

**ADVANCED NETWORK ANALYSES OF RESTING-STATE FUNCTIONAL
CONNECTIVITY TO PROBE EXECUTIVE FUNCTION IN PARKINSON'S DISEASE
AND MULTIPLE SCLEROSIS**

by

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Abstract

This thesis is to probe the systems-level neurobiological bases for executive function in patient populations overarchingly.

We focus on two representative diseases, Parkinson's Disease (PD), and Multiple Sclerosis (MS), as although they have different pathologies, patients often result in similar cognitive deficits. We examine resting-state fMRI data from both PD and MS subjects with novel methods in a network fashion. We employ advanced connectivity analyses to evaluate graph theoretical, static and dynamic resting-state functional connectivity (rsFC) measures. Multivariate statistical methods such as Canonical Correlate Analysis (CCA) and Multiset Canonical Correlate Analysis (MCCA) are used to robustly link rsFC and cognitive performance. PD data used in the thesis research include three cohorts: Parkinson's Progression Markers Initiative (PPMI) and two research projects conducted at UBC (project name: BCT and GFM2). For MS, two cohorts are included: OPERA MS clinical trial and COGMS research project, which are both conducted at UBC.

After a general introduction in the first chapter, in the second chapter we examine multivariate relations between demographic and cognitive profiles with CCA, showing that female gender is associated with better cognitive performance in both diseases possibly due to protective effects of estrogen.

In chapter 3, we use correlation to assess functional connections. Both diseases have significantly altered interhemispheric connectivity, which is associated with altered cognitive performance in MS, but not PD.

In chapter 4, we utilize graph theoretical approaches and find increased segregation of rsFC in PD, supporting a previously-proposed model of *vulnerability of hubs* in disease populations. In MS, higher modularity of the rsFC network is correlated with better executive skills.

In chapter 5, we explore dynamic rsFC and discover that longer disease duration in MS is associated with decreased dynamic rsFC. In both populations, dynamic interhemispheric connectivity is robustly associated with cognitive abilities.

In chapter 6, MCCA is applied to jointly explore the associations between dynamic and stationary rsFC, and behavioural measures. In MS, better executive functioning is supported by higher education, stronger and dynamic rsFC; in PD, better memory function is related to segregated brain networks and dynamics of interhemispheric connections.

Chapter 7 summarizes and concludes these chapters.

Lay Summary

Cognitive deficits are a very troubling symptom for people with neurological disease. Understanding cognitive deficits has been difficult because there does not seem to be a simple relationship between damages to one part of the brain and the deficits. It seems that disease effects over widespread brain areas are more associated with cognitive deficits. In this research, we investigated functional connectivity (FC), i.e. how brain regions communicate through information transfer, and its relations to cognitive deficits in two diseases showing similar cognitive impairments: Parkinson's Disease and Multiple Sclerosis. Novel analyses with functional magnetic resonance imaging (fMRI) data were used to examine FC and advanced statistical methods were used to link FC and cognitive function. In both diseases, we found robust associations between network level descriptions of FC and performance on cognitive tests. Determining the networks associated with cognitive performance is a first step towards targeted therapy attempting to reduce deficits.

Preface

The thesis work was conducted in the Pacific Parkinson's Research Centre at UBC Hospital with collaboration of the UBC MRI Research Centre and Multiple Sclerosis Clinic at UBC Hospital.

For the study design, I contributed to parts of decision such as resting-state fMRI and cognitive tests in order to identify ways to approach the problem. For other parts of the research, I helped with data entry and contributed to annual reports of clinical trials. With some technical help from colleagues and the supervisor, I performed all the analyses that are included in the thesis chapters as well as interpreted the results. Several ethics approvals were issued by the UBC Research Ethics Board (H12-01510, H09-02016, H04-70177, H13-01230).

Chapter 1 is based on a review article written by me with help from Drs. Katrina McMullen, Pratibha Surathi, Silke Appel-Cresswell, and Martin J. McKeown. The manuscript is ready for submission.

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Subjects With Multiple Sclerosis Is Robustly Influenced by Gender in Canonical-Correlation Analysis. *J Neuropsychiatry Clin Neurosci*. 29(2):119-127. The Parkinson's Disease (PD) data in chapter 2 has been included as part of the publication. Lin SJ, Baumeister TR, Gard S, McKeown M. (2018) Cognitive Profiles and Hub Vulnerability in Parkinson's Disease. *Front Neurol*, 2018;9:1-13.

Chapter 3 includes data from the Pacific Parkinson's Research Centre (PPRC) at UBC Hospital and a Phase III clinical trial of MS (OPERA II; NCT01412333) conducted in the MS Clinic at UBC Hospital and supported by F. Hoffmann-La Roche, Ltd. A version of chapter 3 (MS data) has been submitted. I wrote the manuscript and performed analyses with help from coauthors: Kolind S, Liu A, McMullen K, Vavasour I, Wang ZJ, Traboulsee A, McKeown M.

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List of Abbreviations

rsfMRI	resting-state functional magnetic resonance imaging
MS	multiple sclerosis
PD	Parkinson's disease
rsFC	resting-state functional connectivity
sMRI	structural magnetic resonance imaging
BOLD	blood oxygenation level dependent
RSNs	resting-state networks
MCI	mild cognitive impairment
UPDRS	Unified Parkinson's Disease Rating Scale
EDSS	Expanded Disability Status Scale
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
SDMT	Symbol Digit Modalities Test
PASAT	Paced Auditory Serial Addition Test
rmANOVA	repeated measure ANOVA
COV	coefficient of variation
dFC	dynamic functional connectivity
drsFC	dynamic resting-state functional connectivity
PCA	principal component analysis
CCA	canonical correlation analysis
MCCA	multiset canonical correlation analysis

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Dedication

To myself

給這幾年經歷風霜的自己：終於熬過來了

Chapter 1: Introduction

This chapter provides a general introduction of the cognitive deficits, related studies on functional connectivity, and common analyses in two neurological conditions: Parkinson's Disease and Multiple Sclerosis. In addition, the summary relates findings of previous research to a proposed model of higher-order cognitive function. Finally, suggested approaches to study the neuronal bases of cognitive function are made.

Executive function is a set of higher-order cognitive processes that include inhibition, working memory, cognitive flexibility, reasoning, problem-solving, and planning to achieve *goal-directed behaviour*. Executive functions are important for activities of daily living and a satisfactory quality of life [Diamond, 2013], and poor executive function leads to decreased productivity and problem solving abilities at work and school [Bailey, 2007; Blair and Peters Razza, 2007; Brown and Landgraf, 2010]. As a variety of neurological disorders can result in executive dysfunction, understanding the mechanisms of these deficits has become necessary in order to guide therapeutic options [Elliott, 2003]. Attempts at clinicopathological correlation, where damage to specific regions is correlated with particular deficits, were modestly successful at best with cognitive deficits, and this has been referred to as the *clinical-radiological paradox* [Barkhof, 2002]. Traditional clinical imaging focusing on damage to particular brain regions may obscure more diffuse structural and functional connectivity changes which are likely more important for complex cognitive processes such as executive function. To overcome this, a combination of novel brain imaging techniques such as resting-state functional magnetic resonance imaging (rsfMRI) and suitable analyses such as network measures and multivariate approaches can be used to investigate

correlations between different behaviour and associated connectivity patterns [Hackmack et al., 2012; van den Heuvel and Hulshoff Pol, 2010; Smith et al., 2009].

