraction

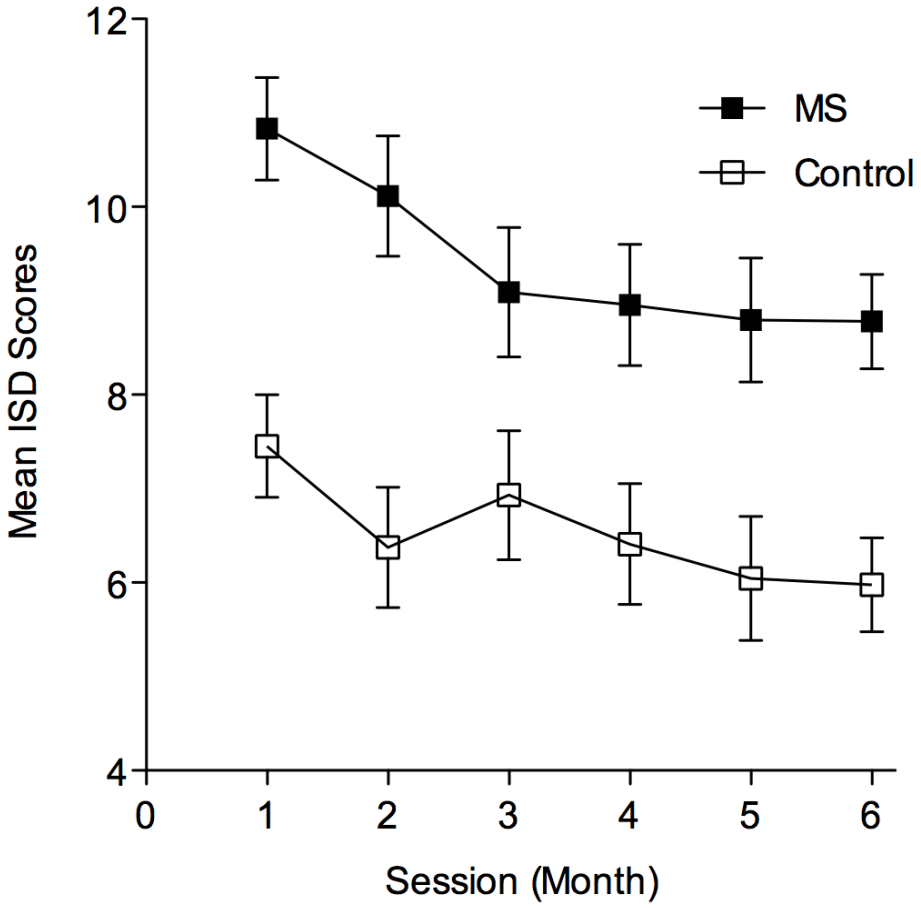
Note: a N=9; see Method section.

Figure 4.1. Mean reaction time for MS participants and controls on the ANT-I tasl across 6 sessions



Error bars represent standard error

Figure 4.2. Mean individual standard deviations for MS participants and controls on the ANT-I task across 6 sessions



Error bars represent standard error

4.7 SUMMARY

Chapter 4 demonstrated that in a group of mildly affected RRMS individuals, IIV was a stable measure of performance differences across six consecutive monthly sessions. Consistent IIV differences were found in individuals with MS who had stable measures of neurologic status, structural MRI measures (i.e. lesion load and brain volume parameters), as well as measures of psychological status (i.e. self-reported depression and fatigue symptoms) and neuropsychological test performance (i.e. PASAT and SDMT scores) over the 6-month period. Thus, IIV appears to represent a consistent phenomenon in reaction time performance that can be identified in MS patients across multiple sessions.

The following chapter will examine how performance variability is represented in the brain. As discussed in Chapter 1, structural magnetic resonance imaging (MRI) metrics such as, lesion load, whole brain atrophy, and width of the third ventricle, demonstrate moderate correlations with cognitive performance (Benedict & Zivadinov, 2011; Chiaravalloti & DeLuca, 2008; Langdon, 2011) but do not provide information regarding functional brain changes potentially occurring in MS. Resting-state fMRI (rsfMRI) presents a means of investigating neural functioning by examining spontaneous BOLD signal fluctuations across brain regions. One of the neural networks identified at rest (i.e. the default mode network; DMN) has been found to relate to IIV in performance in healthy young and older adults (Grady et al., 2010; Kelly et al., 2008). Chapter 5 will explore the neural correlates of IIV in MS by examining its relation to DMN connectivity using rsfMRI.

CHAPTER 5: ALTERATIONS IN FUNCTIONAL CONNECTIVITY AND PERFORMANCE VARIABILITY IN MULTIPLE SCLEROSIS

5.1. METHODOLGICAL CONSIDERATIONS IN RESTING-STATE fMRI

5.1.1. DATA COLLECTION

Resting state fMRI (rsfMRI) investigates spontaneous BOLD signal fluctuations in the brain. As a result, data are collected in the absence of specific inputs (e.g. stimulation) and outputs (e.g. behaviour). The majority of studies collect rsfMRI data during continuous resting conditions (i.e. in the absence of intentional external stimulation), such as during a fixation cross or at eye-open/closed rest. Individuals are most often instructed to lie still with their eyes-closed but to try to not fall asleep (Fox & Raichle, 2007). There are a few important considerations for collecting rsfMRI data. Firstly, the duration of the fMRI scan(s) is an important factor and estimates of correlation strengths across regions have been found to stabilize with acquisition times as brief as 5 minutes (Van Dijk et al., 2010). Scanner background noise has also been found to attenuate DMN functional connectivity (Gaab, Gabrieli, & Glover, 2008) and non-specific instructions in the scanner such as "relax" and "stay still and do nothing" can influence a participant's attention to scanner background noise (Gaab et al., 2008). Furthermore, giving participants more specific instructions (i.e. attend or ignore the scanner noise) results in greater activity within the dorsal medial PFC compared to more neutral instructions (e.g.,'.'relax and stay still'; Benjamin et al., 2010). Some studies have suggested differential resting-state functional connectivity can be found with eyes-open and eyes-closed instructions, with the former resulting in greater DMN activation (e.g.,

Van Dijk et al., 2010). However, Fox and colleagues (2005) reported similar DMN across eyes-open and eyes-closed conditions.

5.1.2. ACCOUNTING FOR NON-NEURAL NOISE

A particular concern for resting state fMRI is that artefacts, such as physiological noise (e.g., breathing/heart beat) or motion, may confound the spontaneous BOLD signal fluctuations. Several post-processing steps have been suggested to try to reduce or remove such confounds (see Fox & Raichle, 2007; Cole, Smith, & Beckmann, 2010). For example, physiological parameters can be measured and regressed from the BOLD signal acquisition. Furthermore, noise sources can be identified from the data using techniques such as independent component analysis (ICA; discussed further in the following section). In addition, regressing non-neural signals (e.g. BOLD signals from white matter and ventricles/cerebrospinal fluid) and signals that are common across all voxels (e.g. global signal) can help eliminate confounds (Fox & Raichle, 2007; Cole et al., 2010).

5.1.2. ANALYSIS APPROACHES TO IDENTIFYING FUNCTIONAL CONNECTIVITY

Two major approaches are commonly employed to examine functional connectivity in rsfMRI: (1) seed-based analyses and (2) independent component analysis (ICA). Although other approaches exist, these two reflect the analysis techniques most commonly implemented in the rsfMRI literature. Seed-based analyses extract a BOLD signal time course from a pre-determined region of interest (ROI) and examine the temporal correlation between this signal and time courses from the rest of the voxels of the brain (Fox & Raichle, 2007). This approach provides a relatively simple and sensitive approach to examining functional connectivity (Zhang & Raichle, 2010). However, it

also has some restrictions, which include the requirement of an *a priori* seed region, and the inability to look at multiple networks at once. Furthermore, interpretation of results is restricted to connectivity between the seed region and other brain areas, as opposed to network-level differences in resting-state functional connectivity.

An alternative approach is to use independent component analysis (ICA). This method uses a mathematical algorithm to decompose the data into maximally independent spatial maps. This results in the data being parceled into several independent components. ICA is a data-driven approach and does not require *a priori* hypotheses or definitions of a seed region (Fox & Raichle, 2007). This approach is also beneficial because it can aid in the isolation of sources of potential noise. However, there are several difficulties in implementing this approach. First, the user must determine which components are 'noise' and which reflect 'neural networks'. This also presents an additional difficulty when potential neural networks are decomposed into more than one component (see Cole et al., 2010). It has also been suggested that approaches such as ICA are biased towards examining neural networks as a single unit (Uddin et al., 2009). The default mode network, in particular, has been demonstrated to contain sub-network hubs, which may be involved in potentially differential functional processes (Buckner et al., 2008; Uddin et al., 2009). Thus, approaches such as ICA, may not be able to investigate these possible differences.

5.2. PUBLICATION STATUS AND AUTHOR CONTRIBUTIONS

The following chapter is based on the manuscript: Wojtowicz, M., Mazerolle, E. L., Bhan, V., Fisk, J. D. (Under Review). Alterations in Functional Connectivity and

Performance Variability in Relapsing Remitting Multiple Sclerosis. Multiple Sclerosis Journal. Manuscript Number: MSJ-13-0437

Magdalena Wojtowicz, the first author, developed the conceptual rationale for the study, collected all of the data and then analyzed and interpreted the data. She was also the primary contributing author to the initial draft of the manuscript.

5.3. ABSTRACT

Background: Patients with MS demonstrate slower and more variable performance on attention and information processing speed tasks. Greater variability in cognitive task performance has been shown to be an important predictor of neurologic status and provides a unique measure of cognitive performance in MS patients.

Objective: This study investigated alterations in resting-state functional connectivity associated with within-person performance variability in MS patients.

Methods: Relapsing remitting MS patients and matched healthy controls completed structural MRI and resting-state fMRI (rsfMRI) scans, as well as tests of information processing speed. Performance variability was calculated from reaction time tests of processing speed. RsfMRI connectivity was investigated within regions associated with the default mode network (DMN). Relations between performance variability and functional connectivity in the DMN within MS patients were evaluated.

Results: MS patients demonstrated greater reaction time performance variability compared to healthy controls ($p < .05$). For MS patients, more stable performance on a complex processing speed task was associated with greater resting-state connectivity between the ventral medial prefrontal cortex and the frontal pole.

Conclusions: Among MS patients, greater functional connectivity between medial

prefrontal and frontal pole regions appears to facilitate performance stability on complex speed-dependent information processing tasks.

5.4. INTRODUCTION

Multiple Sclerosis (MS) causes progressive damage to the central nervous system (Polman et al., 2011) and has wide ranging effects that frequently include cognitive impairments (Chiaravalloti & DeLuca, 2008). Slowed information processing speed is amongst the most commonly reported cognitive problem (Chiaravalloti & DeLuca, 2008), however, persons with MS have also been found to be more variable in their speed of responding on timed tests (Bodling et al., 2012; Bruce et al., 2010; Wojtowicz et al., 2012, 2013). This intra-individual variability (IIV) represents within-subject fluctuations in trial-by-trial performance within a particular task (MacDonald et al., 2006). Persons with MS show greater IIV on tasks of information processing speed than healthy controls, even when potential sensorimotor difficulties are accounted for (Bodling et al., 2012; Wojtowicz et al., 2012, 2013). IIV in persons with MS has been found to increase with higher cognitive task demands (Bodling et al., 2012; Wojtowicz et al., 2012) and appears to better predict neurologic status than performance on clinical measures of information processing speed (Wojtowicz et al., 2013). Such findings suggest that IIV on timed cognitive tasks provides novel insight into the cognitive deficits associated with MS. To date, however, the neural underpinnings of this performance variability remain unclear.

Studies have demonstrated that structural magnetic resonance imaging (MRI) metrics such as, lesion load, whole brain atrophy, and width of the third ventricle, have moderate associations with cognitive performance in MS (Benedict & Zivadinov, 2011; Chiaravalloti & DeLuca, 2008; Langdon, 2011). However, structural imaging measures do not provide information regarding potential functional brain changes associated with

cognition in MS (e.g., Audoin et al., 2003; Mainero et al., 2004). Resting-state fMRI (rsfMRI) presents a means of characterizing spontaneous fluctuations of brain activity via the blood oxygenation level-dependent (BOLD) signal. RsfMRI has identified consistent and distinct networks of functionally connected brain regions that are thought to underlie behavior (Damoiseaux et al., 2006; Fox & Raichle, 2007). This approach offers advantages for use with clinical populations compared with traditional task-based fMRI, including shorter scan times and task independence (Fox & Greicius, 2010).

Among the neural networks identified by rsfMRI, the most frequently investigated in clinical populations is the default mode network (DMN; Buckner et al., 2008; Heine et al., 2012). The functional significance of the DMN is unclear, although it is thought to play a role in self-related and internal processes, such as self-reflection, social cognition, mind wandering, monitoring of the mental self (Buckner et al., 2008). The DMN has also been found to be deactivated when subjects are performing an attention-demanding goal directed task (Raichle, 2001), and failure to suppress this network has been shown to result in attentional lapses (Weissman et al., 2006). Alterations in default mode connectivity associated with cognitive performance have been found in progressive and relapsing-remitting MS (RRMS; Faivre et al., 2012; Hawellek et al., 2011; Rocca et al., 2010), as well as in other neurodegenerative disorders such as Alzheimer's disease, and dementia with Lewy bodies (Franciotti et al., 2013; Greicius, Srivastava, Reiss, & Menon, 2004; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005).

Alterations in default mode connectivity have also been associated with IIV. For example, in healthy older adults, increased IIV on a working memory task was associated

with increased DMN connectivity (Grady et al., 2010). In healthy young adults, increased IIV in response time on a flanker task was associated with poorer suppression of the DMN (Kelly et al., 2008), suggesting that failure to suppress DMN activity during an active task is associated with greater response variability. However, possible changes in functional connectivity associated with IIV in MS have not yet been explored. This study investigated potential changes in DMN resting-state functional connectivity associated with IIV on a clinical test of information processing speed among a mildly affected sample of RRMS patients

5.5. METHOD

5.5.1. PARTICIPANTS

All participants provided informed consent following procedures approved by the Capital District Health Authority Research Ethics Board. Eighteen females with relapsing-remitting MS and 16 healthy female control subjects participated. Females were recruited because of their predominance in the MS population and to limit variation in MS characteristics associated with sex differences (Koch-Henriksen & Sørensen, 2010). MS participants were recruited from patients attending the Dalhousie MS Research Unit (DMSRU), Halifax, Nova Scotia, which is the only clinic providing specialized MS care serving a population of approximately 936,000. MS participants were between 25 and 55 years of age, diagnosed with clinically definite RRMS according to the MacDonald criteria (Mcdonald et al., 2001), and had an Expanded Disability Status Scale (EDSS; Kurtzke, 1983) score between 0 and 6. All MS participants were clinically stable at the time of the study; none had experienced a symptom relapse or had been taking corticosteroids within three months prior to participation. Seventeen MS participants were receiving first-line disease-modifying drug therapy at the time of the study and one

was receiving immunosuppressive medication. None had co-morbid neurodegenerative or psychiatric disorders or a history of: substance abuse, learning disability, stroke, head trauma, or seizures. Those with a past history of depression or anxiety disorder were included only if this was not considered an active clinical problem at the time of the study by clinic staff. Healthy control participants, who met the same inclusion and exclusion criteria except those related to MS, were recruited through local advertisements. All participants reported normal or corrected-to-normal vision at the time of the study and none had MRI contraindications.

5.5.2. CLINICAL MEASURES

Neurologic disability was assessed for all MS participants via the Expanded Disability Status Scale (Kurtzke, 1983). For all participants, self-reported symptoms of depression and fatigue were assessed using the Beck Depression Inventory-Fast Screen (BDI-FS; Beck et al., 2000) and the Daily Fatigue Impact Scale (D-FIS; Fisk & Doble, 2002), respectively. The 2 and 3-second versions of the Paced Auditory Serial addition Test (PASAT; Gronwall, 1977) and the oral version of the Symbol Digit Modalities Test (SDMT; Smith, 1982) were administered as standard clinical assessments of information processing speed and attention.

5.5.3. COMPUTERIZED TEST OF INFORMATION PROCESSING (CTIP)

The CTIP (Tombaugh & Rees, 2008) provided computer-administered reaction time measures of information processing speed. This test includes three distinct reaction time subtests that become progressively more demanding: (1) a Simple Reaction Time (SRT) task in which participants press the spacebar as soon as a single “X” appears on an otherwise blank screen, (2) a Choice Reaction Time (CRT) task in which participants are

presented with either the word “DUCK” or “KITE” and are asked to press a right key (i.e. “/”) for the former and a left key (i.e. “z”) for the latter, and (3) a Semantic Search Reaction Time (SSRT) Task in which participants are asked to decide if a presented word belongs to a designated semantic category. For each trial of this latter condition, one of four semantic categories is presented at random on the computer screen (i.e. Weapon, Furniture, Bird or Fruit) and 2.0 seconds later a word appears below this category. The participants are asked to press the right key (i.e. “/”) if the word belongs to the designated category and to press the left key (i.e. “z”) if it does not belong to the category. Each CTIP task includes 10 practice trials and 30 test trials.