Executive dysfunction is prominent in several neurological and psychiatric illnesses including frontal lobe damage, basal ganglia disorders, depression and schizophrenia [Elliott, 2003]. This dissertation focuses on two neurological disorders known to impact executive function: Multiple Sclerosis (MS) and Parkinson's Disease (PD). These diseases have been chosen because they represent entirely different primary pathologies (myelin damage vs basal ganglia dysfunction), affect different ages and genders, yet still result in executive dysfunction. Contrasting and comparing the cognitive deficits in these two diseases are expected to provide insights into the common origins of executive dysfunction. We focus especially on resting-state functional connectivity (rsFC) in these two neurological conditions, as this will examine distributed representations that are complementary to the traditional clinicopathological correlation model.

1.1 Executive dysfunction and neuroimaging in Multiple Sclerosis and Parkinson's Disease

These two conditions are well-described progressive diseases of the central nervous system, which result in executive dysfunction. MS is characterized by white matter lesions and PD is a basal ganglia disorder with dopamine depletion. This section reviews the executive deficits in MS and PD as well as the relations to traditional neuroimaging measures.

1.1.1 Multiple Sclerosis

MS is a neuroinflammatory disease which shows widespread lesions (demyelinated axons attacked by T cells) mainly in the white matter and spinal cord but occasionally in the grey matter, resulting

in a broad range of deficits such as motor, cognitive, and neuropsychiatric symptoms [Goldenberg, 2012]. Four subtypes of MS have been defined: relapsing-remitting, secondary progressive, primary progressive and progressive-relapsing MS depending upon the pattern of temporal evolution of symptomatology. This review focuses on the most common subtype of MS – relapsing-remitting MS (RRMS).

In RRMS, up to 70% of patients demonstrate cognitive impairment, with the most commonly affected domains being information processing speed, attention, visuospatial ability, memory, and executive function [Chiaravalloti and DeLuca, 2008; Langdon, 2011; Wallin et al., 2006]. The affected domain incorporating *attention* involves complex processes such as alertness, selective/focused/divided attention, and vigilance rather than “simple” attention (e.g. as tested by asking a subject to repeat a series of digits) [Chiaravalloti and DeLuca, 2008; Guimarães and Sá, 2012]. Processing speed, a commonly impaired domain in MS, is required in many cognitive tasks to rapidly react to processed information [Chiaravalloti and DeLuca, 2008; Guimarães and Sá, 2012]. Research has suggested that difficulty in acquiring new knowledge in MS might be a greater problem than information retrieval in the memory domain [Chiaravalloti and DeLuca, 2008]. Executive dysfunction in MS also includes poor planning, decreased working memory, set-shifting and mental flexibility problems [Foong et al., 1997; Holland et al., 2014]. Patients with MS generate significantly fewer words in the Verbal Fluency Test, take longer time to complete the Stroop test, make more errors in the Stroop test and spatial working memory test, and require longer time to initiate motor execution in a test of planning and problem solving [Foong et al., 1997]. In a young MS population, 35% of the subjects score lower than the normative data on the Trail Making Test B (TMT B), suggesting disabilities of mental flexibility [Holland et al., 2014].

Among the cognitive deficits, executive dysfunction seems to impact patients' quality of life and occupational performance the most [Preston et al., 2013].

Traditional MRI methods have been explored in MS as biomarkers for cognitive impairment, but results have only met with modest success. Diffuse lesions observed in fluid-attenuated inversion recovery (FLAIR) MRI sequences and T2-weighted images in the periventricular white matter and the commissural fiber tracts are associated with processing speed deficits, working memory difficulties, perception and spatial processing [Houtchens et al., 2007; Rossi et al., 2012; Stankiewicz et al., 2009]. However, only a few studies have actually shown strong correlations between executive deficits and particular MRI-detectable lesion locations in MS [Filippi et al., 2010]. This has raised concerns whether lesion location (or even overall lesion load) can be a specific indicator of cognitive deficits, especially executive dysfunction [Rocca et al., 2014]. It is this observation that has motivated a network approach to cognitive deficits as done in this thesis.

Newer imaging methods have proved more successful in finding a link between imaging features and cognitive dysfunction in MS. Decreased white matter integrity, as evaluated by fractional anisotropy (FA)-based graphical measures in the frontoparietal network, subcortical regions, and insula are associated with impaired attention and executive performance [Llufriu et al., 2017]. Cortical thinning in the left anterior cingulate, superior frontal, lateral orbitofrontal, and superior parietal regions have been shown to be associated with executive deficits (e.g. verbal fluency) [Geisseler et al., 2016].

1.1.2 Parkinson's Disease

PD is a neurodegenerative movement disorder that is characterized by degeneration of dopaminergic neurons in the substantia nigra *pars compacta* [Dauer and Przedborski, 2003], affecting dopaminergic pathways such as nigrostriatal and mesocortical pathways [Ouchi et al., 2001]. In addition to dopamine depletion, several factors have been considered contributing to the impairments in PD such as protein misfolding, impaired cholinergic activity, and adenosine receptor abnormalities [Aarsland et al., 2017]. This dissertation focuses on *sporadic* PD (i.e. there is no apparent genetic linkage), which is the most common type [Dauer and Przedborski, 2003]. Executive dysfunction has been commonly reported, using tasks which require planning, set-shifting, control of attention, working memory, and timing skills such as the Wisconsin Card Sorting Test (WCST), TMT, Tower of London Test (ToL), and time perception task [Dirnberger and Jahanshahi, 2013; Goldman and Litvan, 2011; Palavra et al., 2013; Parker et al., 2013; Williams-Gray et al., 2007]. In the dual syndrome hypothesis, the *frontal cognitive subtype*, more commonly seen in tremor-predominant PD, is associated with decreased dopamine levels in frontal-striatal circuits, resulting in impaired executive function such as reduced verbal fluency and impaired planning ability [Kehagia et al., 2010; Siepel et al., 2014; Williams-Gray et al., 2007]. *The posterior cognitive subtype*, associated with a more profound cholinergic deficit, demonstrates impaired visuospatial abilities, and dementia [Miller et al., 2013]. Choline acetyltransferase (ChAT) activity can be reduced in the hippocampus, prefrontal cortex, and temporal cortex and the degradation is correlated with global cognitive decline in PD [Mattila et al., 2001]. Positron emission tomography (PET) studies have shown that cholinergic degradation in PD correlates with performance of attention, working memory, and executive tests, while this degradation is not

correlated with motor symptoms [Bohnen et al., 2006]. Thus both dopamine and cholinergic signaling have been shown to affect cognitive domains such as working memory, decision making, and attention [Ballinger et al., 2016; Takahashi et al., 2012]. In fact, decreased cholinergic and dopaminergic signaling and neuronal death may be joint pathological features in PD which affect cognition [Ballinger et al., 2016].

Other pathological changes can also be observed and linked to executive impairment in PD. Cortical thinning in the dorsolateral superior frontal gyrus as well as white matter abnormalities underlying bilateral frontal and temporal cortices have demonstrated relationships to executive dysfunction [Koshimori et al., 2016]. Diffusion tensor imaging (DTI) has demonstrated a positive correlation between FA in frontal-subcortical regions and executive scores [Gallagher et al., 2013]; likewise, executive function has been positively correlated with FA and negatively correlated with mean diffusivity (MD) in frontal white matter tracks such as the anterior limb of the internal capsule and the genu of the corpus callosum [Zheng et al., 2014]. Taken together, structural changes in the frontal areas are associated with executive dysfunction in PD as well as some temporal/posterior regions. Neurotransmitter abnormalities are also related to cognitive impairments in attention, memory, and executive domains.