5.5.4. MRI DATA ACQUISITION

MRI data were acquired using a General Electric 1.5 T scanner and 8-channel head coil. Anatomical sequences included a T1-weighted spoiled gradient recall (SPGR) acquisition (TR/TE: 25/5ms, flip angle= 40°, matrix= 256x192; slice thickness= 1.8mm, slices=192). A T2-weighted fluid-attenuated inversion recovery (FLAIR) image was also acquired with TR/TE/TI = 8000/120/2000 msec, two averages, FOV = 240 mm^2, 256 x 224 matrix, and 56 3mm axial slices. Resting-state fMRI sequence was a T2*-weighted spiral sequence, TR/TE=2000/40ms, 90° flip angle, field of view=24x24cm, 64x64 matrix, 5 mm slice width, no gap, 26 slices, 5 minute scan). For the rsfMRI scan, participants were instructed to rest with their eyes closed but not fall asleep.

5.5.5. MRI DATA PREPROCESSING AND ANALYSIS

T1-weighted images were skull-stripped using the Brain Extraction Tool (BET; Smith, 2002) and registered to a MNI template using FLIRT (FMRIB's Linear Image Registration Tool; Jenkinson & Smith, 2001) The Lesion Segmentation Toolbox (LST;

Schmidt et al., 2012) was used to identify T2 hyperintense MS lesions and total lesion load was calculated for each MS participant. The T1-weighted anatomic images were then lesion-filled using LST and segregated into gray matter, white matter, and CSF tissue classes using Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm/) and its Voxel-Based Morphometry toolbox (VBM8; http://dbm.neuro.uni-jena.de/vbm). A lesion map was created to visualize lesion burden location at the group level by assigning each voxel a value representing the number of patients with a lesion at that voxel. Brain parenchymal fraction (BPF, i.e. gray matter+white matter /gray matter+white matter+ crebrospinal fluid; Phillips et al., 1998) was calculated for all subjects as an indicator of global brain atrophy (De Stefano, Battaglini, & Smith, 2007).

Preprocessing and data analysis was performed using the FMRIB Software Library (FSL) fMRI expert analysis tool (FEAT). Preprocessing steps included brain extraction, removal of the first four volumes, 100s high pass filtering, motion correction (MCFLIRT), slice timing correction, and 6mm FWHM spatial smoothing. In addition, removal of nuisance regressors, including whole brain global mean signal, white matter signal, ventricle (i.e. cerebrospinal fluid) signal, and persistent motion-related signals using the estimated motion parameters from MCFLIRT was performed (Fox & Raichle, 2007). Groups did not differ in mean "relative" (i.e. timepoint-to-timepoint) head motion or absolute displacement motion parameters ($p>.05$). Mean BOLD timeseries were extracted from an anterior seed (vmPFC; x=-2, y=49, z=-4) and a posterior seed (PCC: x=-2, y=-30, z=30) of the DMN (Fox et al., 2005; Toro, Fox, & Paus, 2008) and were used in a seed-based voxelwise connectivity analysis (10mm seed spheres; see Figure

5.4). These two seeds were selected as they are suggested to reflect two main hubs within the DMN (Buckner et al., 2008; Uddin, Kelly, Biswal, Xavier Castellanos, & Milham, 2009). Mean-centered ISD scores from the three CTIP subtests were entered as covariates in the analysis. Images were cluster threshold corrected, $z<2.3$, $p<.05$ (see supplemental Figure 5.1).

5.5.6. BEHAVIOURAL DATA PREPARATION

IIV was measured by calculating individual standard deviations (ISDs) on the CTIP for all participants using methods described previously (Wojtowicz et al., 2012, 2013). Briefly, only correct trials were used and data were screened for outliers (i.e. > than 3 SD from the group means). Mean group RTs were imputed for missing values in order to avoid statistical issues associated with missing data (Hultsch et al., 2000). Systematic differences due to trial and block as well as mean reaction time differences associated with group membership were partialled from the data using linear regression since these can confound the interpretation of differences in within-person variability (Hultsch et al., 2000). Residual scores were then converted to T-scores and an individual standard deviation (ISD) score was calculated for each participant. These ISD scores as well as the remaining behavioural data were analyzed using a series of planned t-tests and mixed model ANOVAs.

5.5.7. PROCEDURE

All participants provided written informed consent following procedures approved by the Capital District Health Authority Research Ethics Board. Participants completed clinical measures as well as the CTIP in a quiet room. They then completed a

MRI session, which included resting-state T2*-weighted fMRI, T1-weighted and T2-weighted scans. Participants were compensated $20 for completing the study.

5.6. RESULTS

5.6.1. DEMOGRAPHIC & CLINICAL CHARACTERISTICS

Demographic and clinical information for all participants is presented in Table 5.1. MS participants and controls were matched on age ($t(32)= -.360$, $p= .58$) and education ($t(32)= -.553$, $p= .58$). Although MS participants made fewer correct responses on the SDMT and on both the 3-second and 2-second PASATs, they did not differ statistically from controls ($p> .05$)**.** The MS group did not report more symptoms of depression than healthy controls on the BDI-FS, ($t(29.39)= 1.66$, $p= .10$), but did report more fatigue symptoms ($t(23.19)= 4.50$, $p< .001$) on the D-FIS. Lesion load and brain parenchymal fractions (BPF) are also presented in Table 5.1. The MS group demonstrated lower BPF than healthy controls ($t(32)= 2.49$, $p= .018$).

5.6.2. CTIP PERFORMANCE

Accuracy data are not available for the SRT subtest. Mean accuracy did not differ between groups on the CTIP CRT subtest ($F(1, 32)= -.217$ $p= .83$) or SSRT subtest ($F(1, 32)= -.326$, $p= .75$). On the CRT, mean (SD) errors for the MS group was .40(.86) and .44(.83) for the control group. On the SSRT, mean (SD) errors for the MS group was 1.0(1.33) and .88(.81) for the control group.

Group mean response latencies (RT) for each CTIP subtest are shown in Table 5.2. A repeated-measures ANOVA with CTIP subtest as the within-subject variable and Group as the between-subject variable was used to analyze the mean RT scores. RTs increased as the tasks became more demanding (Test: $F(2, 64)= 334.63$, $p< .001$) and the MS group had significantly longer RTs than controls (Group: $F(1, 32)= 7.47$, $p= .01$). A

series of one-way ANOVAs revealed that MS participants had significantly longer RTs than controls on the SRT ($F(1, 32)= 9.60$, $p= .004$) and the SSRT ($F(1, 32)= 6.27$, $p= .018$) subtests, though not on the CRT ($F(1, 32)= 3.26$, $p= .08$).

Group ISDs on each CTIP subtest are shown in Table 5.2. A repeated measures ANOVA revealed that ISD increased with subtest difficulty ($F(2, 64)= 4.55$, $p= .014$) but there was no main effect for group ($F(1, 32)= 3.62$ $p= .066$) and no significant group by test interaction ($F(2, 64)= .135$, $p= .87$). A series of planned one-way ANOVAs revealed that MS participants were significantly more variable than controls on the SRT ($F(1, 32)= 4.22$, $p= .048$) and SSRT tasks ($F(1, 32)= 4.25$, $p= .047$) but not on the CRT task ($F(1, 32)= .904$ $p= .349$).

5.6.3. CTIP PERFORMANCE AND STRUCTURAL MRI

Within the MS group, relations between ISD for each CTIP subtest and structural MRI measures of BPF and lesion load were examined by calculating Pearson correlation coefficients. BPF was not related to ISD on any of the CTIP subtest ($p>.05$). Lesion load was also not related to ISD on all three subtests: SRT (Spearman $r= .325$; $p= .19$), CRT (Spearman $r= -.09$; $p= .72$), and SSRT (Spearman $r= .131$ $p= .60$; see Supplemental Figure 5.2).

5.6.4. RSFMRI & CTIP PERFORMANCE

Both the vmPFC and PCC seeds demonstrated functional connectivity with regions that have been associated with the DMN; specifically, vmPFC including ACC, PCC including precuneus, and bilateral posterior inferior parietal cortices (see Figure 5.1 & Table 5.3). No significant differences in the pattern of functional connectivity were found between MS participants and controls using the vmPFC seed (i.e. anterior seed).

However, using the PCC (i.e. posterior seed), healthy controls demonstrated greater functional connectivity between the PCC and ACC and between the PCC and the right inferior frontal gyrus, compared to MS participants (Figure 5.2).

To examine potential modulations in DMN functional connectivity associated with performance variability in MS, ISDs for all CTIP subtests were entered as covariates in the seed-based voxelwise connectivity analysis. Alterations in functional connectivity associated with ISD on the SRT and CRT tasks in MS were not found using the vmPFC seed. MS participants who demonstrated more stable performance (i.e. lower ISD scores) on the SSRT subtest demonstrated greater functional connectivity between the vmPFC and the left frontal pole (FP; See Figure 5.3 & Table 5.3). This relation was not observed in healthy controls and no significant alterations in functional connectivity associated with ISD scores were found using the PCC seed for either group. Qualitative analysis of the MS group lesion map revealed distributed lesion locations that did not appear to be preferentially located near seed regions or the left FP cluster (Figure 5.4).

5.7. DISCUSSION

This study investigated alterations in resting-state functional connectivity within the DMN associated with performance variability in individuals with RRMS. This mildly affected sample of persons with MS did not differ from matched healthy controls on standard clinical tests of information processing speed. However, consistent with previous behavioural studies (Bodling et al., 2012; Bruce et al., 2010; Wojtowicz et al., 2012, 2013), we demonstrated that individuals with MS were both slower and more variable in their performance on simple and more complex reaction time tasks.

Using a seed-based approach we found that both anterior (i.e. vmPFC) and

posterior seeds (i.e. PCC) elicited connectivity in regions commonly associated with the DMN (Buckner et al., 2008; Fox et al., 2005; Toro et al., 2008). While no group differences in functional connectivity were found using the vmPFC seed, greater functional connectivity between the PCC, ACC and the right inferior frontal gyrus was found in healthy controls when using the PCC seed. This difference in the pattern of results for the two seeds is not surprising in light of Buckner and colleagues' (2008) suggestion that anterior (i.e. medial PFC) and posterior nodes (i.e. PCC) may represent sub-network hubs within the DMN. Several other studies have also demonstrated differences in functional connectivity between these two nodes in healthy individuals (e.g., Damoiseaux et al., 2006; Greicius, Krasnow, Reiss, & Menon, 2003; Uddin et al., 2009).

Although literature examining DMN connectivity in persons with RRMS is growing, consistent DMN differences between MS patients and controls have not yet been found. In our study, healthy controls demonstrated greater functional connectivity between the PCC and the ACC as well as between the PCC and right inferior frontal gyrus compared to individuals with RRMS. This relatively reduced ACC functional connectivity within the DMN in the MS groups appears consistent with the report of Bonavita and colleagues (2011), as well as with reports of reduced ACC functional connectivity in persons with progressive MS (Rocca et al., 2010). Together these findings support the possibility of ACC functional connectivity disruption in MS (Bonavita et al., 2011). However, other studies have either failed to find significant differences in DMN functional connectivity between RRMS subjects and controls (Roosendaal et al., 2010) or have shown DMN alterations in neural regions other than the

ACC (e.g., middle temporal gyrus and occipital lobe; Faivre et al., 2012). Given the limited literature and relative inconsistencies in DMN findings across studies to date, group level differences in resting-state network activity between person with MS and healthy controls will require further replication with consistent analytic methods and well-characterized samples.

We also examined differences in functional connectivity associated with performance variability on reaction time tasks and found that MS participants with more stable performance (i.e. less IIV) on the most demanding cognitive task (i.e. SSRT), demonstrated greater connectivity between the vmPFC seed and the frontal pole (FP). This increased functional connectivity may represent greater integrity between those neural regions in MS patients (Fox & Raichle, 2007; Zhang & Raichle, 2010). This integrity likely reflects a combination of structural integrity (e.g., via white matter tracts) as well as temporal correlations due to shared functions (Damoiseaux & Greicius, 2009). Greater functional connectivity between the vmPFC and FP in MS patients may facilitate stability in performance on a complex information-processing task completed outside of the scanner.

Consistent with this notion, increased functional connectivity between DMN regions has been associated with better cognitive performance in at least two studies of MS (Bonavita et al., 2011; Rocca et al., 2010). In RRMS patients, greater resting-state functional connectivity within the PCC of the DMN has been associated with better cognitive performance (Bonavita et al., 2011), while greater PFC and ACC functional connectivity within the DMN has been found to correlate with better PASAT performance in progressive MS patients (Rocca et al., 2010). However, evidence of

maladaptive functional connectivity has been reported in one study of early RRMS subjects in whom increased connectivity in the DMN was associated with worse performance on a semantic fluency task (Faivre et al., 2012). Nonetheless, these findings highlight the importance of examining alterations in rsfMRI connectivity associated with measures of meaningful functional outcomes, such as cognitive test performance.

The precise role(s) and significance of the FP in cognitive functioning is presently unclear. FP involvement has been reported on tasks requiring complex cognitive functions, such as "multi-tasking" and executive function (Gilbert, Spengler, Simons, Frith, & Burgess, 2006; Gilbert, Spengler, Simons, Steele, et al., 2006). As a result, the FP has been proposed to play a central role in "meta-cognitive functions", which include the integration and coordination of initiating and sustaining responses, and the executive skills necessary to complete novel and complex tasks (Stuss, 2011). Task-based fMRI studies have found that, relative to healthy controls, persons with MS often show diffuse increased recruitment of frontal regions, including the FP, for tasks that require information processing speed, attention, and memory (Audoin et al., 2003; Mainero et al., 2004; Staffen et al., 2002). In mildly affected MS individuals, this increased frontal activity is found even when cognitive performance is similar to that of healthy controls, suggesting that it may represent a compensatory function (Mainero et al., 2004; Penner & Rausch, 2003). Our finding, that greater resting-state functional connectivity between frontal cortical regions was associated with better performance of a complex attention task, suggests that this increased functional connectivity may facilitate similar compensatory mechanisms required to sustain cognitive performance in MS patients.

Enrollment into our study was limited to female RRMS patients with a relatively

narrow range of disability and this in turn limits our ability to generalize our findings to the broader MS population. However, our findings suggest that within mildly affected individuals with MS, increased resting-state functional connectivity between frontal cortical regions may facilitate performance stability on a complex speeded cognitive task. Further studies will be necessary to elucidate the role of the FP in facilitating cognitive performance in MS using a broader range of cognitive tasks.

Table 5.1 Demographic, Clinical, and MRI Metrics

	MS Patients	Controls	*p*
Age M(SD)	42.1(7.4)	43.1(7.8)	.70
Education (yrs) M(SD)	14.7(1.8)	15.1(2.3)	.58
SDMT M(SD)	55.2(10.5)	60.6(10.2)	.14
PASAT-3 M(SD)	45.3(8.2)	48.6(9.0)	.27
PASAT-2 M(SD)	33.3(11.5)	36.9(9.6)	.33
BDI-FS M(SD)	1.9(2.07)	0.9(1.34)	.10
D-FIS M(SD)	10.9(7.48)	2.3(3.01)[a]	.001
EDSS scores Md(Range)	2.25(1-3.5)	___	__
Yrs Onset Md(Range)	7.5(1-28)	___	__
Lesion volume (mL) M(SD)	16.73(25.7)	___	__
BPF M(SD)	.82(.03)	.84 (.02)	.02

Note: [a] N= 15; BPF= Brain Parenchymal Fraction, D-FIS= Daily Fatigue Impact Scale

Table 5.2 CTIP performance for both groups.

Measure	MS Patients	Controls	p-value
SRT-Mean RT M(SD)	399.45(59.74)	337.24(56.77)	.004
CRT-Mean RT M(SD)	648.96(113.64)	574.84(125.68)	.080
SSRT-Mean RT M(SD)	952.12(127.52)	824.54(168.76)	.018
SRT-ISD M(SD)	7.87(2.50)	6.19(2.23)	.048
CRT-ISD M(SD)	8.20(3.92)	7.02(3.20)	.349
SSRT-ISD M(SD)	9.27 (2.13)	7.75(2.17)	.047

Note: CRT= Choice Reaction Time; ISD= Individual standard deviation SRT= Simple Reaction Time; SSRT= Semantic Search Reaction time

Table 5.3 Clusters reported as statistically significant (cluster threshold corrected, z<2.3, p<.05)

Contrast	Region	Z	x	y	z
MS+ Controls	ACC/ Medial Frontal Cortex				
(vmPFC Seed)	(L)	8.63	-4	46	-4
	Paracingulate gyrus (L)	6.41	-2	52	8
	ACC (L)	5.76	-4	34	20
	Superior frontal gyrus (L)	5.03	2	56	20
	Middle frontal gyrus (L)	4.85	-2	30	-10
	Superior frontal gyrus (L)	4.76	-20	32	40
	ACC (L)	4.69	-20	28	46
	Superior frontal gyrus (L)	4.66	-16	32	44
	Superior frontal gyrus (L)	4.31	-4	40	46
	Frontal pole (L)	4.48	-10	58	28
	Frontal pole (L)	4.45	-14	60	22
	Precuneus (L)	5.16	-4	-54	14
	PCC (L)	5.01	-10	-54	28
	PCC (L)	4.87	-4	-42	30
	PCC (R)	4.72	8	-52	26
	Inferior parietal lobule (L)	4.66	-50	-56	28
	Inferior parietal lobule (L)	4.56	-50	-52	16
	Inferior parietal lobule (R)	3.63	52	-66	20

	Inferior parietal lobule (R)	3.62	46	-64	22
MS SRT ISD	---	---	---	---	---
MS CRT ISD	---	---	--	---	---
MS SSRT ISD	Frontal pole (L)	4.57	-18	70	-2
	Frontal pole (L)	3.9	-26	56	20
MS+ Controls (PCC Seed)	PCC (L)	8.54	-4	-36	34
	PCC (R)	6.31	8	-42	36
	ACC (L)	5.63	-4	44	6
	Precuneus (L)	5.2	-6	-62	44
	Inferior parietal lobule (R)	4.98	36	-54	40
	Inferior parietal lobule (L)	4.95	-50	-62	40
	Inferior parietal lobule (R)	4.93	44	-50	42
	PCC (L)	4.88	-2	-50	16
	Paracingulate cortex (R)	4.8	4	48	4
	Precuneus (L)	4.77	-4	-78	40
	Frontal Pole (L)	4.73	-2	60	-6
	Inferior temporal gyrus (L)	3.8	-66	-52	-16
	Middle temporal gyrus (L)	3.64	-62	-48	-12
	Middle temporal gyrus (L)	3.02	-68	-28	-16
HC>MS	Inferior frontal gyrus (R)	3.68	58	18	-4
	Inferior frontal gyrus (R)	3.42	50	30	-4
	ACC (R)	3.85	6	6	34

	ACC (R)	3.67	6	28	20
MS SRT ISD	---	---	---	---	---
MS CRT ISD	---	---	---	---	---
MS SSRT ISD	---	---	---	---	---

Note: ACC= Anterior cingulate cortex, PCC= Posterior cingulate cortex.

Figure 5.1. The DMNs across all subjects for the vmPFC (top) and PCC (bottom) seeds.

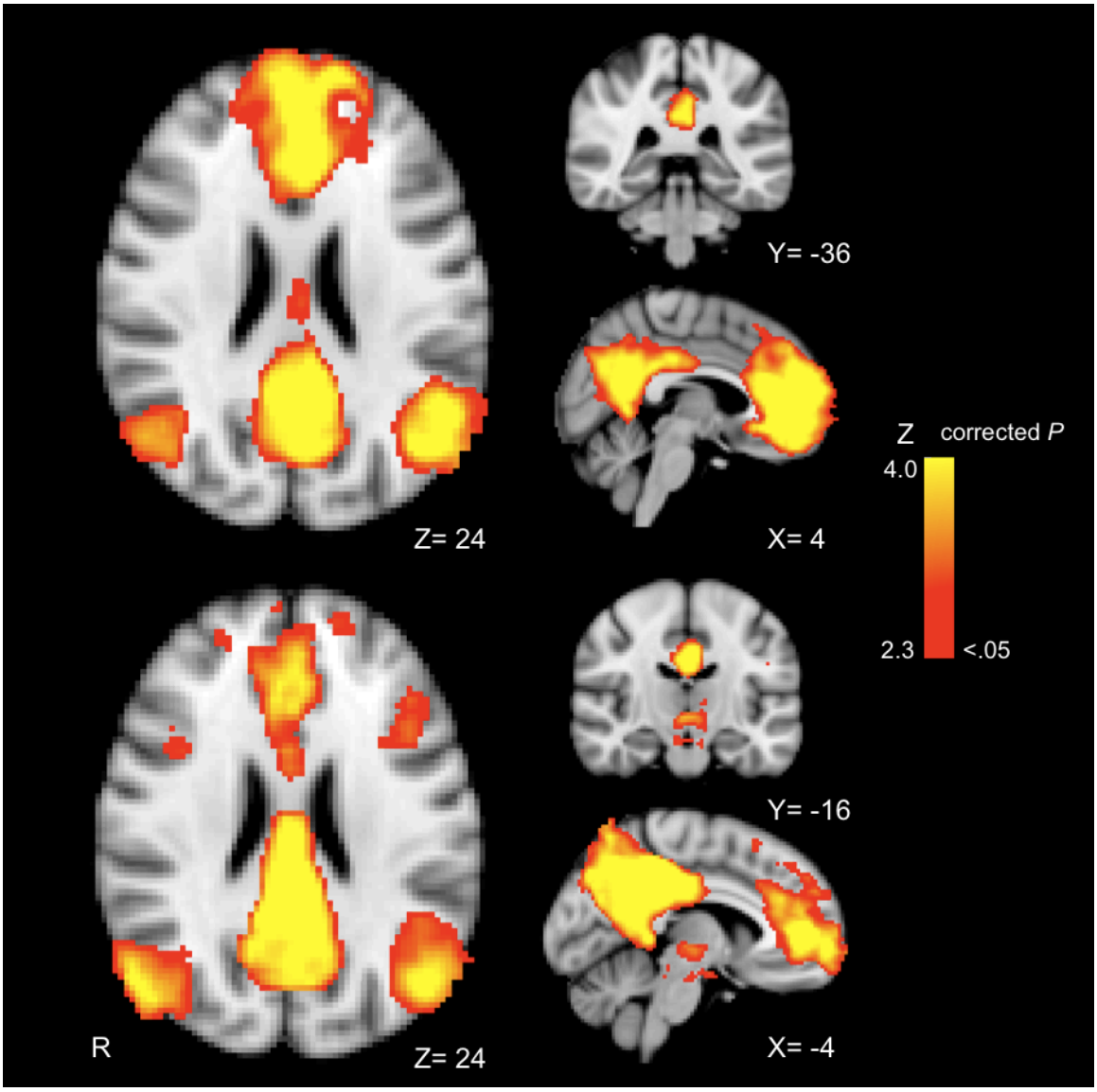


Figure 5.2. Greater functional connectivity in controls than MS participants using the PCC seed.

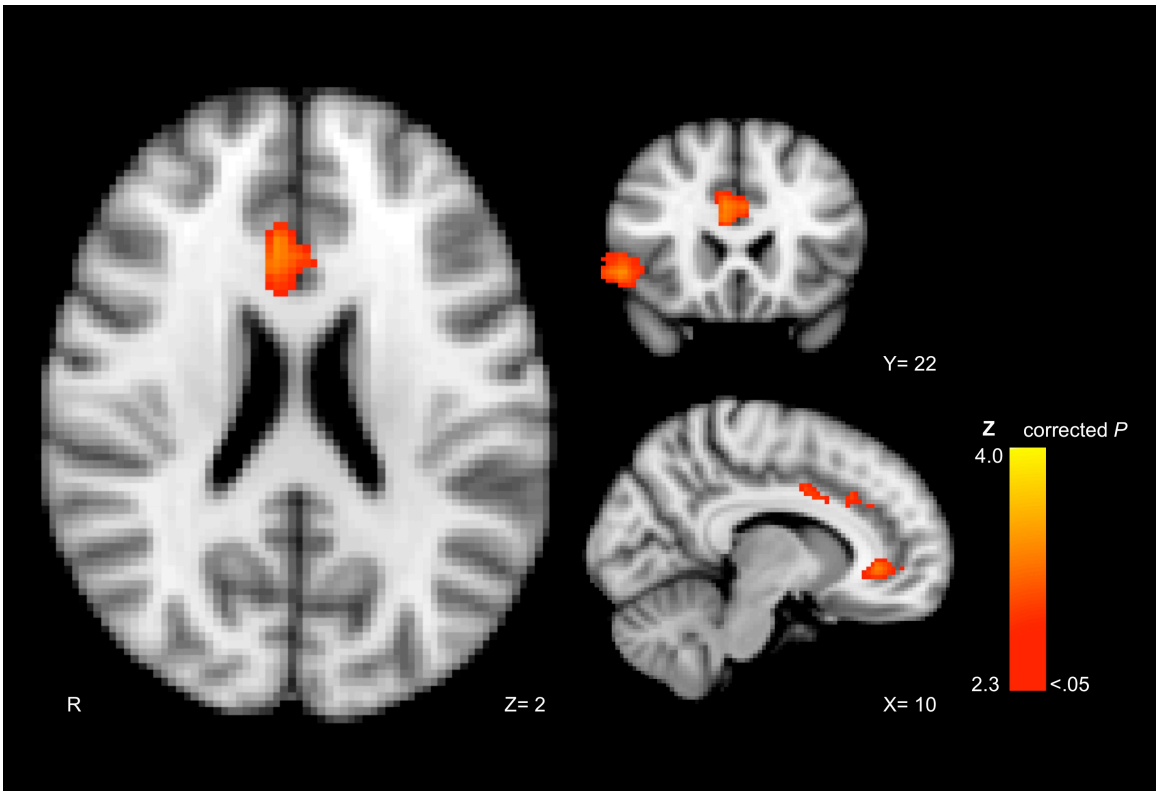


Figure 5.3. Greater connectivity between the vmPFC seed and left lateral frontal pole associated with greater performance stability on the semantic search reaction time task in the MS group.

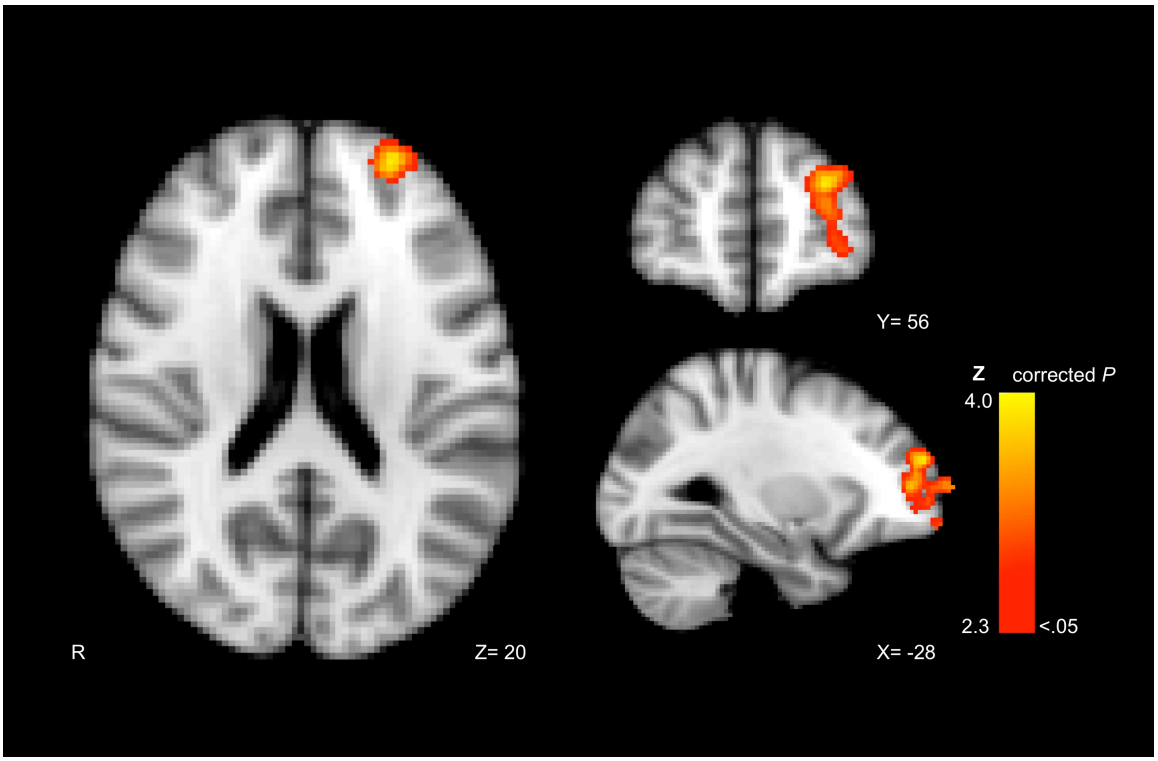
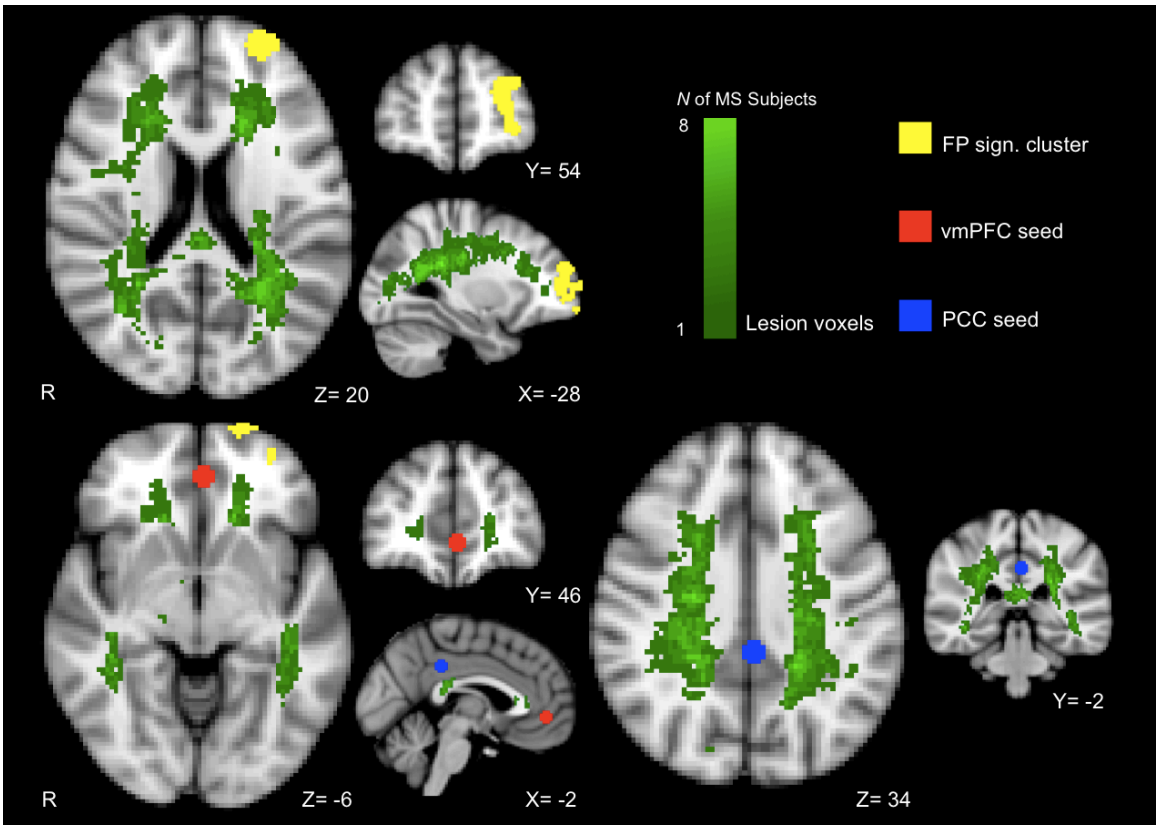


Figure 5.4. Lesion burden map for the MS group, displayed with reference to the frontal pole cluster (see Figure 5.3) and the seed regions used in the rsfMRI connectivity analyses. The lesion maps display the number of MS patients with a lesion at that voxel.