1.1.3 Summary

MS and PD are two distinct neurological conditions, which both present with executive dysfunction regardless of the location of lesions and affected areas/circuits, supporting the notion that executive function requires widely distributed regions to coordinate as a whole rather than engaging one specific region of the cerebral cortex such as the prefrontal cortex [Alvarez and Emory, 2006; Elliott, 2003; Heyes, 2012; McIntosh, 2000; McIntosh, 2004; Miller and Wallis,

2009]. Newer techniques such as fMRI allow observing neural events with a broader outlook and examining brain regions that are active under certain conditions. When these techniques are used to look at the temporal co-activation of regions they move beyond a **simple localization approach** (*which* region does *what* function) to looking at **distributed networks of activation** (which regions are acting in concert or sequence with each other). This approach is referred to as functional connectivity, which allows investigations of how anatomically segregated brain regions communicate [Elliott, 2003; van den Heuvel and Hulshoff Pol, 2010].

1.2 Functional connectivity and analysis approaches in clinical research

1.2.1 Resting-state functional connectivity

Neuroimaging techniques have been applied to study executive function in order to understand its neurobiological correlates [Bunge and Souza, 2009; Chung et al., 2014]. With structural magnetic resonance imaging (sMRI), structural changes such as grey matter atrophy and altered cortical thickness in brain regions have been compared with the performance of executive tasks that are assessed outside of the MRI scanner. With functional modalities, such as fMRI and PET, subjects perform executive tasks in the scanner while the functional images are being acquired to monitor neuronal activation patterns and metabolism triggered by the cognitive demands of the tasks.

Recently, rsfMRI has been used rather than, or in conjunction with, task-driven fMRI to study brain activity. rsfMRI involves scanning participants who are awake but not engaged in direct cognitive action (subjects are asked to not think about anything in particular, also known as spontaneous or non-directed cognition) and may be more appropriate for disease populations where poor behavioural performance in task based studies may affect interpretation of studies.

Analysis of task-driven fMRI studies is usually based on testing hypothesized amplitude-related blood oxygenation level dependent (BOLD) changes at different brain regions. With rsfMRI one does not have *a priori* hypothesized waveform as participants are not performing specific tasks and data driven methods, such as assessing rsFC are used for analysis. rsFC describes the statistical association of neural patterns between distinct brain regions during rest [Friston, 1994; van den Heuvel and Hulshoff Pol, 2010]. This ability to apply an exploratory approach is advantageous when considering compensatory and adaptive mechanisms as there is little *a priori* knowledge of which brain areas may demonstrate such behaviour. Although subjects do not perform specific cognitive tasks during rsfMRI studies, patterns of rsFC have been linked to performance on subsequent cognitive tasks [Diez et al., 2015; van den Heuvel and Hulshoff Pol, 2010; Rosazza and Minati, 2011; Smith et al., 2009; Smith et al., 2013; Spreng et al., 2012].

Connectivity in rsfMRI can be divided into functional connectivity and effective connectivity [Friston, 1994; Friston, 2011]. This literature review focuses on functional connectivity due to the paucity of research using effective connectivity to look at clinical populations to date. Functional connectivity describes the temporal correlation between spatially segregated events and it does not contain information about directionality, meaning that the analysis reports only the covariance between brain regions/voxels (i.e. how much the neural activity changes in different locations are related to each other). Several approaches have been used to assess rsFC in healthy subjects and patients with neurological conditions to explore brain organization and neuroimaging biomarkers, respectively [Bowman, 2014b; Lindquist, 2008; Margulies et al., 2010; Pievani et al., 2014].

1.2.1.1 Common analyses and applications

Several common approaches have been applied to clinical studies such as Independent Component Analysis (ICA), seed-based correlation, whole brain correlation, and graphical analysis. In brief, ICA decomposes the data into maximally spatially independent components (spatial maps) and corresponding time courses [McKeown et al., 2003]. Voxels within the same maps may be considered functionally connected. Maps may correspond with areas associated with the default mode network, sensorimotor processing, visual processing and saliency [Damoiseaux et al., 2006].

Another approach for determining rsFC is to utilize a seed-based approach. In this technique, one must pre-specify seed region(s) and correlation between the time course of the seed region(s) and other voxels are calculated [Greicius et al., 2003]. Whole-brain correlational analysis takes into account several brain regions at the same time and evaluates the covariance/correlation between regions rather than looking at specific seed regions [Prodoehl et al., 2014].

Once connectivity strengths between brain regions have been computed, the results are usually collected into a matrix and summarized. One such summarizing method is graph theory. In mathematics, a “graph” consists of nodes and edges, and in this context, the nodes represent brain regions and the edges represent the statistical relation between their respective time courses (e.g. correlation, possibly after thresholding and setting small correlational values to zero). Recently, graphical analyses have become a popular tool to describe how networks are organized and how the information is coordinated through biological fundamentals in connectome studies [Rubinov and Sporns, 2010]. Topological features reveal that the brain is a *small-world organization* (i.e. networks are highly clustered like a scale-free network but nodes are linked by small path lengths like a random network) with a balance between how well the information is processed within one

system (i.e. functional segregation) and how efficient the information is integrated throughout the brain (i.e. functional integration) [Deco et al., 2015; Sporns, 2013]. These organization principles aim to reduce wiring cost yet enhance the efficiency of information flow [Bullmore and Sporns, 2012; Sporns, 2013]. As the volume of the human brain has increased during evolution, neural signaling is required to travel longer distance along white matter, resulting in longer travel time (i.e. wiring cost) [Hofman, 2014]. Other adaptations have also been proposed as strategies to reduce wiring cost in addition to segregation, integration, and small world organization. As the travel distance increases, “short cuts” of the brain have been developed such as long-range connections so neuronal signals can bypass other regions through these short cuts [Hofman, 2014]. In addition, studies have proposed that several regions are more densely connected to other regions either within one network or between networks, forming high traffic spots in the brain called “hubs” [Achard et al., 2006; van den Heuvel and Sporns, 2013; Power et al., 2013]. Therefore, neuronal signals can “transfer” between these hubs to reduce wiring cost as the information flow can be more efficiently carried out across the brain.

1.2.2 Dynamic functional connectivity

The above-mentioned methods assume that connectivity patterns are relatively temporally stationary and estimate the average connectivity patterns that represent neurophysiological events across the scanning time. However, new studies with computational models implemented have suggested that functional connectivity is not stationary and this aspect has been referred to as *dynamic functional connectivity* [Hutchison et al., 2013b; Hutchison et al., 2013a], i.e., the neuronal patterns fluctuate across time (in seconds/minutes) in order to maintain brain function in

response to different environmental stimuli. This temporal connectivity pattern is also a crucial component of brain organization.