5.7. SUPPLEMENTAL DATA

Figure S.1 Diagram of data processing steps

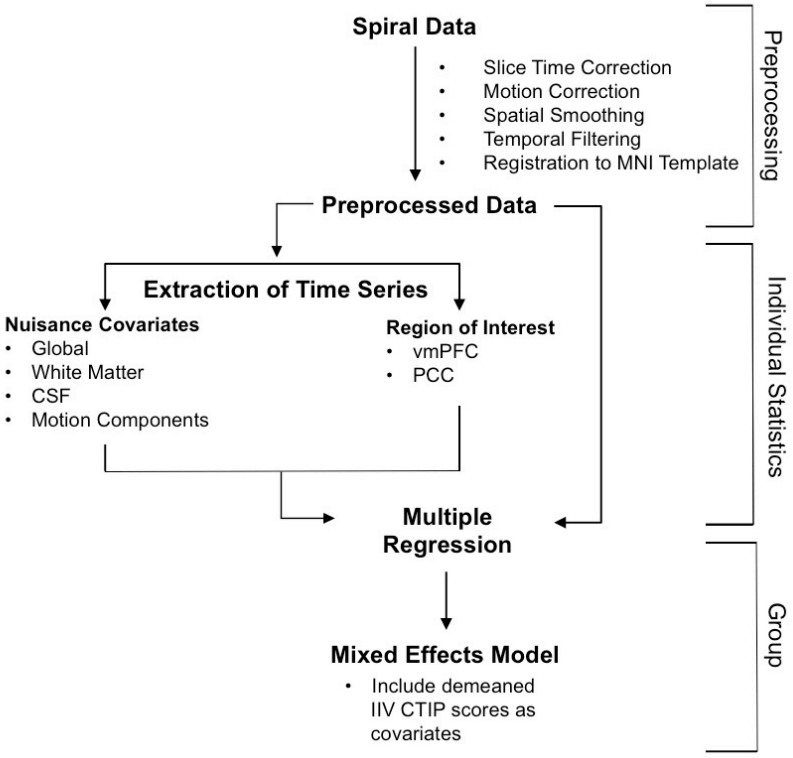
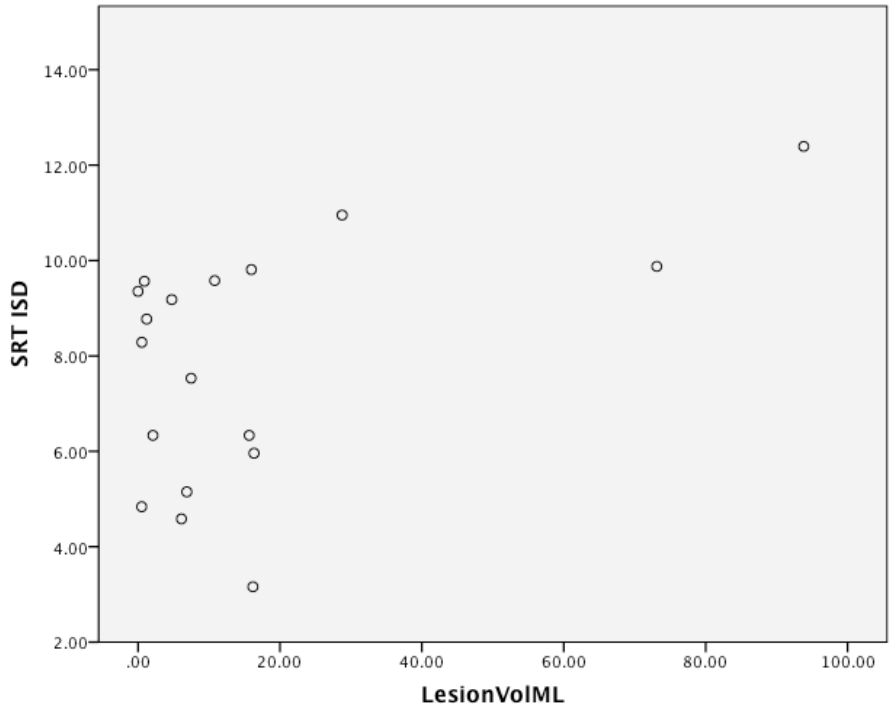
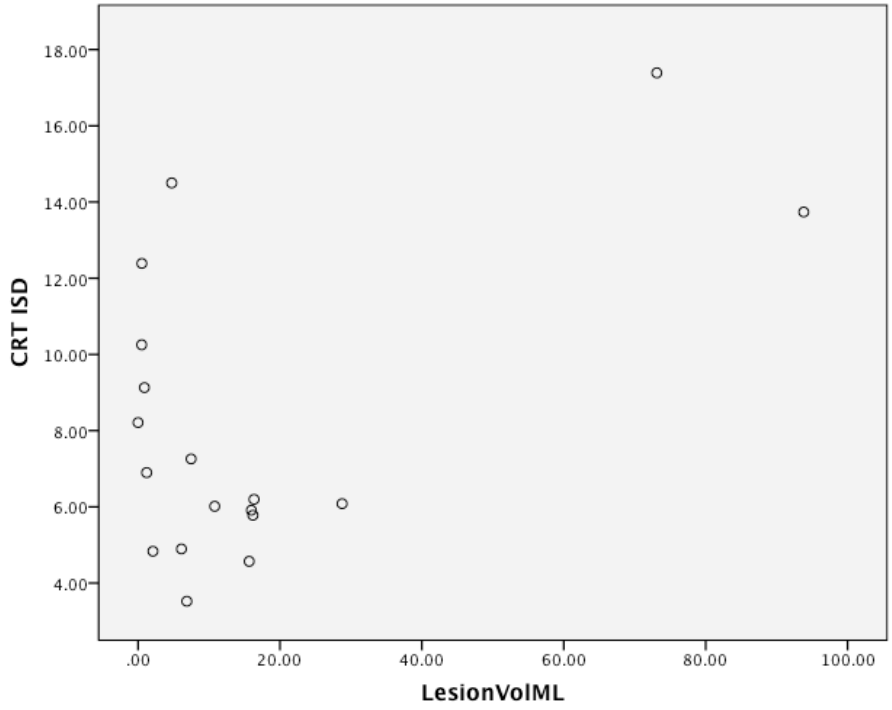
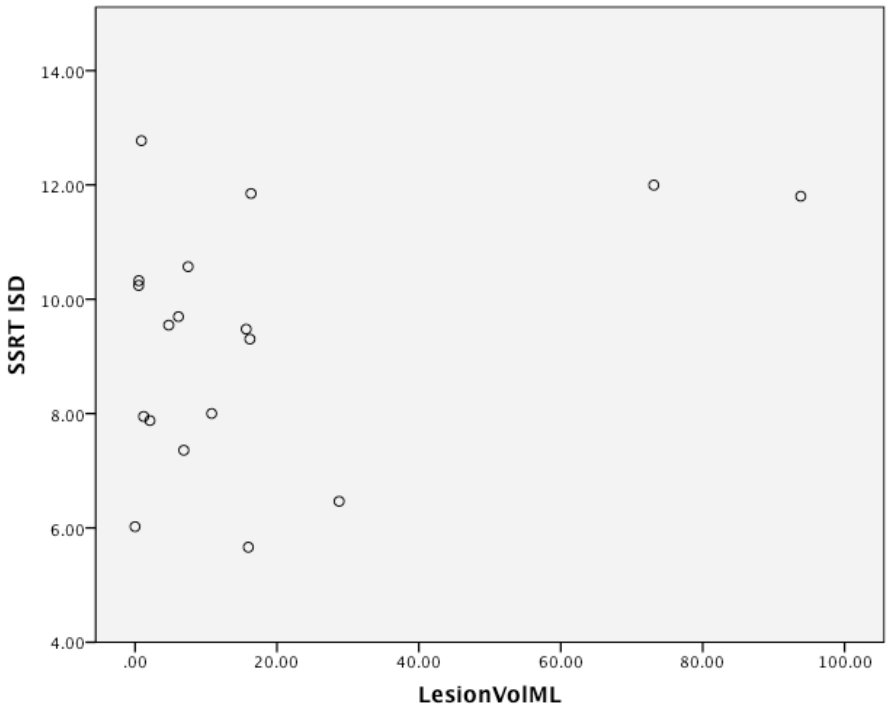


Figure S.2 Correlation scatterplots between lesion load volume and ISD on the CTIP tasks in MS






SSRT ISD
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CHAPTER 6: DISCUSSION

6.1. SUMMARY

Cognitive deficits are common in MS and have a negative impact on daily life (Chiaravalloti & DeLuca, 2008). Information processing speed is one of the most commonly reported and studied cognitive deficits in MS (Chiaravalloti & DeLuca, 2008), yet our clinical tools of information processing speed (e.g. SDMT and PASAT) do not provide an accurate assessment of speed and/or are used to assess group-level differences in mean performance. IIV is an indicator of an individual's stability in performance across a series of trials and has been demonstrated to be a significant predictor of cognitive performance and decline in several neurodegenerative and neurodevelopmental conditions (MacDonald et al., 2006, 2009). The research presented in this dissertation examined IIV in performance as an indicator of cognitive functioning in MS.

The results of Chapter 2 demonstrated that individuals with RRMS were not only slower on the CTIP subtests but were also more variable in their performance. This difference in IIV was best observed when the ISD approach was taken, which examines individual standard deviations after controlling for mean-level group differences as well as practice and learning effects. IIV was also found to increase with greater task demands and was observed to be the best predictor of group membership. In Chapter 3, individuals with MS again demonstrated greater IIV on a different computerized cognitive task, the ANT-I. This IIV in performance was not correlated with disease characteristics (e.g. EDSS, disease duration, depression scores) or attention network scores (i.e. Alerting, Orienting, and Executive). Individuals with MS also demonstrated more difficulty with conflict resolution (i.e. an Executive network effect) than controls. IIV, followed by

PASAT-2 scores, were also found to be the most significant predictors of group membership. Chapter 4 examined the stability of IIV across multiple testing sessions. Individuals with MS demonstrated consistent differences in IIV compared to healthy controls on the ANT-I across 6 consecutive monthly assessments. These consistent IIV differences were demonstrated in individuals with MS who also had stable measures of neurologic status (i.e. EDSS scores), structural MRI measures (i.e. lesion load and brain volume parameters), measures of psychological status (i.e. self-reported depression and fatigue symptoms) and neuropsychological test performance (i.e. PASAT and SDMT scores) over the 6-month period.

Lastly, Chapter 5 examined the neural underpinnings of IIV in MS using rsfMRI. Specifically, alterations in functional connectivity in regions of the DMN associated with IIV on the CTIP in MS patients were examined. Individuals with MS who had more stable performance on the SSRT subtest of the CTIP demonstrated greater functional connectivity between the anterior DMN seed (i.e. vmPFC) and the left lateral FP. This relation was not found in the controls subjects nor were there any group-level differences between MS subjects and controls in functional connectivity using this seed. Control subjects demonstrated greater functional connectivity between the PCC and the ACC as well as the PCC and the right inferior frontal gyrus compared to MS subjects. No relations between variability and functional connectivity were found using the PCC seed (i.e. posterior seed).

6.2. FURTHER CONSIDERATIONS

6.2.1. CALCULATION OF IIV

IIV involves the examination of inconsistencies in scores across several measurements within an individual (Ram, Lindenberger, & Blanchard-Fields, 2009). Quantification of IIV in empirical cognitive research most commonly involves the examination of variability in RTs across a series of trials. However, examining inconsistencies in RT performance presents several methodological issues. First, variability in performance can be influenced by mean level differences in performance. Furthermore, systematic influences that can affect repeated measurements, such as practice and learning, may also confound variability (see Hultsch et al., 2000; MacDonald et al., 2006). The ISD approach described in Chapters 2-4, attempts to extract a 'pure' measurement of variability by controlling for potential factors that may influence variability. The rationale behind this approach is that in order for IIV to be a unique indicator of performance, and not just a statistical artefact, it should be observed after systematic variables that can influence variability (e.g., practice, learning, boredom, etc.) are removed (Hultsch et al., 2000). An alternative approach to examining IIV is to calculate COV, which is an individual's standard deviation in performance divided by an individual's mean. However, the ISD approach has been suggested to be a more sensitive and often a more 'conservative' measure of IIV (Hultsch et al., 2000). In Chapter 2, both ISD and COV approaches were examined and ISD was found to be more sensitive to IIV differences between groups.

6.2.2. TASK DEPENDENCE

An additional consideration for IIV is the influence of task demands on performance variability. Tasks requiring more cognitive demand will likely require more information processing and hence affect mean reaction time measures (e.g. Tombaugh et

al., 2010). It has been suggested that this effect of cognitive demand may also influence IIV. In fact, some studies have demonstrated increases in IIV associated with larger cognitive demands (e.g. Hultsch et al., 2000; Burton et al., 2004). Consistent with these findings, in Chapter 2 individuals with MS demonstrated greater ISD on a more complex semantic search task (i.e. SSRT) compared to simple and choice reaction time tasks. In this study, the range of ISD scores for MS subjects was larger for the CRT than for other CTIP subtests, perhaps reflecting the relative change in task demands for this subtest. Specifically, for the CTIP, the transition from the SRT to CRT subtests requires shifting from a unimanual response to a single target stimulus, to the requirement for a bimanual response based on a decision between two options. In Chapter 5, using a somewhat different subsample of MS and healthy controls, MS individuals again demonstrated greater IIV on the more complex SSRT task. However, a significant difference between MS patients and controls in IIV on the CRT was not found. Hence, IIV appears be influenced by cognitive demands (i.e. task complexity) as well as by task specific features (e.g. form of response).

Although individuals with MS demonstrated greater IIV on both the CTIP (Chapter 2) and ANT-I tasks (Chapter 3) relative to matched controls, a correlation between IIV on these two tasks was not found when MS subjects, who completed both tasks, were examined (see Appendix 1). This lack of relationship may again reflect the influence of task demands (e.g., cognitive, sensory, and material) on IIV in MS. In contrast, healthy control subjects demonstrated a moderately sized positive relation (r = .56) between ISD on the SSRT and the ANT-I (see Appendix 1). No significant relations were found between ISD on the other CTIP subtests and the ANT-I for healthy controls.

Of the three CTIP tasks the SSRT task most resembles the demands of the ANT-I in that both involve a bi-manual response and require an individual to process complex information (i.e., search semantic information and ignore conflicting information, respectively) in order to make a correct response. Hence, a relation between IIV on these two tests may reflect the influence of cognitive complexity on performance variability. The fact that MS subjects did not demonstrate a relation in IIV between these tasks, suggests that differences in task dynamics may influence performance variability more so in persons with MS than in healthy controls. Although, both the SSRT and ANT-I may be characterized as "complex information processing tasks", important differences in task demands exist between the two. In particular, the SSRT task requires processing of semantic language information, whereas the ANT-I requires visual conflict resolution (i.e. flanker task). Functional neuroimaging in healthy individuals has shown that performance on the SSRT elicits left PFC activity (within Broca's area; Smith et al., 2012), whereas performance on the ANT, a variant of the ANT-I, elicits activity in the right anterior cingulate (i.e. incongruent minus congruent trials contrast; Fan et al., 2005). Furthermore, similar to ISD, there was no significant correlation between mean RT scores on the SSRT and ANT-I for MS patients (Appendix 1), although though this relationship was found for healthy controls. This further supports the possibility that differences in IIV across these two tasks reflect variations in the relative cognitive difficulties amongst MS subjects (e.g., spared semantic processing and impaired conflict resolution and/or vice versa). As discussed in Chapter 1, MS patients demonstrate variability in their profile of cognitive impairments (i.e. variability in impairments across cognitive domains). Thus, the lack of relation between IIV across tasks that require

different cognitive abilities (e.g., semantic search and conflict resolution) in MS patients may be attributable to potential differences in cognitive impairments present within the MS group. Alternatively, the absence of significant relations between IIV on the CTIP and ANT-I tasks in MS may also suggest the possibility that IIV in MS and IIV in healthy controls represent different underlying etiologies. Nevertheless, the issue of task dependence on IIV in healthy and clinical populations requires further investigation.

In Chapter 3, it was also found that individuals with MS demonstrated more difficulty with conflict resolution (i.e. slower reaction times) despite equivalent accuracy. These findings differ somewhat from previous studies using the original version of the ANT (Crivelli et al., 2012; Urbanek et al., 2010), which found that MS patients demonstrated deficits in the alerting network, with difficulties in response inhibition only in found the context of an "alerting" cue. Methodological differences between the ANT and the ANT-I may account for this discrepancy in findings, as the alerting and orienting networks in the ANT are confounded (see Ishigami & Klein, 2009; Ishigami & Klein, 2010). Using the ANT-I, Omisade et al. (2012) also found executive network inefficiency when MS patients were in the alerted state, but in keeping with our study, they did not find differences in the alerting network in individuals with MS. Our findings confirm the presence of executive network inefficiency among patients with MS when using the ANT-I, though an alerting by executive network effect was not observed. Nonetheless, despite some discrepancies in the findings of studies examining ANT and ANT-I performance in MS, all have demonstrated some degree of inefficiency in executive control in MS.

At face value, the finding that conflict resolution efficiency (i.e. the ANT-I Executive Network scores) did not correlate with IIV in the MS group could be considered surprising, given that IIV has been suggested to reflect failures in executive control (West et al., 2002). However, IIV on the ANT-I may not only reflect variability in performance on a flanker task but may also reflect fluctuations in sustained attention. The ANT-I, unlike the CTIP, includes 288 trials and requires 20-25 minutes to complete. In this regard, IIV exhibited on the ANT-I may have also been influenced by difficulties in sustaining attention across trials. This is consistent with the conceptualization of IIV as representing momentary lapses of attention (Bunce, Warr, & Cochrane, 1993). Both interpretations, however, support the concept of IIV as reflecting frontal cortical mediated processes, including attention maintenance and executive control (MacDonald et al., 2009).

6.2.3. REPEATED MEASUREMENTS

Chapter 4 examined the stability of repeated IIV measurements across 6 monthly sessions. Decreases in IIV in the MS group were observed during the first 3 sessions, likely representing the effect of previous exposures to the ANT-I on IIV. A similar pattern was found for IIV in healthy controls and group level differences in IIV between persons with MS and healthy controls were maintained across all sessions. This supports the suggestion that IIV in performance reflects a stable within-person characteristic (MacDonald et al., 2006; 2009). If IIV reflected transient somatic and psychological influences on performance, such as variations in stress, sleep, and motivation, one would expect to see less stability in IIV across occasions and more variability in group level differences across time. However, consistent increases in IIV relative to controls have

been demonstrated in individuals with dementia (Hultsch et al., 2000), Alzheimer's disease, Parkinson's disease (Burton et al., 2004) and now in individuals with MS. The stability in IIV group differences across sessions was found in a sample of MS patients who also demonstrated stable clinical (i.e. EDSS, lesion load, BPF), psychological (i.e. BDI and self-reported fatigue), and neuropsychological (i.e. PASAT and SDMT) performance. This finding supports the potential use of IIV as an indicator of performance differences between groups across multiple sessions. In the aging literature, IIV has been found to be a strong marker of cognitive impairment (Dixon et al., 2007) and has been found to predict terminal decline (i.e. the accelerated cognitive deterioration that occurs close to death among older adults; Macdonald et al., 2008). Whether IIV and changes in IIV can predict cognitive decline in MS remains to be determined but the findings of short-term stability of IIV in clinically stable individuals with MS suggest that studies examining the responsiveness of IIV to clinically meaningful changes in disease status are warranted.

6.2.4. CLINICAL IMPLICATIONS OF IIV

Chapters 2-5 have demonstrated that IIV in reaction time performance is a consistent and stable finding in RRMS. IIV was not found to correlate with other cognitive test scores (i.e. PASAT) or clinical ratings of neurologic disability (i.e. EDSS scores) and distinguished group membership better than mean RT and PASAT performance. This suggests that IIV is an important and unique characteristic of MS cognitive performance that can provide novel insight into information processing problems in MS. Although these studies examined IIV in mildly affected individuals with RRMS, these participants still demonstrated information processing speed deficits (i.e.

mean RT differences). Future research should examine whether IIV is a sensitive indicator in even earlier stages of MS, such as in individuals with CIS or in whom deficits are not present on RT measures. Further examination of the influence of task demands and relations between IIV in different cognitive domains will be necessary in order to more clearly determine the clinical applications of this measure. Such investigations will likely require larger and more representative sample sizes that include participants with a greater range of disability as well as a larger array of cognitive tasks. As noted above, the potential of IIV as a predictor of future cognitive decline warrants further investigation. If IIV can identify individuals with MS at risk of further cognitive decline, then this measure may help identify those most in need of cognitive intervention/rehabilitation programs and/or be used as an outcome measure for evaluating the efficacy of such programs. Furthermore, the clinical samples used in this dissertation included only females with stable and relatively mild RRMS. The presence, nature and responsiveness of IIV in progressive forms of MS remain to be explored. Although, more research is required to elucidate the potential clinical applications of IIV, the findings of the studies comprising this dissertation demonstrate that IIV has promise as an indicator of cognitive dysfunction in MS.

6.2.4. RESTING STATE FUNCTIONAL CONNECTIVITY AND IIV

The final study of this dissertation explored the functional neural underpinnings of performance variability in information processing in MS using resting-state functional connectivity. Some associations between cognitive performance variability and alterations in one resting-state network (i.e. the DMN) have been previously identified. In a task-based fMRI study, greater suppression of the DMN was associated with less

performance variability in young healthy adults (Kelly et al., 2008). In healthy older adults, overall increased DMN connectivity during rest periods between tasks was associated with greater IIV (Grady et al., 2010). Hence, this network was targeted in Chapter 5.

Although the DMN is described as a unified network, it is also considered to be organized into sub-network hubs. The vmPFC, PCC and pIPL hubs demonstrate the most complete overlap (i.e. intrinsic correlations) with all regions associated with the DMN (i.e. vmPFC, PCC, dmPFC, pIPLs, and HF; See Buckner et al., 2008). However, the HF and dmPFC appear to form sub-systems, which may be distinct from the other DMN components. These two subsytems have been found to correlate with the core DMN hubs but not with each other in young healthy adults (Buckner et al., 2008). Seed-based analyses using vmPFC and PCC seeds have demonstrated that even within these core sub-network hubs, differences in functional connectivity patterns exist (Uddin et al., 2009; Greicius, Krasnow, Reiss, & Menon, 2003). Uddin and colleagues (2009) investigated the heterogeneity of the DMN and found that although both anterior (vmPFC) and posterior (PCC) hubs demonstrated similar patterns of connectivity, there were also unique positive correlations for each hub. For the anterior hub, greater connectivity was found in bilateral frontal and temporal gyri, whereas greater connectivity in lateral parietal cortices was found with the posterior hub (Uddin et al., 2009). Anti-correlated networks, thought to represent networks with competing or opposite function (Fox et al., 2005), were also examined in the two hubs. The anterior hub was found to have greater anti-correlations with areas associated with visual and spatial attention regions (i.e., superior IPL and extrastriate cortices) thought to comprise

the ‘task positive network’ (Fox et al., 2005). In contrast, the posterior hub exhibited greater anti-correlations with the human mirror neuron network (i.e. premotor cortex; BA 6) involved in observing and executing actions (Rizzolatti, 2005). Such findings support the rationale of investigating both anterior and posterior hubs of the DMN, as their unique connectivity patterns may underlie different functional roles within the DMN.

In tasked based fMRI, the vmPFC has been associated with tasks involving “mentalizing” (i.e., reflecting on mental states of others; Gilbert, Spengler, Simons, Steele, et al., 2006) as well as representing self-knowledge and self-referential thinking (Macrae, Moran, Heatherton, Banfield, & Kelley, 2004). In contrast, the PCC has been most commonly associated with episodic memory retrieval and visual-spatial imagery (e.g., Cavanna & Trimble, 2006; Lundstrom, Ingvar, & Petersson, 2005). Differences in the functional significance of these two regions further support the possibility of their differential roles within the DMN. In Chapter 5, despite finding DMN functional connectivity patterns using either the vmPFC or PCC seeds, different between- and within-group results were found. Between-group differences were only found using the PCC seed, with healthy controls demonstrating greater connectivity between the PCC and the ACC as well as the PCC and the right inferior frontal gyrus. As discussed in Chapter 5, this finding is consistent with previous reports indicating that MS patients have decreased functional connectivity within the DMN at the level of the ACC compared to controls (Bonavita et al., 2011; Rocca et al., 2010). In fact, it has been suggested that disrupted DMN connectivity with the ACC may be specific to MS as investigations using rsfMRI in mild cognitive impairment and AD have reported dysfunction within PCC and HF regions of the DMN (Qi et al., 2010; Sorg, 2007; Bonavita et al., 2011). However, the

significance of this reduced ACC connectivity with the DMN is unclear. Furthermore, findings of DMN connectivity alterations in MS have been inconsistent across studies (see Chapter 5). These inconsistencies are likely due to several important methodological differences across studies. These include differences in study design, such as examining the DMN during rest and examining the DMN during task-based fMRI. Differences in data analysis approaches (i.e., ICA and seed-based) and sample selection characteristics (i.e., CIS, RRMS, SPMS, PPMS, mixed) also likely contribute to inconsistencies across studies. Hence, group level differences in resting-state network connectivity in MS will require further replication with more consistent methods and well-characterized samples.

In addition to MS subjects having relatively less functional connectivity between the PCC seed and the ACC and right inferior frontal gyrus, MS subjects also demonstrated, alterations in functional connectivity that were associated with IIV on the SSRT task. Individuals with MS who were more stable (i.e. less IIV) on the SSRT demonstrated greater functional connectivity between the vmPFC and the left FP. This relationship was only found in MS patients and only when using the vmPFC seed, suggesting that this may represent an anterior hub specific relationship rather than a DMN network level effect. This is an important distinction as any seed-based analysis only examines relationships associated with a specific seed region, which may be part of a larger network. In contrast, as discussed in Chapter 5, the ICA approach allows for examination of network-level differences in functional connectivity (see Chapter 5). However, the fact that this increased FP functional connectivity was only found with the vmPFC seed suggests that the seed-based approach may be more sensitive to alterations in functional connectivity within hubs of the DMN. Uddin and colleagues (2009) also

emphasize that ICA approaches to identifying the DMN typically capture the common variance and hence may miss hub specific findings. Combination approaches, using both data-driven ICA and *a priori* seed analyses, are likely the most comprehensive method for understanding functional connectivity within resting-state networks.

As proposed in Chapter 5, greater functional connectivity between the vmPFC and FP at rest may well represent greater integrity between those regions that in turn facilitate greater stability in performance on a complex information processing speed task[1]. This integrity may represent a combination of structural integrity (e.g., white matter connections) as well as temporal correlations due to shared functions (Damoiseaux & Greicius, 2009). Increased functional connectivity within DMN regions has been associated with better cognitive performance in at least two studies of MS (e.g., Bonavita et al., 2011; Rocca et al., 2010; see Chapter 5). Specifically, greater resting-state functional connectivity between the PCC, left medial PFC and ACC of the DMN has been associated with better cognitive performance (i.e., across several clinical cognitive measures as well as on the PASAT) in MS patients (Bonavita et al., 2011; Rocca et al., 2010). Furthermore, poorer maintenance of the DMN during a sustained attention task has been found to predict worse memory performance outside of the scanner in MS patients (Sumowski, Wylie, Leavitt, Chiaravalloti, & Deluca, 2013). Together, these

[1] Note: There were no significant relations between the frontal pole cluster and IIV on the ANT-I in MS (Appendix 1). This likely reflected the differential influence of task demands on IIV in MS and is further supported by the lack of correlation between ANT-I IIV and SSRT IIV scores in MS (Appendix 1).

studies suggest that increased functional connectivity within DMN regions in MS may facilitate compensatory processes in regards to cognitive function.

In contrast, increased connectivity in the posterior DMN (i.e. primarily the PCC) was associated with worse performance on a word list generation test of semantic fluency in one study in early RRMS (i.e. 13 month mean disease duration; Faivre et al., 2012). Thus, greater connectivity within the posterior DMN was associated with fewer generated words in MS patients. The authors suggest that the increased functional connectivity observed in their study is evidence of "limited" compensatory processes in early RRMS. These authors used an ICA approach (see Chapter 5) to parcel the data into 51 components of which 8 were selected to match previously reported resting-state networks using visual inspection (Faivre et al., 2012). This is a common method for identifying resting-state networks using ICA, though it is susceptible to subjective judgment differences across individuals and studies (Cole et al., 2010). A negative relationship between increased functional connectivity and poor semantic fluency was found only with the posterior DMN and not with an anterior DMN component (i.e. including ACC and mPFC). This 'posterior DMN' component included regions that appeared to be in the PCC, middle occiptal gyrus, and cerebellum[2], which may not be the most complete representation of the DMN as based on previous descriptions (Buckner et al., 2008; Roosendaal et al., 2010). Together these observations suggest that the findings of Faivre and colleagues (2012) should be interpreted with caution.

As discussed in Chapter 5, the FP has been associated with a variety of "meta-

[2] Note: No cluster/voxel coordinates were provided in this study and hence these regions are described based on visual inspection.

cognitive" functions (Stuss, 2011). These include multi-tasking, initiating and sustaining responses, as well as executive skills necessary to complete novel and complex tasks (Stuss, 2011; Gilbert et al., 2006). FP involvement has been demonstrated on tasks requiring subjects to switch between different subtests while following specific rules (e.g., Six Elements Test; Burgess, Gilbert, & Dumontheil, 2007), as well as tests involving working memory and episodic retrieval (Gilbert et al., 2006). The proposed function of the FP in initiating and sustaining responses, as well as in "executive skills", may provide further support for the possibility that the increased functional connectivity observed in Chapter 5 represents a compensatory mechanism in MS. Furthermore, task-based fMRI studies in persons with MS often report diffuse increased recruitment of frontal regions, including the FP, for tasks that require information processing speed, attention, and memory (Audoin et al., 2003; Mainero et al., 2004; Staffen et al., 2002). Such findings also lend support for the suggestion that additional connectivity across frontal regions may facilitate compensatory mechanisms that aid in cognitive performance in MS.

In Chapter 5, direct relations between structural MRI metrics (i.e. BPF and lesion load) and IIV on the CTIP were not observed. This lack of relationship may have been due to the relatively small and mildly affected MS sample (N = 18). Larger and more representative samples of MS may reveal more direct relations between IIV and structural brain integrity. Furthermore, the relation between rsfMRI connectivity and IIV was found within regions of the frontal lobe, which suggests that examining structural relations specifically within the frontal lobe and IIV may be an important next step. As discussed in Chapter 1, lesions in frontal gray matter (i.e., particularly in the prefrontal cortex) have

been associated with greater IIV (Sowell et al., 2003) and individuals with focal frontal lesions have been shown to have greater variability on reaction time tasks than healthy controls or individuals with lesions in other regions (Stuss et al., 2003). Hence, structural integrity in the frontal lobes (e.g., gray/white matter volume, lesion load, and integrity of white matter as captured by DTI) may mediate the relationship between frontal lobe functional connectivity and IIV on complex reaction time tasks. However, larger MS patient samples are required to appropriately explore such models.

Performance variability appears to be an important metric in MS and the neural underpinnings of this variability were examined using BOLD rsfMRI. However, an interesting alternative approach to studying IIV in the brain may be to examine variability in the BOLD signal itself. Most fMRI studies examine mean BOLD timeseries in order to identify the most relevant brain activations. However, recent work on variability in BOLD signal (BOLD-SD) has reported reductions in BOLD-SD that accompany increases in age (Garrett, Kovacevic, McIntosh, & Grady, 2010). Furthermore, BOLD-SD was found to predict age five times better than mean BOLD signal (Garrett et al., 2010). Younger adults who demonstrate more BOLD-SD than older adults also demonstrate faster and more consistent performance on reaction time tasks (Garrett, Kovacevic, McIntosh, & Grady, 2011). Thus, variability in BOLD signal appears to have an inverse relationship with performance variability. The authors suggest that higher BOLD-SD may reflect a more complex neural system that can be flexible and explore multiple "functional states" or "functional network configurations" (e.g., default mode, task positive mode; Garrett et al., 2010, 2011). When BOLD-SD is too low, there is less flexibility within the system that hence the system is more likely to remain in a single

state (Garrett et al., 2010, 2011). As discussed in Chapter 1, performance variability may result from various changes to CNS integrity (e.g., changes in white matter, gray matter, lesions, altered functional connections; MacDonald et al., 2009) this may, in turn, result in reduced brain BOLD variability. Hence, exploring BOLD-SD within MS patients, in combination with structural integrity measures (i.e. MRI structural metrics and diffusion tensor imaging; DTI), may help elucidate alterations in neural network functioning that underlie performance variability in MS.

6.3. LIMITATIONS AND FUTURE DIRECTIONS

The studies that comprise this dissertation all included relatively small and homogenous groups of individuals with RRMS, which limits the generalizability of these findings to a broader MS population. The MS subjects were also mildly affected (i.e. in terms of cognition and neurologic impairment), which allowed for the examination of the sensitivity of IIV in detecting group level differences within mildly affected patients, but again limits the generalizability to more impaired MS groups. Furthermore, as discussed in section 6.2.4 (Clinical Implications), MS is a progressive disease and examining the potential responsiveness of IIV to neurologic changes or the sensitivity of IIV as a predictor of future cognitive decline is an important next step.

The dissertation examined the neural underpinning of IIV in MS using functional connectivity rsfMRI that was limited to seed-based analyses of the DMN. Explorations of relations between IIV and other resting-state networks (e.g., sensorimotor[3] and the

[3] Includes regions: somatomotor cortex, secondary somatosensory regions (S1), thalamus, putamen, cerebellum (Fox & Raichle, 2007)

frontal-parietal network[4]) are warranted as these network are thought to underlie sensorimotor functioning and working memory/cognitive control (e.g., see Vincent, Kahn, Snyder, Raichle, & Buckner, 2008) and would likely reveal a more complete picture of resting-state functional connectivity relations to IIV. Furthermore, the relations of structural and/or microstructural brain integrity with IIV were not explored in detail and should be examined in the future. Finally, IIV appears to have an inverse relationship with BOLD-SD and increased BOLD-SD may reflect the neural redundancy required to maintain stable performance of complex cognitive tasks in the face of damage/dysfunction (Garrett et al., 2010; 2011). Therefore, examining whether reduced BOLD-SD is associated with increased behavioral IIV in MS patients (and whether this reflects other relevant disease indicators) is worth pursuing.

[4] Includes regions: dorsolateral PFC, middle frontal gyrus, anterior IPL and anterior insular cortex (Vincent et al., 2008)

REFERENCES

Amann, M., Dössegger, L. S., Penner, I.-K., Hirsch, J. G., Raselli, C., Calabrese, P., Weier, K., et al. (2011). Altered functional adaptation to attention and working memory tasks with increasing complexity in relapsing-remitting multiple sclerosis patients. *Human brain mapping*, *32*(10), 1704–19. doi:10.1002/hbm.21142

Andreasen, A. K., Spliid, P. E., Andersen, H., & Jakobsen, J. (2010). Fatigue and processing speed are related in multiple sclerosis. *European journal of neurology□: the official journal of the European Federation of Neurological Societies*, *17*(2), 212–8. doi:10.1111/j.1468-1331.2009.02776.x

Anstey, K. J., Mack, H. A., Christensen, H., Li, S.-C., Reglade-Meslin, C., Maller, J., Kumar, R., et al. (2007). Corpus callosum size, reaction time speed and variability in mild cognitive disorders and in a normative sample. *Neuropsychologia*, *45*(8), 1911–20. doi:10.1016/j.neuropsychologia.2006.11.020

Archibald, C. J., & Fisk, J. D. (2000). Information processing efficiency in patients with multiple sclerosis. *J. Clin. Exp. Neuropsychol.*, *22*, 686–701. Retrieved from http://dx.doi.org/10.1076/1380-3395(200010)22:5

Arnett, P. A, & Strober, L. B. (2011). Cognitive and neurobehavioral features in multiple sclerosis. *Expert review of neurotherapeutics*, *11*(3), 411–24. doi:10.1586/ern.11.12

Audoin, B., Ibarrola, D., Ranjeva, J.-P., Confort-Gouny, S., Malikova, I., Ali-Chérif, A., Pelletier, J., et al. (2003). Compensatory cortical activation observed by fMRI during a cognitive task at the earliest stage of MS. *Human brain mapping*, *20*(2), 51–8. doi:10.1002/hbm.10128

Beck, A.T., Steer, R. A., Brown, G. (2000). *BDI Fast Screen for Medical Patients*. The Psychological Corporation.