1.2.2.1 Methods and applications

The most common analytical model for dynamic functional connectivity is perhaps a sliding window approach, with pairwise correlation implemented [Hutchison et al., 2013b; Hutchison et al., 2013a]. This model estimates correlations between brain regions within a fixed-length, sliding window, with the (possibly overlapping) windows ultimately moved over the entire data. As a result, each correlation matrix represents the connectivity at each window. With *post hoc* analyses, features that summarizes connectivity changes across time can be calculated [Liao et al., 2015]. Another approach is to apply clustering methods (i.e. to separate matrices into different states) and calculate the “dwell time” of each state [Damaraju et al., 2014]. Alternatively, principal component analysis (PCA) can be applied to study whole brain dynamics based on windowed correlation matrices [Leonardi et al., 2013]. Nevertheless, there are potential pitfalls with sliding window approaches [Hindriks et al., 2016; Hutchison et al., 2013b]; if the window is too long, important dynamic changes may be missed. If the window is too short, the connectivity estimates may be unstable as too few samples are available for the statistical inferences. A window length of 30-60 seconds for fMRI data has been heuristically suggested [Leonardi and Van De Ville, 2015; Zalesky and Breakspear, 2015]. Other time-varying approaches have also been implemented to investigate dynamic functional connectivity such as the combination of sliding window and Hidden Markov Model [Chiang et al., 2016], the Sticky Weighted Regression Model [Liu et al., 2015], and Dynamic Conditional Correlations [Lindquist et al., 2014]. Other methods which investigate dynamics in frequency domain and integrate with graph analysis have been proposed [Chang and

Glover, 2010; Chiang et al., 2016]. A comprehensive review has pinpointed the strengths and issues of each method [Prete et al., 2017]. Although some of them have been applied to clinical studies, the majority studies which explore the links between disease, cognition, and dynamic functional connectivity still favour the sliding window approach.

Dynamic functional connectivity allows for different degrees of engagement in areas/networks across different time scales (i.e. a given brain area gets involved in the connectivity network at a certain time point, but in a different time frame the area is not engaged in the network). Studies in behaviour and simultaneous recording of functional connectivity and electrophysiological data suggest that temporal variations link neuronal origin, cognitive processes and behaviour [Chang et al., 2013; Thompson et al., 2013]. For example, increased temporal variability of neural activity is associated with stable performance in an electroencephalography (EEG) memory task [McIntosh et al., 2008]. Moreover, recently both rsfMRI and tasked fMRI research has further suggested that these dynamic and topological features have been linked to cognitive architecture -- especially higher-order cognitive processes [Mattar et al., 2015; Shafto and Tyler, 2014]. Compared to motor tasks, the performance of the N-back memory task requires more functional integration between regions and relies on the ability to flexibly integrate information across regions and networks especially in frontoparietal and frontotemporal networks [Braun et al., 2015; Shine et al., 2016]. Such brain organization has been seen in rsfMRI as well, whereby the rsFC network related to cognition requires flexibility [Mattar et al., 2015]. In addition, it has been concluded that dynamic interaction between networks supports cognitive functions, especially ones which requires complex processes such as language [Chai et al., 2016; Shafto and Tyler, 2014].

1.3 Resting-state functional connectivity and executive function in Multiple Sclerosis and Parkinson's Disease

Table 1.1 summarizes the studies which have explored the associations between executive deficits and rsFC in MS and PD. Figure 1.1 visualizes the rsFC patterns related to executive function.

1.3.1 Multiple Sclerosis

Many studies have reported decreased functional connectivity in MS in resting-state networks (RSNs) including the default mode, salience, executive control, working memory, and sensorimotor networks [Bonavita et al., 2011; Rocca et al., 2012]. The decreased connectivity indicates that cortical regions fail to integrate information (especially the medial prefrontal cortex and posterior cingulate cortex) and has been associated with worsening executive function in cognitively impaired patients [Cruz-Gómez et al., 2014; Louapre et al., 2014], which supports the idea that cognitive deficits in MS may be the result of disconnection. In addition, studies which investigate whole-brain rsFC have revealed weaker connectivity among widespread regions including frontal, parietal, temporal, and subcortical areas as well as interhemispheric connectivity [Richiardi et al., 2012; Zhou et al., 2013].

Research with novel approaches such as graph theoretical analysis provides insight into alterations of functional connectivity in a topological fashion [Gamboa et al., 2014; Rocca et al., 2016b; Schoonheim et al., 2013]. Patients with MS exhibit reduced global efficiency, node degree, centrality, and increased path length on average compared to normal subjects, demonstrating altered rsFC in network organization [Rocca et al., 2016b]. As global efficiency calculates the average inverse of shortest path lengths, the reduced measure indicates that the shortest path length

increases, and thus a marker of inefficient information transfer in the brain. Decreased node degree suggests that brain regions lose connections to/from other regions, indicating a reduction in overall connectivity. Centrality represents the “importance” of a given region (i.e. the fraction of shortest paths that pass through a given node) and a small value implies that 1) the region loses shortest paths and 2) hubs potentially vanish. As a consequence, the organized brain network structure, which is meant to reduce wiring cost, fails. These topological changes in MS illustrate impaired functional integration and the impairment is associated with executive dysfunction such as reduced accuracy in dual-task performance [Gamboa et al., 2014; Schoonheim et al., 2013]. This implies that the MS brain becomes more segregated and will be less efficient to support complex behaviour. In addition, the loss of hub regions in MS (include the superior frontal gyrus, precuneus, and anterior cingulate cortex) leads to impaired functional integration, as hubs are an important aspect of functional integration where several networks are integrated [Rocca et al., 2016b]. As many of these regions are highly related to executive function, the results imply that higher cognitive function requires not only the frontal cortex but other cortices, such as the parietal cortex in case of the precuneus, to coordinate information flow.

However, other studies have also reported that increased functional connectivity in some RSNs is associated with *reduced* cognitive efficiency, indicating that cognitive deficits may be associated with enhanced functional coupling in MS possibly reflecting compensatory and/or adaptive mechanisms at different stages of disease progression [Faivre et al., 2012; Hawellek et al., 2011b]. Moreover, the authors reported that the major connectivity which modulated behaviour required shifts between the default mode network and the central executive network depending on the degree of patient’s cognitive impairments, in which connectivity shifted toward executive network

in patients with higher cognitive efficiency [Hawellek et al., 2011b]. The networks with increased connectivity lost “flexibility” in network interactions and resulted in stronger connectivity at a longer time scale. As these networks commonly require coordinated information flow across cortices via long-range fibers, it has been postulated that cognition-related connections may constantly shift between regions and increased functional connectivity reflects a loss of diversity in network interactions.

With a seed-based approach, other studies have demonstrated that *increased functional connectivity*, which was observed in the frontal regions, anterior cingulate cortex, and posterior areas, was related to better performance of executive ability [Loitfelder et al., 2012]. As the seed regions in the studies are all important hubs in cognitive processes (i.e. the anterior cingulate cortex, ventral medial prefrontal cortex, and posterior cingulate cortex), the results imply that core cognitive regions may first demonstrate compensatory effects. Yet these studies focus on a limited number of seed regions, which may lose sensitivity to detect connectivity patterns in other regions. In addition, studies often report both increased and decreased activation as a function of disease stage and cognitive impairments. Perhaps rather than increased or decreased activity *per se*, the “interactions” between networks with altered activation/connectivity would be more informative to cognitive impairments and disease severity. Therefore, studying *whole brain connectivity* may prove beneficial. Effects of age and disease stage on cognitive deficits may also lead to inconsistent results. This may be related to cognitive reserve capacity whereby in early stages of the disease there is altered connectivity and normal cognitive performance, but over time or under higher cognitive demands, the capacity for compensation diminishes and the altered connectivity becomes aberrant.

1.3.2 Parkinson's Disease

The majority of research into rsFC in PD focuses on the connectivity between the motor cortex and subcortical areas such as cortico-striatal connections as well as how rsFC correlates with clinical scores [Helmich et al., 2010; Kwak et al., 2012; Luo et al., 2014; Sharman et al., 2013; Wu et al., 2009]. Since non-motor symptoms such as cognitive deficits in PD have profound effects on quality of life, a few studies have started investigating whole-brain functional connectivity and its association with cognitive deficits [Amboni et al., 2014a; Baggio et al., 2014; Disbrow et al., 2014; Hirano et al., 2012; Olde et al., 2014; Owen, 2004].