Bellmann-Strobl, J., Wuerfel, J., Aktas, O., Dörr, J., Wernecke, K. D., Zipp, F., & Paul, F. (2009). Poor PASAT performance correlates with MRI contrast enhancement in multiple sclerosis. *Neurology*, *73*(20), 1624–7. doi:10.1212/WNL.0b013e3181c1de4f

Benedict, R. H. B. (2007). Diffusion-weighted imaging predicts cognitive impairment in multiple sclerosis. *Mult. Scler.*, *13*, 722–730. Retrieved from http://dx.doi.org/10.1177/1352458507075592

Benedict, R. H. B., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., & Weinstock-Guttman, B. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Journal of the International Neuropsychological Society : JINS*, *12*(4), 549–58. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16981607

Benedict, R., Fishman, I., McClellan, M., Bakshi, R., & Weinstock-Guttman, B. (2003). Validity of the Beck Depression Inventory-Fast Screen in multiple sclerosis. *Multiple Sclerosis*, *9*(4), 393–396. doi:10.1191/1352458503ms902oa

Benedict, Ralph H B, & Zivadinov, R. (2011). Risk factors for and management of cognitive dysfunction in multiple sclerosis. *Nature reviews. Neurology*, *7*(6), 332–42. doi:10.1038/nrneurol.2011.61

Benjamin, C., Lieberman, D. a., Chang, M., Ofen, N., Whitfield-Gabrieli, S., Gabrieli, J. D. E., & Gaab, N. (2010). The influence of rest period instructions on the default mode network. *Frontiers in human neuroscience*, *4*(December), 218. doi:10.3389/fnhum.2010.00218

Bigi, S., & Banwell, B. (2012). Pediatric multiple sclerosis. *Journal of child neurology*, *27*(11), 1378–83. doi:10.1177/0883073812452784

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic resonance in medicine official journal of the Society of Magnetic Resonance in Medicine Society of Magnetic Resonance in Medicine*, *34*(4), 537–541. Retrieved from http://www3.interscience.wiley.com/journal/112151513/abstract

Bobholz, J. A., & Rao, S. M. (2003). Cognitive dysfunction in multiple sclerosis: a review of recent developments. *Current opinion in neurology*, *16*(3), 283–8. doi:10.1097/01.wco.0000073928.19076.84

Bodling, A. M., Denney, D. R., & Lynch, S. G. (2012). Individual variability in speed of information processing: an index of cognitive impairment in multiple sclerosis. *Neuropsychology*, *26*(3), 357–67. doi:10.1037/a0027972

Bonavita, S., Gallo, A., Sacco, R., Corte, M. Della, Bisecco, A., Docimo, R., Lavorgna, L., et al. (2011). Distributed changes in connectivity in multiple sclerosis, *17*(4), 411–422. doi:10.1177/1352458510394609

Boorman, E. D., Behrens, T. E. J., Woolrich, M. W., & Rushworth, M. F. S. (2009). How green is the grass on the other side? Frontopolar cortex and the evidence in favor of alternative courses of action. *Neuron*, *62*(5), 733–43. doi:10.1016/j.neuron.2009.05.014

Brochet, B., Deloire, M. S. A, Bonnet, M., Salort-Campana, E., Ouallet, J. C., Petry, K. G., & Dousset, V. (2008). Should SDMT substitute for PASAT in MSFC? A 5-year longitudinal study. *Multiple sclerosis (Houndmills, Basingstoke, England)*, *14*(9), 1242–9. doi:10.1177/1352458508094398

Bronnum-Hansen, H., Koch-Henriksen, N., & Stenager, E. (2004). Trends in survival and cause of death in Danish patients with multiple sclerosis. *Brain*, *127*(4), 844–850.

Bruce, J. M., Bruce, A. S., & Arnett, P. A. (2010). Response variability is associated with self-reported cognitive fatigue in multiple sclerosis. *Neuropsychology*, *24*(1), 77–83. doi:10.1037/a0015046

Buckner, R L, Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann. NY Acad. Sci.*, *1124*, 1–38. Retrieved from http://dx.doi.org/10.1196/annals.1440.011

Bunce, D., Anstey, K. J., Christensen, H., Dear, K., Wen, W., & Sachdev, P. (2007). White matter hyperintensities and within-person variability in community-dwelling adults aged 60-64 years. *Neuropsychologia*, *45*(9), 2009–15. doi:10.1016/j.neuropsychologia.2007.02.006

Bunce, D. J., Warr, P. B., & Cochrane, T. (1993). Blocks in choice responding as a function of age and physical fitness. *Psychology and aging*, *8*(1), 26–33. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8461111

Bunce, D., Bielak, A.A., Cherbuin, N., Batterham , P.J., Wen, W., Sachdev, P., Anstey, K.J. (2013). Utility of intraindividual reaction time variability to predict white matter hyperintensities: A potential assessment tool for clinical contexts? *Journal of the International Neuropsychological Society*. Aug 8:1-6. [Epub ahead of print] doi:10.1017/S1355617713000830.

Burgess, P. W., Gilbert, S. J., & Dumontheil, I. (2007). Function and localization within rostral prefrontal cortex (area 10). *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *362*(1481), 887–99. doi:10.1098/rstb.2007.2095

Burton, C. L., Strauss, E., Hultsch, D. F., Moll, A., & Hunter, M. A. (2006). Intraindividual variability as a marker of neurological dysfunction: a comparison of Alzheimer's disease and Parkinson's disease. *Journal of clinical and experimental neuropsychology*, *28*(1), 67–83. doi:10.1080/13803390490918318

Callejas, A., Lupiàñez, J., Funes, M. J., & Tudela, P. (2005). Modulations among the alerting, orienting and executive control networks. *Experimental brain research. Experimentelle Hirnforschung. Expérimentation cérébrale*, *167*(1), 27–37. doi:10.1007/s00221-005-2365-z

Callejas, A., Lupiáñez, J., & Tudela, P. (2004). The three attentional networks: on their independence and interactions. *Brain and cognition*, *54*(3), 225–7. doi:10.1016/j.bandc.2004.02.012

Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain□: a journal of neurology*, *129*(Pt 3), 564–83. doi:10.1093/brain/awl004

Charcot, J. M. (1877). Lectures on the Diseases of the Nervous System.

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *Lancet neurology*, *7*(12), 1139–51. doi:10.1016/S1474-4422(08)70259-X

Cole, D. M., Smith, S. M., & Beckmann, C. F. (2010). Advances and pitfalls in the analysis and interpretation of resting-state FMRI data. *Frontiers in systems neuroscience*, *4*(April), 8. doi:10.3389/fnsys.2010.00008

Compston, A., & Coles, A. (2008). Multiple sclerosis. *The Lancet*, *372*(9648), 1502–1517. Retrieved from http://ezproxy.library.dal.ca/login?url=http://search.proquest.com/docview/199028158?accountid=10406

Crivelli, L., Farez, M. F., González, C. D., Fiol, M., Amengual, A., Leiguarda, R., & Correale, J. (2012). Alerting network dysfunction in early multiple sclerosis. *Journal of the International Neuropsychological Society : JINS*, *18*(4), 757–63. doi:10.1017/S1355617712000410

Damoiseaux, J S, Rombouts, S. A R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(37), 13848–53. doi:10.1073/pnas.0601417103

Damoiseaux, Jessica S, & Greicius, M. D. (2009). Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. *Brain structure & function*, *213*(6), 525–33. doi:10.1007/s00429-009-0208-6

De Luca, M., Smith, S., De Stefano, N., Federico, A., & Matthews, P. M. (2005). Blood oxygenation level dependent contrast resting state networks are relevant to functional activity in the neocortical sensorimotor system. *Experimental brain research. Experimentelle Hirnforschung. Expérimentation cérébrale*, *167*(4), 587–94. doi:10.1007/s00221-005-0059-1

De Stefano, N., Battaglini, M., & Smith, S. M. (2007). Measuring brain atrophy in multiple sclerosis. *Journal of neuroimaging□: official journal of the American Society of Neuroimaging*, *17 Suppl 1*, 10S–15S. doi:10.1111/j.1552-6569.2007.00130.x

DeLuca, J, Chelune, G. J., Tulsky, D. S., Lengenfelder, J., & Chiaravalloti, N. D. (2004). Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *J. Clin. Exp. Neuropsychol.*, *26*, 550–562. Retrieved from http://dx.doi.org/10.1080/13803390490496641

Demaree, H. A., Gaudino, E., & DeLuca, J. (2003). The relationship between depressive symptoms and cognitive dysfunction in multiple sclerosis. *Cognitive neuropsychiatry*, *8*(3), 161–71. doi:10.1080/13546800244000265

Dixon, R. A., Garrett, D. D., Lentz, T. L., MacDonald, S. W. S., Strauss, E., & Hultsch, D. F. (2007). Neurocognitive markers of cognitive impairment: exploring the roles of speed and inconsistency. *Neuropsychology*, *21*(3), 381–99. doi:10.1037/0894-4105.21.3.381

Drake, A. S., Weinstock-Guttman, B., Morrow, S. A., Hojnacki, D., Munschauer, F. E., & Benedict, R. H. B. (2010). Psychometrics and normative data for the Multiple Sclerosis Functional Composite: replacing the PASAT with the Symbol Digit Modalities Test. *Multiple sclerosis (Houndmills, Basingstoke, England)*, *16*(2), 228–37. doi:10.1177/1352458509354552

Drew, M., Tippett, L. J., Starkey, N. J., & Isler, R. B. (2008). Executive dysfunction and cognitive impairment in a large community-based sample with Multiple Sclerosis from New Zealand: a descriptive study. *Archives of clinical neuropsychology□: the official journal of the National Academy of Neuropsychologists*, *23*(1), 1–19. doi:10.1016/j.acn.2007.09.005

Elian, M., Nightingale, S., & Dean, G. (1990). Multiple sclerosis among United Kingdom-born children of immigrants from the Indian subcontinent, Africa and the West Indies. *Journal of Neurology, Neurosurgery & Psychiatry*, *53*(10), 906–911. doi:10.1136/jnnp.53.10.906

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, *16*(1), 143–149. doi:10.3758/BF03203267

Evans, C., Beland, S.-G., Kulaga, S., Wolfson, C., Kingwell, E., Marriott, J., Koch, M., et al. (2013). Incidence and Prevalence of Multiple Sclerosis in the Americas: A Systematic Review. *Neuroepidemiology*, *40*(3), 195–210. doi:10.1159/000342779

Faivre, A., Rico, A., Zaaraoui, W., Crespy, L., Reuter, F., Wybrecht, D., Soulier, E., et al. (2012). Assessing brain connectivity at rest is clinically relevant in early multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)*, *18*(9), 1251–8. doi:10.1177/1352458511435930

Fan, J., McCandliss, B. D., Fossella, J., Flombaum, J. I., & Posner, M. I. (2005). The activation of attentional networks. *NeuroImage*, *26*(2), 471–9. doi:10.1016/j.neuroimage.2005.02.004

Fan, J., McCandliss, B. D., Sommer, T., Raz, A., & Posner, M. I. (2002). Testing the efficiency and independence of attentional networks. *Journal of cognitive neuroscience*, *14*(3), 340–7. doi:10.1162/089892902317361886

Filippi, M., & Rocca, M. A. (2010). MRI and cognition in multiple sclerosis. *Neurological sciences□: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *31*(Suppl 2), S231–4. doi:10.1007/s10072-010-0367-5

Fischer, J. S., Rudick, R. a, Cutter, G. R., & Reingold, S. C. (1999). The Multiple Sclerosis Functional Composite measure (MSFC): an integrated approach to MS clinical outcome assessment. *Multiple Sclerosis*, *5*(4), 244–250. doi:10.1177/135245859900500409

Fisk, J. D., & Doble, S. . (2002). Construction and validation of a fatigue impact scale for daily administration (D-FIS). *Quality of life research*, *11*(3), 263–272.

Fisniku, L. K., Brex, P. A., Altmann, D. R., Miszkiel, K. A., Benton, C. E., Lanyon, R., Thompson, A. J., et al. (2008). Disability and T[sub]2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain*, *131*(3), 808–817. doi:http://dx.doi.org/10.1093/brain/awm329

Forn, C., Belenguer, A., Belloch, V., Sanjuan, A., Parcet, M. A., & Avila, C. (2011). Anatomical and functional differences between the Paced Auditory Serial Addition Test and the Symbol Digit Modalities Test. *Journal of clinical and experimental neuropsychology*, *33*(1), 42–50. doi:10.1080/13803395.2010.481620

Forn, C., Rocca, M. A., Boscá, I., Casanova, B., Sanjuan, A., & Filippi, M. (2013). Analysis of "task-positive" and "task-negative" functional networks during the performance of the Symbol Digit Modalities Test in patients at presentation with clinically isolated syndrome suggestive of multiple sclerosis. *Experimental Brain Research*, *225*(3), 399–407. doi:10.1007/s00221-012-3380-5

Fox, M D. (2005). The human brain is intrinsically organized into dynamic, anti-correlated functional networks. *Proc. Natl Acad. Sci. USA*, *102*, 9673–9678. Retrieved from http://dx.doi.org/10.1073/pnas.0504136102

Fox, M.D, Corbetta, M., Snyder, A. Z., Vincent, J. L., & Raichle, M. E. (2006). Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(26), 10046–51. doi:10.1073/pnas.0604187103

Fox, M. D., & Greicius, M. (2010). Clinical applications of resting state functional connectivity. *Frontiers in systems neuroscience*, *4*(June), 19. doi:10.3389/fnsys.2010.00019

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature reviews. Neuroscience*, *8*(9), 700–11. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17704812

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673–8. doi:10.1073/pnas.0504136102

Fox, M D, Snyder, A. Z., Zacks, J. M., & Raichle, M. E. (2006). Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nature Neurosci.*, *9*, 23–25. Retrieved from http://dx.doi.org/10.1038/nn1616

Fox, M. D., Zhang, D., Snyder, A. Z., & Raichle, M. E. (2009). The global signal and observed anticorrelated resting state brain networks. *Journal of neurophysiology*, *101*(6), 3270–83. doi:10.1152/jn.90777.2008

Franciotti, R., Falasca, N. W., Bonanni, L., Anzellotti, F., Maruotti, V., Comani, S., Thomas, A., et al. (2013). Default network is not hypoactive in dementia with fluctuating cognition: an Alzheimer disease/dementia with Lewy bodies comparison. *Neurobiology of aging*, *34*(4), 1148–58. doi:10.1016/j.neurobiolaging.2012.09.015

Frohman, E. M., Racke, M. K., & Raine, C. S. (2006). Multiple sclerosis — the plaque and its pathogenesis. *N. Engl. J. Med.*, *354*, 942–955. Retrieved from http://dx.doi.org/10.1056/NEJMra052130

Gaab, N., Gabrieli, J. D. E., & Glover, G. H. (2008). Resting in peace or noise: scanner background noise suppresses default-mode network. *Human brain mapping*, *29*(7), 858–67. doi:10.1002/hbm.20578

Garrett, D. D., Kovacevic, N., McIntosh, A. R., & Grady, C. L. (2010). Blood oxygen level-dependent signal variability is more than just noise. *The Journal of neuroscience□: the official journal of the Society for Neuroscience*, *30*(14), 4914–21. doi:10.1523/JNEUROSCI.5166-09.2010

Garrett, D. D., Kovacevic, N., McIntosh, A. R., & Grady, C. L. (2011). The importance of being variable. *The Journal of neuroscience□: the official journal of the Society for Neuroscience*, *31*(12), 4496–503. doi:10.1523/JNEUROSCI.5641-10.2011

Geurts, J. J. G., & Barkhof, F. (2008). Grey matter pathology in multiple sclerosis. *Lancet neurology*, *7*(9), 841–51. doi:10.1016/S1474-4422(08)70191-1

Gilbert, S. J., Spengler, S., Simons, J. S., Frith, C. D., & Burgess, P. W. (2006). Differential functions of lateral and medial rostral prefrontal cortex (area 10) revealed by brain-behavior associations. *Cerebral cortex (New York, N.Y.□: 1991)*, *16*(12), 1783–9. doi:10.1093/cercor/bhj113

Gilbert, S. J., Spengler, S., Simons, J. S., Steele, J. D., Lawrie, S. M., Frith, C. D., & Burgess, P. W. (2006). Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. *Journal of cognitive neuroscience*, *18*(6), 932–48. doi:10.1162/jocn.2006.18.6.932

Grady, C. L., Protzner, A. B., Kovacevic, N., Strother, S. C., Afshin-Pour, B., Wojtowicz, M., Anderson, J. A. E., et al. (2010). A multivariate analysis of age-related differences in default mode and task-positive networks across multiple cognitive domains. *Cerebral cortex (New York, N.Y.□: 1991)*, *20*(6), 1432–47. doi:10.1093/cercor/bhp207

Greicius, M D, Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc. Natl Acad. Sci. USA*, *100*, 253–258. Retrieved from http://dx.doi.org/10.1073/pnas.0135058100

Greicius, M D, Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc. Natl Acad. Sci. USA*, *101*, 4637–4642. Retrieved from http://dx.doi.org/10.1073/pnas.0308627101

Greicius, M. (2008). Resting-state functional connectivity in neuropsychiatric disorders. *Current Opinion in Neurology*.

Greicius, Michael D, Supekar, K., Menon, V., & Dougherty, R. F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral cortex (New York, N.Y.□: 1991)*, *19*(1), 72–8. doi:10.1093/cercor/bhn059

Gronwall, D. M. A. (1977). Paced auditory serial addition task: a measure of recovery from concussion. *Percept. Mot. Skills*, *44*, 367–373.

Hampson, M., Driesen, N. R., Skudlarski, P., Gore, J. C., & Constable, R. T. (2006). Brain connectivity related to working memory performance. *J. Neurosci.*, *26*, 13338–13343. Retrieved from http://dx.doi.org/10.1523/JNEUROSCI.3408-06.2006

Hawellek, D. J., Hipp, J. F., Lewis, C. M., Corbetta, M., & Engel, A. K. (2011). Increased functional connectivity indicates the severity of cognitive impairment in multiple sclerosis. doi:10.1073/pnas.1110024108/-/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1110024108

Hayton, T., Furby, J., Smith, K. J., Altmann, D. R., Brenner, R., Chataway, J., Hunter, K., et al. (2012). Clinical and imaging correlates of the multiple sclerosis impact scale in secondary progressive multiple sclerosis. *Journal of neurology*, *259*(2), 237–45. doi:10.1007/s00415-011-6151-5

Heaton, R. K., Nelson, L. M., Thompson, D. S., Burks, J. S., & Franklin, G. M. (1985). Neuropsychological findings in relapsing-remitting and chronic-progressive multiple sclerosis. *Journal of consulting and clinical psychology*, *53*(1), 103–10. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3980815

Heine, L., Soddu, A., Gómez, F., Vanhaudenhuyse, A., Tshibanda, L., Thonnard, M., Charland-Verville, V., et al. (2012). Resting state networks and consciousness: alterations of multiple resting state network connectivity in physiological, pharmacological, and pathological consciousness States. *Frontiers in psychology*, *3*(August), 295. doi:10.3389/fpsyg.2012.00295

Hulst, H. E., Steenwijk, M. D., Versteeg, A., Pouwels, P. J. W., Vrenken, H., Uitdehaag, B. M. J., Polman, C. H., et al. (2013). Cognitive impairment in MS: Impact of white matter integrity, gray matter volume, and lesions. *Neurology*, *80*(11), 1025–32. doi:10.1212/WNL.0b013e31828726cc

Hultsch, D. F., Macdonald, S. W. S., Hunter, M. A., Levy-bencheton, J., & Strauss, E. (2000). Intraindividual Variability in Cognitive Performance in Older Adults□: Comparison of Adults With Mild Dementia , Adults With Arthritis , and Healthy Adults, *14*(4), 588–598. doi:10.1037//0894-4105.14.4.588

Ishigami, Y., & Klein, R. M. (2009). Are Individual Differences in Absentmindedness Correlated with Individual Differences in Attention? *Journal of Individual Differences*, *30*(4), 220–237. doi:10.1027/1614-0001.30.4.220

Ishigami, Y., & Klein, R. M. (2010). Repeated measurement of the components of attention using two versions of the Attention Network Test (ANT): stability, isolability, robustness, and reliability. *Journal of neuroscience methods*, *190*(1), 117–28. doi:10.1016/j.jneumeth.2010.04.019

Ishigami, Y., & Klein, R.M. (2011). Repeated measurement of the components of attention of older adults using two versions of the Attention Network Test (ANT): stability, isolability, robustness, and reliability. *Frontiers of Aging Neuroscience*. *3*:17. doi:10.3389/fnagi.2011.00017.

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical image analysis*, *5*(2), 143–56. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11516708

Jønsson, A., Andresen, J., Storr, L., Tscherning, T., Soelberg Sørensen, P., & Ravnborg, M. (2006). Cognitive impairment in newly diagnosed multiple sclerosis patients: a 4-year follow-up study. *Journal of the neurological sciences*, *245*(1-2), 77–85. doi:10.1016/j.jns.2005.09.016

Kelly, A. M. C., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2008). Competition between functional brain networks mediates behavioral variability. *NeuroImage*, *39*(1), 527–37. doi:10.1016/j.neuroimage.2007.08.008

Koch-Henriksen, N., & Sørensen, P. S. (2010). The changing demographic pattern of multiple sclerosis epidemiology. *Lancet neurology*, *9*(5), 520–32. doi:10.1016/S1474-4422(10)70064-8

Korostil, M., & Feinstein, A. (2007). Anxiety disorders and their clinical correlates in multiple sclerosis patients. *Multiple Sclerosis*, *13*(1), 67–72. doi:10.1177/1352458506071161

Kurtzke, J. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*, *33*(11), 1444–52.

Langdon, D. W. (2011). Cognition in multiple sclerosis. *Current opinion in neurology*, *24*(3), 244–9. doi:10.1097/WCO.0b013e328346a43b

Leavitt, V. M., Lengenfelder, J., Moore, N. B., Chiaravalloti, N. D., & DeLuca, J. (2011). The relative contributions of processing speed and cognitive load to working memory accuracy in multiple sclerosis. *Journal of clinical and experimental neuropsychology*, *33*(5), 580–6. doi:10.1080/13803395.2010.541427

Leavitt, V. M., Wylie, G., Genova, H. M., Chiaravalloti, N. D., & DeLuca, J. (2012). Altered effective connectivity during performance of an information processing speed task in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)*, *18*(4), 409–17. doi:10.1177/1352458511423651

Levin, L. I., Munger, K. L., Rubertone, M. V, Peck, C. A., & al, et. (2003). Multiple sclerosis and Epstein-Barr virus. *JAMA*, *289*(12), 1533–1536. Retrieved from http://ezproxy.library.dal.ca/login?url=http://search.proquest.com/docview/211410455?accountid=10406.

Li, S., Aggen, S. H., Nesselroade, R., & Baltes, P. B. (2001). Short-Term Fluctuations in Elderly People ' s Sensorimotor Functioning Predict Text and Spatial Memory Performance□: The MacArthur Successful Aging Studies, 100–116.

Loitfelder, M., Fazekas, F., Petrovic, K., Fuchs, S., Ropele, S., Jehna, M., Aspeck, E., et al. (2011). Reorganization in cognitive networks with progression of multiple sclerosis.

Lowe, M. J., Dzemidzic, M., Lurito, J. T., Mathews, V. P., & Phillips, M. D. (2000). Correlations in low-frequency BOLD fluctuations reflect cortico-cortical connections. *NeuroImage*, *12*(5), 582–7. doi:10.1006/nimg.2000.0654

Ludwin, S. K. (2006). The pathogenesis of multiple sclerosis: relating human pathology to experimental studies. *Journal of neuropathology and experimental neurology*, *65*(4), 305–18. doi:10.1097/01.jnen.0000225024.12074.80

Lundstrom, B. N., Ingvar, M., & Petersson, K. M. (2005). The role of precuneus and left inferior frontal cortex during source memory episodic retrieval. *NeuroImage*, *27*(4), 824–34. doi:10.1016/j.neuroimage.2005.05.008

MacDonald, S. W. S., Hultsch, D. F., & Dixon, R. A. (2003). Performance variability is related to change in cognition: evidence from the Victoria Longitudinal Study. *Psychology and aging*, *18*(3), 510–23. doi:10.1037/0882-7974.18.3.510

Macdonald, S. W. S., Hultsch, D. F., & Dixon, R. A. (2008). Predicting impending death: inconsistency in speed is a selective and early marker. *Psychology and aging*, *23*(3), 595–607. doi:10.1037/0882-7974.23.3.595

MacDonald, S. W. S., Li, S.-C., & Bäckman, L. (2009). Neural underpinnings of within-person variability in cognitive functioning. *Psychology and aging*, *24*(4), 792–808. doi:10.1037/a0017798

MacDonald, S. W. S., Nyberg, L., & Bäckman, L. (2006). Intra-individual variability in behavior: links to brain structure, neurotransmission and neuronal activity. *Trends in neurosciences*, *29*(8), 474–80. doi:10.1016/j.tins.2006.06.011

MacDonald, S. W. S., Nyberg, L., Sandblom, J., Fischer, H., & Bäckman, L. (2008). Increased response-time variability is associated with reduced inferior parietal activation during episodic recognition in aging. *Journal of cognitive neuroscience*, *20*(5), 779–86. doi:10.1162/jocn.2008.20502

Macrae, C. N., Moran, J. M., Heatherton, T. F., Banfield, J. F., & Kelley, W. M. (2004). Medial prefrontal activity predicts memory for self. *Cerebral cortex (New York, N.Y.□: 1991)*, *14*(6), 647–54. doi:10.1093/cercor/bhh025

Mainero, C., Caramia, F., Pozzilli, C., Pisani, A., Pestalozza, I., Borriello, G., Bozzao, L., et al. (2004). fMRI evidence of brain reorganization during attention and memory tasks in multiple sclerosis. *NeuroImage*, *21*(3), 858–67. doi:10.1016/j.neuroimage.2003.10.004

Marrie, R. A. (2004). Environmental risk factors in multiple sclerosis aetiology. *The Lancet Neurology*, *3*(12), 709–718. Retrieved from http://ezproxy.library.dal.ca/login?url=http://search.proquest.com/docview/201513061?accountid=10406

Marrie, R. A., Fisk, J.D., Stadnyk, K. J., Bo, N. Y., Tremlett, H., Wolfson, C., Warren, S., Bhan, V., CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis. (In press). The incidence and prevalence of multiple sclerosis in Nova Scotia, Canada.

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science (New York, N.Y.)*, *315*(5810), 393–5. doi:10.1126/science.1131295

Mazerolle, E. L., Wojtowicz, M. a., Omisade, A., & Fisk, J. D. (2013). Intra-individual variability in information processing speed reflects white matter microstructure in multiple sclerosis. *NeuroImage: Clinical*, *2*, 894–902. doi:10.1016/j.nicl.2013.06.012

McCarthy, M., Beaumont, J. G., Thompson, R., & Peacock, S. (2005). Modality-specific aspects of sustained and divided attentional performance in multiple sclerosis. *Archives of clinical neuropsychology□: the official journal of the National Academy of Neuropsychologists*, *20*(6), 705–18. doi:10.1016/j.acn.2005.04.007

Mcdonald, W. I., Compston, A., Edan, G., Goodkin, D., Hartung, H., Lublin, F. D., Mcfarland, H. F., et al. (2001). Recommended Diagnostic Criteria for Multiple Sclerosis□: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Annals of Neurology*, (April), 121–127.

Mitchell, A. J., Benito-León, J., González, J.-M. M., & Rivera-Navarro, J. (2005). Quality of life and its assessment in multiple sclerosis: integrating physical and psychological components of wellbeing. *Lancet neurology*, *4*(9), 556–66. doi:10.1016/S1474-4422(05)70166-6

Murtha, S., Cismaru, R., Waechter, R., & Chertkow, H. (2002). Increased variability accompanies frontal lobe damage in dementia. *Journal of the International Neuropsychological Society*, *8*(3), 360–72. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11939695

Nebel, K., Wiese, H., Seyfarth, J., Gizewski, E. R., Stude, P., Diener, H.-C., & Limmroth, V. (2007). Activity of attention related structures in multiple sclerosis patients. *Brain research*, *1151*, 150–60. doi:10.1016/j.brainres.2007.03.007

Noseworthy, J. H., Lucchinetti, C., Rodriguez, M., & Weinshenker, B. G. (2000). Multiple sclerosis. *N. Engl. J. Med.*, *343*, 938–952. Retrieved from http://dx.doi.org/10.1056/NEJM200009283431307

Omisade, A., Fisk, J. D., Klein, R. M., Schmidt, M., Darvesh, S., & Bhan, V. (2012). Information Processing and Magnetic Resonance Imaging Indices of Brain Pathology in Multiple Sclerosis. *International Journal of MS Care*, *14*(2), 84–91. doi:10.7224/1537-2073-14.2.84

Orton, S.-M., Herrera, B. M., Yee, I. M., Valdar, W., Ramagopalan, S. V, Sadovnick, A. D., & Ebers, G. C. (2006). Sex ratio of multiple sclerosis in Canada: a longitudinal study. *Lancet neurology*, *5*(11), 932–6. doi:10.1016/S1474-4422(06)70581-6

Otten, L. J., & Rugg, M. D. (2001). When more means less: neural activity related to unsuccessful memory encoding. *Current biology : CB*, *11*(19), 1528–30. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11591321

O'Connor, P., & Devonshire, V. (2008). The use of disease-modifying agents in multiple sclerosis--by the Canadian Network of MS Clinics. *Canadian Journal of Neurological Sciences*, *35*(2), 127–129. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18574923

Paul, R. H., Beatty, W. W., Schneider, R., Blanco, C., & Hames, K. (1998). Impairments of attention in individuals with Multiple Sclerosis. *Multiple Sclerosis*, *4*(5), 433–439. doi:10.1177/135245859800400506

Penner, I., & Rausch, M. (2003). Analysis of Impairment Related Functional Architecture in MS Patients during Performance of Different Attention Tasks. *Journal of Neurology*, 461–472. doi:10.1007/s00415-003-1025-0

Phillips, M. D., Grossman, R. I., Miki, Y., Wei, L., Kolson, D. L., Van Buchem, M. A., Polansky, M., et al. (1998). Comparison of T2 lesion volume and magnetization transfer ratio histogram analysis and of atrophy and measures of lesion burden in patients with multiple sclerosis. *American journal of neuroradiology*, *19*(6), 1055–60.

Polman, C. H., Reingold, S. C., Banwell, B., Clanet, M., Cohen, J. A., Filippi, M., Fujihara, K., et al. (2011). Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of neurology*, *69*(2), 292–302. doi:10.1002/ana.22366

Posner, M I, & Petersen, S. E. (1990). The attention system of the human brain. *Annual review of neuroscience*, *13*, 25–42. doi:10.1146/annurev.ne.13.030190.000325

Posner, M. (1994). Attention□: The mechanisms of consciousness. *Proceedings of the National Academy of …*, *91*(August), 7398–7403. Retrieved from http://www.pnas.org/content/91/16/7398.short

Posner, Michael I. (1980). Orienting of attention. *Quarterly Journal of Experimental Psychology*, *32*(1), 3–25. doi:10.1080/00335558008248231

Qi, Z., Wu, X., Wang, Z., Zhang, N., Dong, H., Yao, L., & Li, K. (2010). Impairment and compensation coexist in amnestic MCI default mode network. *NeuroImage*, *50*(1), 48–55. doi:10.1016/j.neuroimage.2009.12.025

Raichle, M. E. (2001). A default mode of brain function. *Proc. Natl Acad. Sci. USA*, *98*, 676–682. Retrieved from http://dx.doi.org/10.1073/pnas.98.2.676

Raichle, Marcus E, & Mintun, M. A. (2006). Brain work and brain imaging. *Annual review of neuroscience*, *29*, 449–76. doi:10.1146/annurev.neuro.29.051605.112819

Ram, N., Lindenberger, U., & Blanchard-Fields, F. (2009). Introduction to the special section on intraindividual variability and aging. *Psychology and aging*, *24*(4), 775–7. doi:10.1037/a0017909

Ramagopalan, S. V, Dobson, R., Meier, U. C., & Giovannoni, G. (2010). Multiple sclerosis: risk factors, prodromes, and potential causal pathways. *Lancet neurology*, *9*(7), 727–39. doi:10.1016/S1474-4422(10)70094-6

Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology*, *41*, 685–691.

Rao, S.M, Leo, G.J., Ellington, L., Nauertz, T., Bernadin, L., Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology*, *41*(5), 692–696.

Reicker, L. I., Tombaugh, T. N., Walker, L., & Freedman, M. S. (2007). Reaction time: An alternative method for assessing the effects of multiple sclerosis on information processing speed. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists*, *22*(5), 655–64. doi:10.1016/j.acn.2007.04.008

Rizzolatti, G. (2005). The mirror neuron system and its function in humans. *Anatomy and embryology*, *210*(5-6), 419–21. doi:10.1007/s00429-005-0039-z

Rocca, M. A, Valsasina, P., Absinta, M., Riccitelli, G., Rodegher, M. E., Misci, P., Rossi, P., et al. (2010). Default-mode network dysfunction and cognitive impairment in progressive MS. *Neurology*, *74*(16), 1252–9. doi:10.1212/WNL.0b013e3181d9ed91

Rodriguez, M., & Scheithauer, B. (1994). Ultrastructure of multiple sclerosis. *Ultrastruct. Pathol.*, *18*, 3–13.

Rombouts, S. A. R. B., Barkhof, F., Goekoop, R., Stam, C. J., & Scheltens, P. (2005). Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. *Human brain mapping*, *26*(4), 231–9. doi:10.1002/hbm.20160

Roosendaal, S. D., Schoonheim, M. M., Hulst, H. E., Sanz-arigita, E. J., Smith, S. M., Geurts, J. J. G., & Barkhof, F. (2010). Resting state networks change in clinically isolated syndrome, 1612–1621. doi:10.1093/brain/awq058

Rovaris, M. (2002). Cognitive dysfunction in patients with mildly disabling relapsing-remitting multiple sclerosis: an exploratory study with diffusion tensor MR imaging. *J. Neurol. Sci.*, *195*, 103–109. Retrieved from http://dx.doi.org/10.1016/S0022-510X(01)00690-6

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological review*, *103*(3), 403–28. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8759042

Schmidt, P., Gaser, C., Arsic, M., Buck, D., Förschler, A., Berthele, A., Hoshi, M., et al. (2012). An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. *NeuroImage*, *59*(4), 3774–83. doi:10.1016/j.neuroimage.2011.11.032

Seeley, W. W. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *J. Neurosci.*, *27*, 2349–2356. Retrieved from http://dx.doi.org/10.1523/JNEUROSCI.5587-06.2007

Seeley, William W, Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., et al. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *27*(9), 2349–56. doi:10.1523/JNEUROSCI.5587-06.2007

Seewann, A. (2009). Diffusely abnormal white matter in chronic multiple sclerosis: imaging and histopathologic analysis. *Arch. Neurol.*, *66*, 601–609.

Shipley, B. A., Der, G., Taylor, M. D., & Deary, I. J. (2006). Cognition and all-cause mortality across the entire adult age range: health and lifestyle survey. *Psychosomatic medicine*, *68*(1), 17–24. doi:10.1097/01.psy.0000195867.66643.0f

Shulman, G. L. (1997). Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. *J. Cogn. Neurosci.*, *9*, 648–663.