Through a seed-based approach with a seed in the caudate, demented PD patients exhibited decreased connectivity to frontal regions [Seibert et al., 2012], suggesting that alterations in the connections between frontal and subcortical regions are important contributors to dementia in PD. Research on whole brain functional connectivity showed that the inferior frontal gyrus and posterior regions of the brain (e.g. superior parietal lobes and multiple occipital regions) had decreased connectivity and demonstrated stronger correlation with global cognitive function (including orientation, language, memory, praxis, attention, abstract thinking, perception and calculation) than motor deficits [Olde et al., 2014]. Connectivity alterations in frontal and parietal areas have also been shown to be associated with mild cognitive impairment (MCI) in PD [Amboni et al., 2014b]. Furthermore, decreased activity in the ICA-derived default mode network was independent of patients' cognitive states but decreased frontoparietal connectivity was associated with worsening visuospatial, memory, and executive functions [Amboni et al., 2014b]. However, another study has proposed the opposite pattern: namely that executive performance in PD is related to the default mode network rather than the executive control network [Disbrow et al.,

2014]. In addition, inter-network connectivity (i.e. correlations between RSNs) between the default mode network (DMN), salience network (SN), and central executive network (CEN) was altered in PD with increased coupling between the DMN/CEN and decreased coupling between the CEN/SN in PD with a particularly reduced interaction between the SN and striatum [Putcha et al., 2015].

The discrepancies between rsFC in PD imply that a more robust measure across cohorts is needed to study how connectivity is related to cognition. Graph-theory based analysis of rsfMRI data suggests that PD manifests as a disconnection syndrome [Göttlich et al., 2013]. Graphical measures demonstrated that PD showed lower connectivity (lower node degree) in the medial and middle orbitofrontal cortex, while the superior parietal, posterior cingulate, supramarginal, and supplementary motor areas presented increased connectivity (higher node degree), the latter being interpreted as compensation for cortico-striatal dysfunction. The connections between subcortical areas and orbitofrontal/temporal regions as well as within cortical regions were weaker in the PD group, indicating that PD is associated with widely disrupted resting-state networks [Göttlich et al., 2013]. Baggio et al. investigated the relationship between graphical measures and cognition in PD [Baggio et al., 2014]: MCI-PD subjects presented with increased modularity and clustering coefficients. Modularity quantifies the degree to which the network may be subdivided into separate groups and it is an index of functional segregation, i.e. how well the information is carried out within one system. Clustering coefficient measures the degree to which nodes in a network tend to gather together, which is also a measure of functional segregation. In PD, functional connectivity has become more segregated as the long-range connections were affected between frontal, parietal, and occipital areas. Hub reorganization has been identified in MCI-PD, where

normal hubs in the parietal and superior temporal lobes lose their central role and non-hubs in the middle frontal gyrus gain importance, implying an association between cognitive deficits and hub distribution [Baggio et al., 2014]. Furthermore, these graphical measures were correlated with test scores of worsening attention, executive function, memory, and visuospatial functions in MCI-PD compared to control subjects, indicating that segregated brain networks measured by graphical approaches reflect decreased cognitive ability including executive functions. Hub reorganization has been described in another study where patients with PD no longer had prominent connectivity in the insula but caudate connectivity became more prominent, however, no cognitive scores were related to the changes [Koshimori et al., 2016].

To summarize, weakened connections between frontal and other regions are associated with cognitive dysfunction in PD. Although many studies have shown that cognitive deficits are related to widespread *dysconnectivity* between frontal and other cortical regions (i.e. posterior and occipital areas), we cannot exclude the importance of frontostriatal circuits as the impaired dopamine pathways may cause inefficient feedback to frontal areas, leading to cognitive dysfunction [Owen, 2004]. In fact, studies have reported the links between impaired dopamine signaling in the frontal areas and executive dysfunction such as working memory and set-shifting deficits [Narayanan et al., 2013]. In addition to dopaminergic system, cholinergic dysfunction (which affects frontal, temporal, occipital, and forebrain areas) has been suggested as another contribution to executive dysfunction [Narayanan et al., 2013; Pagonabarraga and Kulisevsky, 2012]; therefore, investigating distributed regions is necessary rather than focusing on specific circuits. Meanwhile, the finding of increased connectivity patterns, which have been interpreted as compensatory effects, is not consistent across studies. We speculate that this might be because

the nature of dynamic functional connectivity in PD is not captured by traditional analyses and the appropriate emphasis of “hub regions” has been neglected. As switching ability is impaired in PD [Cools et al., 2001], patients demonstrate cognitive inflexibility and perhaps neuronal inflexibility, which is implied by the studies showing that dopamine signaling can impact dynamic neural phase coordination and play a role in cognitive processes [Dzirasa et al., 2009]. **Therefore, we hypothesize that how rsFC changes (i.e. network dynamics or dynamic functional connectivity) together with how hub regions and networks are remapped might be a feature which reflects cognitive rigidity in PD.** Further studies with time-varying approaches and graphical analyses are necessary to reveal hidden patterns in rsFC.

Disease	Authors	Methods for rsFC	Purposes and methods for neuropsychological tests	Subjects	Main findings in patients
Multiple Sclerosis (MS)	Bonavita et al., 2011	ICA-RSNs	determine CI and CP	CI-RRMS, CP-RRMS, NC	DMN showed decreased rsFC in the anterior cingulate cortex but increased rsFC in the posterior cingulate cortex
	Rocca et al., 2012	ICA-RSNs	NA	RRMS	- decreased rsFC in the salience, executive control, working memory, sensorimotor, visual networks as well as DMN - increased rsFC in the executive control and auditory networks
	Cruz-Gómez et al., 2014	ICA-RSNs	- determine CI and CP - regression analysis	CI-RRMS, CP-RRMS, NC	- All RSNs in CI decreased compare to NC and CP - CP showed decreased rsFC in the left frontoparietal network - rsFC was related to radiological variables not cognition
	Louapre et al., 2014	ICA-RSNs	determine CI and CP	CI-RRMS, CP-RRMS, NC	- increased rsFC in CP at the attention network - decreased rsFC in CI at DMN and the attention network especially between the medial PFC and PCC
	Richiardi et al., 2012	Pearson's r whole brain matrix and classification	NA	RRMS, NC	the connections in subcortical and fronto-parieto-temporal areas were the most discriminative as well as inter-hemispheric connections
	Zhou et al., 2013	Pearson's r in symmetric interhemispheric voxels	NA	RRMS, NC	- decreased rsFC in high-order cognitive regions including frontal, temporal, and occipital regions - increased rsFC in the OFC, insula, thalamus, cerebellum, subcortical, and inferior temporal areas
	Gamboa et al., 2014	graph theory – the Brain Connectivity Toolbox	correlation analysis	RRMS, CIS, NC	- reshaped modules in MS were negatively correlated with the accuracy of dual task performance and indicated impaired functional integration
	Rocca et al., 2014	graph theory - the Brain Connectivity Toolbox	determine CI and CP	RRMS, benign MS, SPMS, NC	- MS lost hubs in the superior frontal gyrus, precuneus, and anterior cingulum but gain hubs in the temporal pole and cerebellum - decreased degree, clustering coefficient, global efficiency, hierarchy as well as increased path

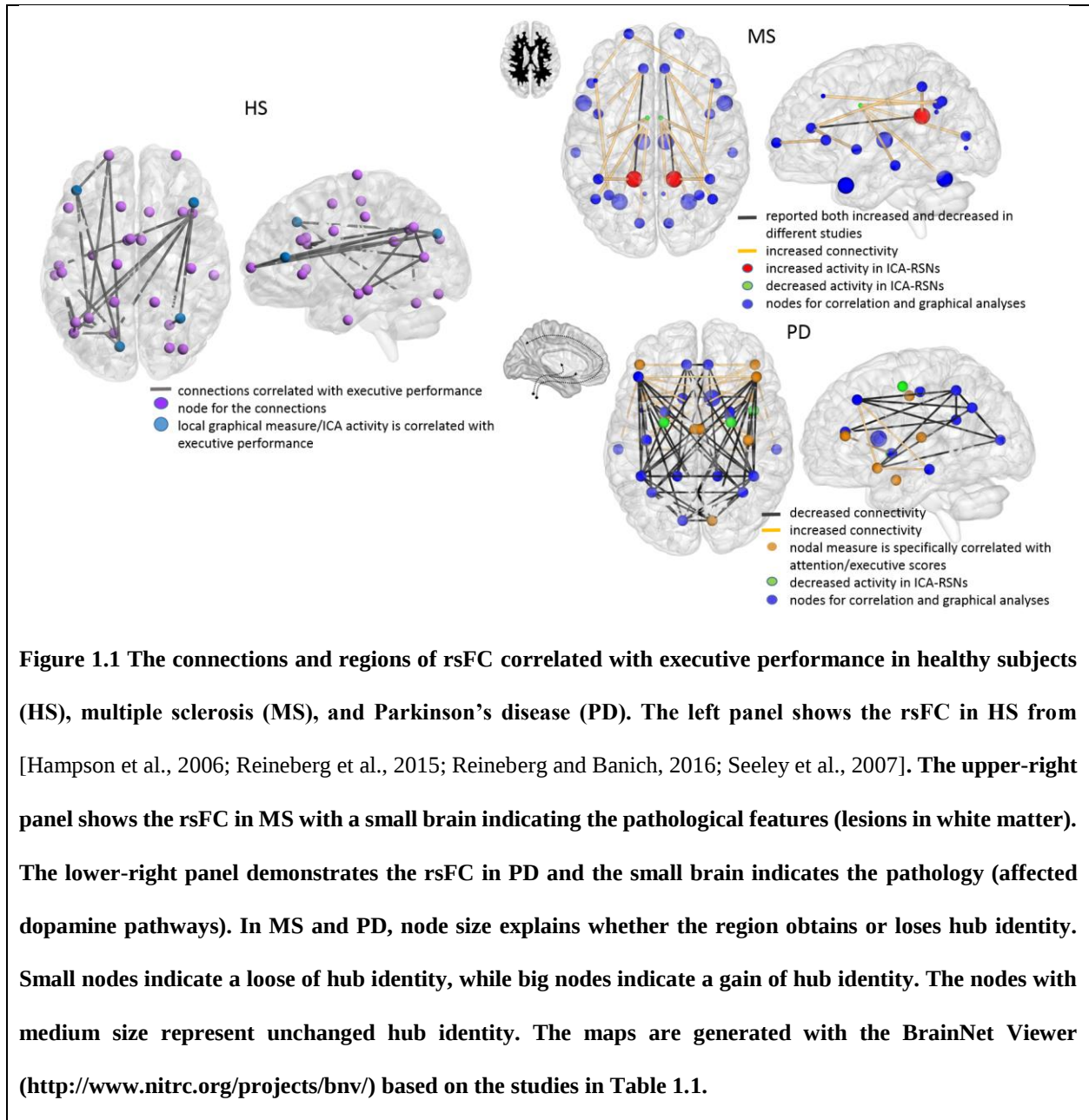
					length and assortativity in MS indicated impaired functional integration - functional integration was more impaired in CI
	Schoonheim et al., 2013	graph theory – eigenvector centrality mapping	correlation analysis	RRMS, PPMS, SPMS, NC	- increased centrality/importance in the thalamus and PCC - decreased centrality/importance in sensorimotor (related to EDSS) and ventral stream areas (related to poor executive function and processing speed)
	Faivre et al., 2012	ICA-RSNs	correlation analysis	RRMS, NC	- increased rsFC in DMN and the fronto-parietal network was correlated with decreased semantic fluency and increased PASAT scores
	Hawellek et al., 2011	ICA-RSNs	factor analysis and correlation analysis	relapse-free MS, NC	higher rsFC in the cognitive control network and DMN was related to reduced executive function (set-shifting)
	Loitfelder et al., 2012	seed-based	multiple regression model	CIS, RRMS, SPMS, NC	- increased rsFC in the ACC, PCC, angular gyrus, and postcentral gyrus - better executive abilities were related to increased rsFC in the cerebellum, middle temporal gyrus, occipital areas, and angular gyrus
	Wojtowicz et al., 2014	seed-based	act as covariates in connectivity analysis	RRMS, NC	better processing speed was related to greater rsFC between the ventral PFC and left frontal pole
Parkinson's Disease (PD)	Helmich et al., 2010	seed-based	NA	PD, NC	- decreased rsFC between the posterior putamen and motor areas/inferior parietal cortex - increased rsFC between the anterior putamen and inferior parietal/temporal cortex (this study was not related to executive function)
	Kwak et al., 2012	amplitude of low frequency fluctuations (*measure fMRI signal intensity)	measure overall cognition	PD, NC	- with OFF medication, increased rsFC was seen in the primary and secondary motor areas, middle/medial prefrontal cortex - with ON medication, reduced rsFC in the prefrontal and motor cortical areas - poor motor task performance was associated with higher rsFC (this study was not related to executive function)
	Luo et al., 2014	seed-based	measure overall cognition	PD, NC	- reduced rsFC in the mesolimbic-striatal and corticostriatal loops

					- decreased functional integration across striatum, mesolimbic cortex, and sensorimotor areas - higher non-motor symptom indices were related to reduced rsFC in amygdala-putamen circuits (but not restricted to executive function)
Sharman et al., 2013	seed-based	NA	PD, NC		- increased rsFC in the limbic and associative cortex, limbic cortex and thalamus, putamen and thalamus - decreased rsFC in the sensorimotor cortex and thalamus, globus pallidus and putamen/thalamus, substantia nigra and globus pallidus/putamen/thalamus (this study was not related to executive function)
Wu et al., 2009	regional homogeneity	measure overall cognition	PD, NC		- decreased rsFC in the putamen, thalamus, and supplementary motor areas - increased rsFC in the cerebellum, primary sensorimotor cortex, and premotor area (this study was not related to executive function)
Seibert et al., 2012	seed-based	NA	PDD, PD, NC		- PDD showed decreased rsFC in middle frontal regions
Olde et al., 2014	synchronization likelihood for whole brain connectivity	generalized estimated equations (combine correlation and linear regression)	PD, NC		- decreased rsFC in the inferior frontal gyrus, superior parietal lobes, and occipital regions showed stronger correlations to cognitive function including executive function rather than motor symptoms
Amboni et al., 2014	ICA - RSNs	correlation analysis	PD, MCIPD, NC		- decreased DMN in PD and MCIPD was not correlated with cognition - decreased rsFC in the frontoparietal network in MCIPD was related to worse executive function but not clinical variables
Disbrow et al., 2014	seed-based	- measure cognitive profile - correlation analysis	PD, NC		- No changes in the executive control network - decreased rsFC within DMN was seen in PD and greater DMN rsFC was related to faster processing speed
Putchal et al., 2015	ICA – RSNs and Pearson's r	measure overall cognition	PD, NC		- interactions between RSNs were altered in PD - decreased interactions between the salience and executive networks