Slifkin, A., & Newell, K. (1998). Is variability in human performance a reflection of system noise? *Current directions in psychological science*. Retrieved from http://www.jstor.org/stable/10.2307/20182536

Smallwood, J., Brown, K., Baird, B., & Schooler, J. W. (2012). Cooperation between the default mode network and the frontal-parietal network in the production of an internal train of thought. *Brain research*, *1428*, 60–70. doi:10.1016/j.brainres.2011.03.072

Smith, A. M., Walker, L. A. S., Freedman, M. S., Berrigan, L. I., St Pierre, J., Hogan, M. J., & Cameron, I. (2012). Activation patterns in multiple sclerosis on the Computerized Tests of Information Processing. *Journal of the neurological sciences*, *312*(1-2), 131–7. doi:10.1016/j.jns.2011.08.003

Smith, A. (1982). *Symbol Digit Modalities Test*. Los Angeles: Western Psychological Services.

Smith, S. M. (2002). Fast robust automated brain extraction. *Human brain mapping*, *17*(3), 143–55. doi:10.1002/hbm.10062

Snyder, P., & CappelJeri, J. (2001). Information processing speed deficits may be better correlated with the extent of white matter sclerotic lesions in multiple sclerosis than previously suspected. *Brain and cognition*, (1985), 279–284.

Sorg, C. (2007). Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. *Proc. Natl Acad. Sci. USA*, *104*, 18760–18765. Retrieved from http://dx.doi.org/10.1073/pnas.0708803104

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature neuroscience*, *6*(3), 309–15. doi:10.1038/nn1008

Staffen, W., Mair, A., Zauner, H., Unterrainer, J., Niederhofer, H., Kutzelnigg, a, Ritter, S., et al. (2002). Cognitive function and fMRI in patients with multiple sclerosis: evidence for compensatory cortical activation during an attention task. *Brain□: a journal of neurology*, *125*(Pt 6), 1275–82. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12023316

Stuss, D. T. (2011). Functions of the frontal lobes: relation to executive functions. *Journal of the International Neuropsychological Society□: JINS*, *17*(5), 759–65. doi:10.1017/S1355617711000695

Stuss, D. T., Murphy, K. J., Binns, M. A., & Alexander, M. P. (2003). Staying on the job: the frontal lobes control individual performance variability. *Brain□: a journal of neurology*, *126*(Pt 11), 2363–80. doi:10.1093/brain/awg237

Stys, P. K., Zamponi, G. W., Van Minnen, J., & Geurts, J. J. G. (2012). Will the real multiple sclerosis please stand up? *Nature reviews. Neuroscience*, *13*(7), 507–14. doi:10.1038/nrn3275

Sumowski, J. F., Wylie, G. R., Deluca, J., & Chiaravalloti, N. (2010). Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: functional magnetic resonance imaging evidence for cognitive reserve. *Brain□: a journal of neurology*, *133*(Pt 2), 362–74. doi:10.1093/brain/awp307

Sumowski, J. F., Wylie, G. R., Leavitt, V. M., Chiaravalloti, N. D., & Deluca, J. (2013). Default network activity is a sensitive and specific biomarker of memory in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)*, *19*(2), 199–208. doi:10.1177/1352458512448267

Tombaugh, T. N. (2006). A comprehensive review of the Paced Auditory Serial Addition Test (PASAT). *Archives of clinical neuropsychology□: the official journal of the National Academy of Neuropsychologists*, *21*(1), 53–76. doi:10.1016/j.acn.2005.07.006

Tombaugh, T. N., Berrigan, L. I., Walker, L. a S., & Freedman, M. S. (2010). The Computerized Test of Information Processing (CTIP) offers an alternative to the PASAT for assessing cognitive processing speed in individuals with multiple sclerosis. *Cognitive and behavioral neurology□: official journal of the Society for Behavioral and Cognitive Neurology*, *23*(3), 192–8.

Tombaugh, T. N., Rees, L., Stormer, P., Harrison, A. G., & Smith, A. (2007). The effects of mild and severe traumatic brain injury on speed of information processing as measured by the computerized tests of information processing (CTIP). *Archives of clinical neuropsychology□: the official journal of the National Academy of Neuropsychologists*, *22*(1), 25–36. doi:10.1016/j.acn.2006.06.013

Tombaugh, T.N. Rees, L. M. (2008). *Computerized Test of Information Processing*. Toronto: Multi-Health System Inc.

Toro, R., Fox, P. T., & Paus, T. (2008). Functional coactivation map of the human brain. *Cerebral cortex (New York, N.Y.□: 1991)*, *18*(11), 2553–9. doi:10.1093/cercor/bhn014

Tyszka, J. M., Kennedy, D. P., Adolphs, R., & Paul, L. K. (2011). Intact bilateral resting-state networks in the absence of the corpus callosum. *The Journal of neuroscience□: the official journal of the Society for Neuroscience*, *31*(42), 15154–62. doi:10.1523/JNEUROSCI.1453-11.2011

Uddin, L. Q., Kelly, A. M., Biswal, B. B., Xavier Castellanos, F., & Milham, M. P. (2009). Functional connectivity of default mode network components: correlation, anticorrelation, and causality. *Human Brain Mapping*, *30*(2), 625–637. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18219617

Urbanek, C., Weinges-Evers, N., Bellmann-Strobl, J., Bock, M., Dörr, J., Hahn, E., Neuhaus, A. H., et al. (2010). Attention Network Test reveals alerting network dysfunction in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)*, *16*(1), 93–9. doi:10.1177/1352458509350308

Van den Heuvel, M. P., Mandl, R. C. W., Kahn, R. S., & Hulshoff Pol, H. E. (2009). Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Human brain mapping*, *30*(10), 3127–41. doi:10.1002/hbm.20737

Van Dijk, K. R. A., Hedden, T., Venkataraman, A., Evans, K. C., Lazar, S. W., & Buckner, R. L. (2010). Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. *Journal of neurophysiology*, *103*(1), 297–321. doi:10.1152/jn.00783.2009

Venkateswaran, S., & Banwell, B. (2010). Pediatric multiple sclerosis. *The neurologist*, *16*(2), 92–105. doi:10.1097/NRL.0b013e3181c923d5

Vercellino, M., Plano, F., Votta, B., Mutani, R., Giordana, M. T., & Cavalla, P. (2005). Grey matter pathology in multiple sclerosis. *Journal of neuropathology and experimental neurology*, *64*(12), 1101–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16319720

Vincent, J L, Kahn, I., Snyder, A. Z., Raichle, M. E., & Buckner, R. L. (2008). Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *J. Neurophysiol.*, *100*, 3328–3342. Retrieved from http://dx.doi.org/10.1152/jn.90355.2008

Vincent, J L, Patel, G. H., Fox, M. D., Snyder, A. Z., Baker, J. T., Van Essen, D. C., Zempel, J. M., et al. (2007). Intrinsic functional architecture in the anaesthetized monkey brain. *Nature*, *447*(7140), 83–6. doi:10.1038/nature05758

Vincent, Justin L, Snyder, A. Z., Fox, M. D., Shannon, B. J., Andrews, J. R., Raichle, M. E., & Buckner, R. L. (2006). Coherent spontaneous activity identifies a hippocampal-parietal memory network. *Journal of neurophysiology*, *96*(6), 3517–31. doi:10.1152/jn.00048.2006

Weinges-Evers, N., Brandt, A. U., Bock, M., Pfueller, C. F., Dörr, J., Bellmann-Strobl, J., Scherer, P., et al. (2010). Correlation of self-assessed fatigue and alertness in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)*, *16*(9), 1134–40. doi:10.1177/1352458510374202

Weissenbacher, A., Kasess, C., Gerstl, F., Lanzenberger, R., Moser, E., & Windischberger, C. (2009). Correlations and anticorrelations in resting-state functional connectivity MRI: A quantitative comparison of preprocessing strategies. *NeuroImage*, *47*, 1408–1416. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19442749

Weissman, D. H., Roberts, K. C., Visscher, K. M., & Woldorff, M. G. (2006). The neural bases of momentary lapses in attention. *Nature neuroscience*, *9*(7), 971–8. doi:10.1038/nn1727

West, R., Murphy, K. J., Armilio, M. L., Craik, F. I. M., & Stuss, D. T. (2002). Lapses of Intention and Performance Variability Reveal Age-Related Increases in Fluctuations of Executive Control. *Brain and Cognition*, *49*(3), 402–419. doi:10.1006/brcg.2001.1507

Westerberg, H., & Hirvikoski, T. (2004). Visuo-spatial working memory span: A sensitive measure of cognitive deficits in children with ADHD. *Child Neuropsychology*, (May 2013), 37–41. Retrieved from http://www.tandfonline.com/doi/full/10.1080/09297040409609806

Willer, C. J., Dyment, D. A., Risch, N. J., Sadovnick, A. D., Ebers, G. C., & Group, T. C. C. S. (2003). Twin concordance and sibling recurrence rates in multiple sclerosis. *Proceedings of the National Academy of Sciences* , *100* (22), 12877–12882. doi:10.1073/pnas.1932604100

Williams, B. R., Hultsch, D. F., Strauss, E. H., Hunter, M. A., & Tannock, R. (2005). Inconsistency in reaction time across the life span. *Neuropsychology*, *19*(1), 88–96. doi:10.1037/0894-4105.19.1.88

Wojtowicz, M., Berrigan, L. I., & Fisk, J. D. (2012). Intra-individual Variability as a Measure of Information Processing Difficulties in Multiple Sclerosis. *International Journal of MS Care*, *14*(2), 77–83. doi:10.7224/1537-2073-14.2.77

Wojtowicz, M., Omisade, A., & Fisk, J. D. (2013). Indices of Cognitive Dysfunction in Relapsing-Remitting Multiple Sclerosis: Intra-individual Variability, Processing Speed, and Attention Network Efficiency. *Journal of the International Neuropsychological Society□: JINS*, 1–8. doi:10.1017/S1355617713000027

Zhang, D., & Raichle, M. E. (2010). Disease and the brain's dark energy. *Nature reviews. Neurology*, *6*(1), 15–28. doi:10.1038/nrneurol.2009.198

APPENDIX 1: FUNCTIONAL CONNECTIVITY BETWEEN THE VMPFC AND FRONTAL POLE ASSOCIATED WITH IIV ON THE ANT-I

In Chapter 5, greater functional connectivity between the anterior node of the DMN (i.e. vmPFC) and the left FP was found in MS patients who demonstrated more stability (i.e. less IIV) on the SSRT of the CTIP. As part of a follow up analysis, functional connectivity between the vmPFC and FP associated with IIV on the ANT-I in MS was examined. The purpose of these follow-up analyses were to (1) examine relations between IIV on the CTIP and IIV on the ANT-I in MS patients and controls and (2) explore whether a similar relation between vmPFC and FP connectivity would be found with IIV on the ANT-I in MS patients.

A.1 PARTICIPANTS

The same sample of participants was used in this follow-up analysis as described in Chapter 5. However, one control subject was removed from the analysis because of an excessive number of outliers on the ANT-I making a final sample of 18 MS subjects and 15 control subjects.

A.2 METHOD

A.2.1 DATA PREPARATION

Intra-individual variability was measured by calculating individual standard deviations (ISDs) for all participants. This method of estimating intra-individual variability has been found to be more sensitive than alternative measures, like coefficient of variation (COV; Wojtowicz et al., 2012). Only correct trials were used. Data were screened for outliers (i.e. > than 3 SD from the group means) with mean group RTs imputed for missing values, representing a conservative approach to estimating individual variability (Hultsch

et al., 2000). Systematic differences in RT due to trial and block as well as mean level differences in RT associated with group membership were then removed (Hultsch et al., 2000). Residual scores were converted to T-scores and an ISD score was calculated for each participant.

A.2.1 NEUROIMAGING ANALYSIS

Please refer to the Method section of Chapter 5. The contrast involving the vmPFC and FP was used as a pre-threshold mask and results were constrained to voxels within that region. De-meaned ISD scores from the ANT-I were then entered as covariates in the analysis. Images were cluster threshold corrected, $z<2.3$, $p<.05$.

A.3 RESULTS

A.3.1 DEMOGRAPHICS

MS participants were matched on age ($t(31) = -.021$, $p= .98$) and education ($t(31) = -.842$, $p= .41$). Mean (SD) of age for the MS group was 42.28(7.55) and 42.33(7.21) for the control group. Mean (SD) of education was 14.67(1.85) for the MS group and 16.27(2.25) for the control group.

A.3.2 ANT-I MEAN AND IIV PERFORMANCE

Mean accuracy on the ANT-I was examined between groups and the two groups did not differ in terms of accuracy ($t(31) = -1.17$ $p = .25$). The MS group demonstrated overall slower mean reaction time (RT) ($t(31) = 2.79$, $p = .01$; M(SD) MS Group: 758.63(74.05); M(SD) Control Group: 675.36(97.48)) and more IIV compared to Controls ($t(21.78) = 2.89$, $p = .01$; M(SD) MS Group: 9.13(.99); M(SD) Control Group: 7.71(1.68)).

A.3.2 ANT-I IIV AND CTIP IIV

Comparison of IIV on the ANT-I and CTIP revealed that these two measures were not correlated in MS patients (SRT: $r = .06$, $p = .82$; CRT: $r = .07$, $p = .79$; SSRT: r

= -.13, p = .60) However, a positive correlation between IIV on the SSRT task and IIV on the ANT-I was found within controls (r = .56; p = .03). No significant correlations were found between IIV on the SRT or CRT and IIV on the ANT-I in controls (SRT: r = .24, p = .39; CRT: r = .47, p = .08).

A.3.2 ANT-I RT AND CTIP RT

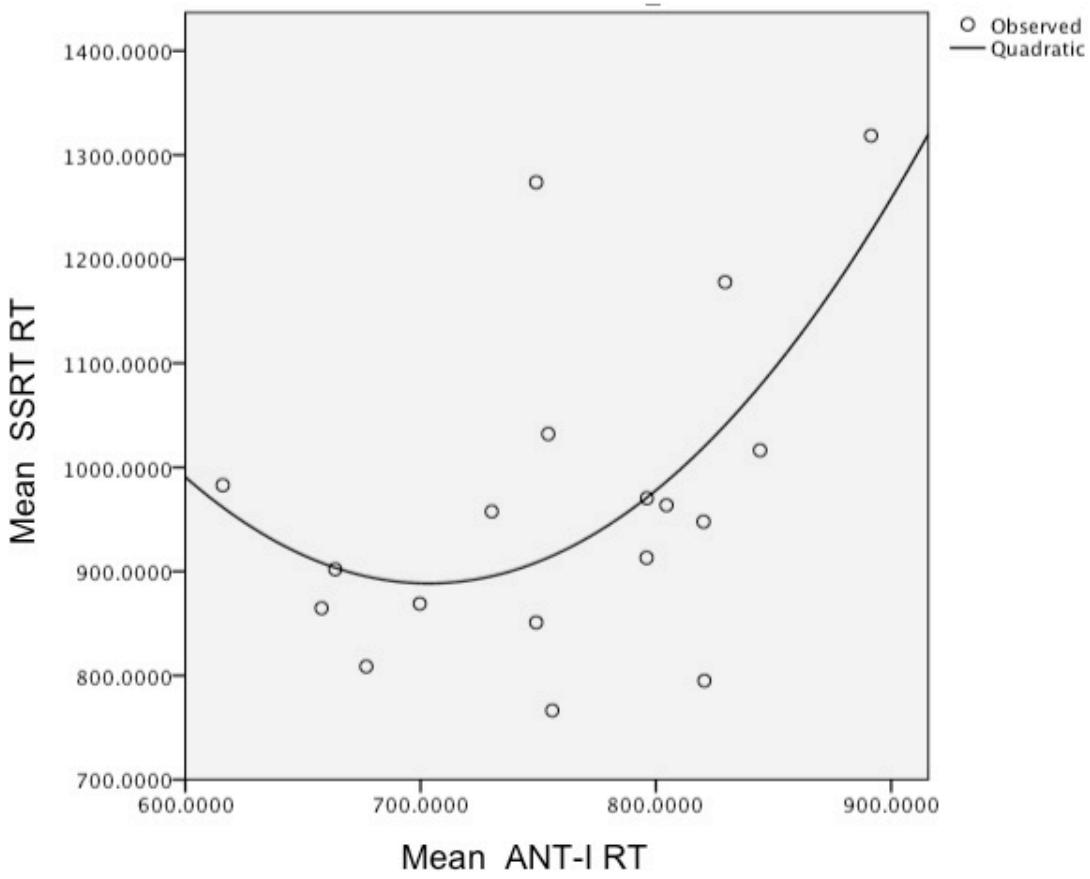
Relations between mean RT performance between CTIP and ANT-I were also examined. In the MS group mean RT on the SRT was significantly correlated with ANT-I mean RT (SRT: r = .47, p = .05). However, no linear relations were found with mean RT on the other CTIP subtests and the ANT-I (CRT: r = .25 p = .32; SSRT: r = .43, p = .08). Examination of scatterplots revealed a potential non-linear relation between mean SSRT RT and mean ANT-I RT (See Figure A.1). Curve estimation analysis of the relation between RT on these two tasks revealed that a quadratic curve best fit the data, though this relation still did not reach statistical significance (p = .056).

In the control group, only RT on the SSRT task significantly correlated with RT on the ANT-I (SRT: r = .24, p = .39; CRT: r = .47, p = .08; SSRT: r = .56, p = .03).

A.3.3 NEUROIMAGING RESULTS

No significant relation was found regarding functional connectivity between the vmPFC seed and the left FP associated with ANT-I IIV in MS.

Figure A.1. Scatterplot of SSRT RT and ANT-I RT in MS patients



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