					- increased interactions between the DMN and executive network
Göttlich et al., 2013	graph theory – the Brain Connectivity Toolbox	NA	PD, NC		- lower node degree in the medial/middle OFC and occipital pole - increased node degree in the superior parietal, PCC, supramarginal, and supplementary motor areas - decreased rsFC between the subcortical, medical OFC and temporal regions
Baggio et al., 2014	graph theory - the Brain Connectivity Toolbox	- determine PD and MCIPD - linear regression analysis	MCIPD, PD, NC		- both MCIPD and PD showed reduced rsFC in long-range connections which include frontal, occipital, and parietal regions - increased local rsFC in MCIPD including higher clustering, local efficiency, and modularity in the frontal areas was correlated attention/executive scores - MCIPD showed reduced importance in hubs
Koshimori et al., 2016	seed-based and graph theory – Graph-Theoretical Analysis Toolbox	correlation analysis	PC, NC		- hub reorganization was seen in PD, which PD lost the insula but gained the caudate as a new hub in cognitive networks - increased rsFC in the DLPFC and insula of cognitive networks - reduced intrahemispheric rsFC within insula and supplementary motor areas was related to medication not cognition

Table 1.1 Summary of the rsFC studies in MS and PD. The inclusion criteria for the studies are 1) performing neuropsychological tests, 2) using statistical analyses to link fMRI measures and cognitive scores and 3) the reported results are associated with executive performance or dementia if the neuropsychological tests are used for determining dementia.

[NC: normal controls, CI: cognitive impaired, CP: cognitive preserved, DMN: the default mode network, ICA – RSNs: independent component analysis derived resting state networks, RRMS: relapsing-remitting MS, SPMS: secondary progressive MS, CIS: clinically isolated syndrome, PASAT: Paced Auditory Serial Addition Test, PDD: demented PD, MCIPD: mild cognitive impairment PD, PFC: prefrontal cortex, PCC: posterior cingulate cortex, ACC: anterior cingulate cortex, OFC: orbitofrontal cortex, DLPFC: dorsal lateral prefrontal cortex]



1.3.3 Summary

It is becoming increasingly common to interpret cognitive performance as a result of coordination of information between brain regions and rapid re-configuration among connectivity states [McIntosh, 2000; Shaw et al., 2015; Sridharan et al., 2008]. Regardless of distinct pathology, early rsFC studies either applied exploratory methods to discover specific brain areas and networks, or they focused on pathways based on prior hypotheses related to the disorders, which has led to a paucity of research exploring the role of other regions and networks. For example, the default mode network has been intensively studied in MS, and most studies have reported decreased connectivity. Functional connectivity within frontostriatal loops in PD has been extensively examined due to affected dopaminergic pathways and reduced connectivity in the loops has been linked to clinical deficits. However, with the approaches which assess whole brain functional connectivity, widespread connectivity alterations have been revealed rather than abnormalities in just one circuit.

1.4 Impacts and contributions of studies on resting-state functional connectivity to clinical neuroscience

1.4.1 Key connections in cognitive deficits

Long-range connections, such as frontal and parietal links, seem to play an important role in executive functions regardless of distinct neurological impairments. From an evolutionary perspective, the human brain has increased in size dramatically and intrahemispheric connections have been shown to be stronger in larger brains [Hänggi et al., 2014; Hofman, 2014]. In addition, it has been proposed that long range communication networks in humans linking prefrontal areas

to other regions, such as parietal areas, are important adaptations in evolution compared to other species, and these connections are necessary for complex behaviour and sophisticated cognitive abilities in humans [Hofman, 2014; Shaw et al., 2015].

A review of neurological disorders based on network analyses has proposed that *hub overload and failure* potentially affect long-range connections by disrupting the normal hierarchical architecture of connectivity networks (i.e. imbalance between local process and global process via hubs) and the changes are related to executive dysfunction, which may be a common pathway leading to cognitive impairments in neurological disorders [Stam, 2014]. However, how hub reorganization alters spatial and temporal coordination between brain regions through long-range connections (i.e. flexibility in long-range connections) remains unclear. Long-range connections propagate neural information, which is essential for high-order cognition between segregated brain regions, and these information flows can be better organized and coordinated through hubs so that wiring cost is minimized. In order to investigate these associations, more research on the links between brain topology and dynamic functional connectivity is required.

The idea proposed by Stam [Stam, 2014] is consistent with the studies we have discussed in the review sections of this chapter, in which many investigations have reported impaired long-range connectivity between frontal, parietal, and occipital regions in different neurological conditions. Research has also demonstrated the associations between frontal-parietal connectivity and high-order cognitive processes including executive function, emphasizing the importance of long-range connections in human cognition. For instance, a study which combined fMRI meta-analysis and DTI tractography revealed that a ventral branch of the superior longitudinal fasciculus, which connects inferior frontal and inferior parietal lobes, is associated with several cognitive functions

such as working memory, decision making, language process, inhibition, and attention [Parlatini et al., 2016]. Moreover, another study has demonstrated that diffusion measures in the superior longitudinal fasciculus are correlated with performance in executive function, information processing speed, and memory domains [Sasson et al., 2013]. These studies further emphasize the strong links between long-range connections and cognition.

Long-range connections are impaired in neurological disorders, and may be inferred by structural MRI studies. Cortical thinning in frontal and parietal cortices has been correlated with worse executive function in PD, while poor executive performance can be predicted by cortical thinning in the anterior cingulate cortex in MS [Duncan et al., 2016; Geisseler et al., 2016]. In addition, based on our unpublished studies, higher myelin integrity in the bilateral inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and superior longitudinal fasciculus, which connect frontal/parietal/occipital areas, is associated with better executive function in MS, supporting that long-range connections are important for higher-order functions [Baumeister et al.,]. Therefore, the literature suggests that *executive dysfunction may be partially caused by disruptions between frontal regions and the posterior part of the brain (especially frontal and parietal cortices) in both neurological conditions presented in this chapter.*

1.4.2 Three components of executive function

Why would the disconnection between frontal and parietal regions contribute to executive dysfunction in neurological conditions? In other words, what are the roles of frontal and parietal regions in executive function? Research has concluded that the prefrontal cortex (PFC) is a core area in executive function, but it also relies on the inputs from other regions such as the posterior cortex to facilitate the process [Bunge and Souza, 2009; Carpenter et al., 2000; Miller and Cohen,

2001; Miller and Wallis, 2009]. Miller and Cohen have proposed a model of executive function, which includes three components of neuronal activity: *inputs*, *internal states*, and *outputs* [Miller and Cohen, 2001]. The PFC receives sensory inputs such as visual, somatosensory, and auditory information from the occipital, temporal, and parietal regions as the PFC is connected to secondary or association sensory cortex. The intrinsic connections communicating between sub-regions in the PFC allow information to be processed and distributed to other sub-regions, which facilitates the core process (i.e. intensive “thinking”) of executive function. Finally, the processed information has to be executed through motor outputs such as motor association areas and subcortical regions as recent research states [Monchi et al., 2006; Owen, 2004]. Therefore, the connections between frontal regions and sensory cortices become indispensable as these are the inputs for executive processes. Of note, the central executive network identified by rsfMRI includes both prefrontal areas as well as parietal areas. Only a few of the studies included in this chapter report connectivity alterations in the temporal cortex [Richiardi et al., 2012], and there is not enough information to conclude whether connectivity in the temporal areas is strongly associated with executive functions in PD and MS. Although several imaging studies have reported cortical changes in the temporal areas, not all the cortical alterations show strong correlation to executive dysfunction [Achiron et al., 2013; Möller et al., 2016; Tam et al., 2005]. Overall, the results of connectivity in temporal regions are inconsistent. Therefore, we concluded that impaired long-range connections bridging frontal, parietal, and occipital areas possibly damage the “*inputs*” component, resulting in executive dysfunction seen in clinical presentation (Figure 1.2).

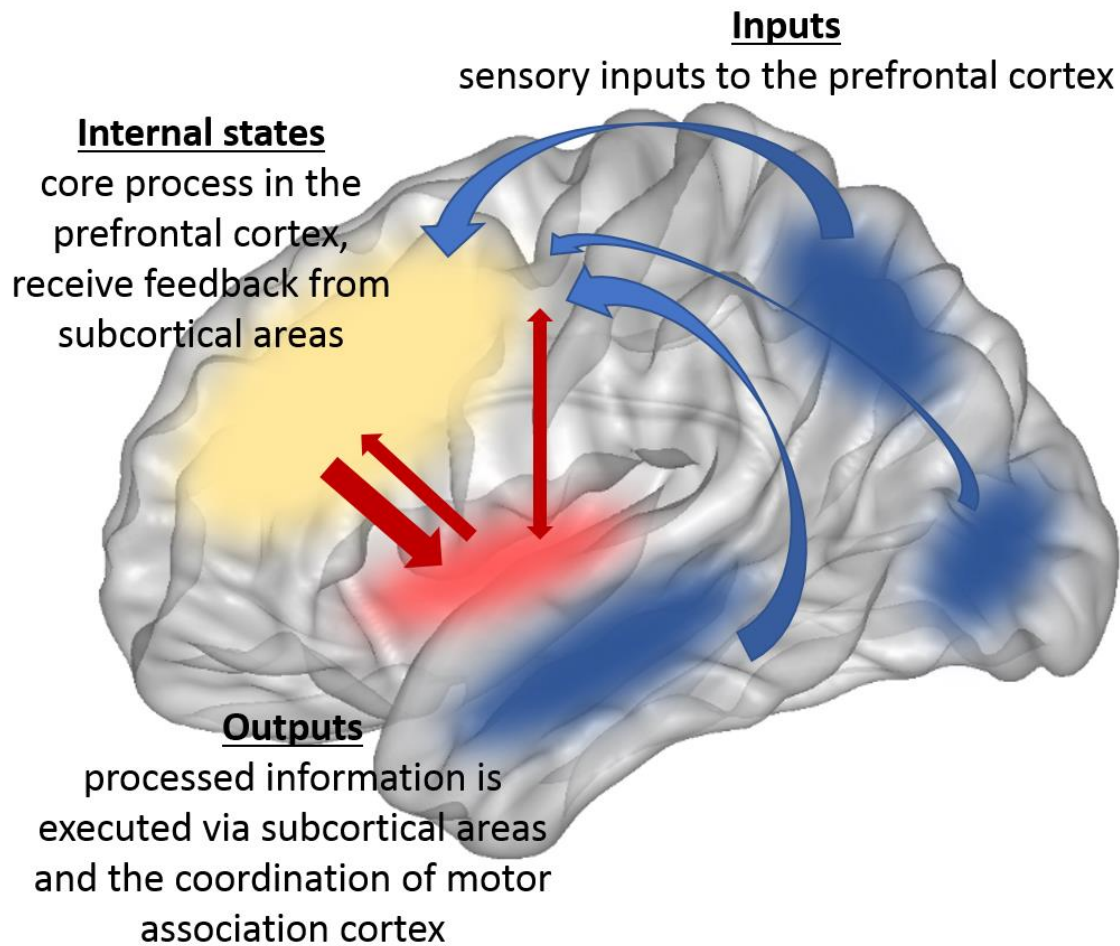


Figure 1.2 A model of executive function. This diagram incorporates anatomical information into the model proposed by Miller and Cohen [Miller and Cohen, 2001] and illustrates how information flows between the three components: inputs, internal states, and outputs. The blue curved arrows represent the sensory inputs coming from parietal, occipital, and temporal lobes to the prefrontal cortex. The yellow gradient illustrates where the core process happens in internal states, which is the prefrontal cortex. Red straight arrows show the outputs are sent to subcortical areas to execute (thick red arrow) as well as the feedback information (thin red arrow) coming from subcortical regions, which are labeled with red gradients. The thin red double arrow indicates the coordination between subcortical regions and the motor association cortex.

Another well-known model of executive function is the dorsolateral prefrontal circuit, which is one of the frontal-subcortical circuits [Bonelli and Cummings, 2007]. The dorsolateral prefrontal circuit mediates executive function through the neurons which originate in the prefrontal lobes and project between the dorsolateral prefrontal cortex, caudate nucleus, globus pallidus, and thalamus. Early evidence that patients with lesions in this loop demonstrated executive deficits measured in neuropsychological assessments emphasized the role of the dorsolateral prefrontal circuit in executive function [Bonelli and Cummings, 2007]; however, the model neglects regions which are not directly linked to this circuit, potentially providing an over-simplified viewpoint of executive functioning in humans.

Working memory has been proved to be strongly correlated with executive function and also relies on connections in prefrontal-parietal regions. For example, in neuroimaging studies, the dorsolateral prefrontal cortex and parietal regions were involved in both working memory and executive tasks [Carpenter et al., 2000], while behavioural studies showed the correlation between working memory capacity and executive function was higher than that between other domains [McCabe et al., 2010]. However, executive function is not the same as working memory even though certain activation patterns overlap. In fact, many tasks which assess executive function also require working memory ability, which makes it difficult to isolate working memory from executive function explicitly. The literature presented in this chapter suggests that long-range connections between prefrontal and parietal regions are essential for executive function in neurological disease, and are also important for working memory. Further neuroimaging research is needed to profile the neural patterns of these domains, such as network dynamics and cortical coordination.

1.4.3 Unique features of brain organization in different neurological conditions may all result in executive dysfunction

We have proposed that impaired long-range connectivity might be one of the common causes of executive dysfunction in MS and PD. In addition to this common impairment, there are unique features which may contribute to cognitive deficits. As executive function requires flexibility to switch approaches [Diamond, 2013], it has been shown that the neuronal connectivity of executive function involves abilities to dynamically recruit different brain regions and coordinate information in a flexible manner, including or excluding networks based on the neuronal need to overcome the trade-offs between wiring cost and connectivity [Braun et al., 2015; Bullmore and Sporns, 2012; Mattar et al., 2015]. This brain organization principle, which has been mentioned previously (section 1.2.2) as *dynamic functional connectivity*, has been referred to as one of the fundamental aspects of higher-order cognition (i.e. the cognitive processes that require intensive thinking and planning) [Bressler and Scott Kelso, 2001; Hutchison et al., 2013a; Stephens et al., 2013]. Furthermore, as human brain volume has increased in evolution, the efficiency of information transfer in long-range connections has become more important for cognition [Hofman, 2014]. Proposals have been made that *hub regions* are formed to better propagate information flow between distinct brain regions by reducing wiring cost and these hubs are especially active in higher-order cognition [Baggio et al., 2015; van den Heuvel and Sporns, 2013; Hofman, 2014; Power et al., 2013]. Altered hub organization reduces efficiency of information flow between anatomically segregated regions in MS, contributing to cognitive deficits. The executive deficits in PD are perhaps also caused by impaired frontostriatal connectivity [Owen, 2004], which may damage the “output” component of execution function. Moreover, abnormal brain organization

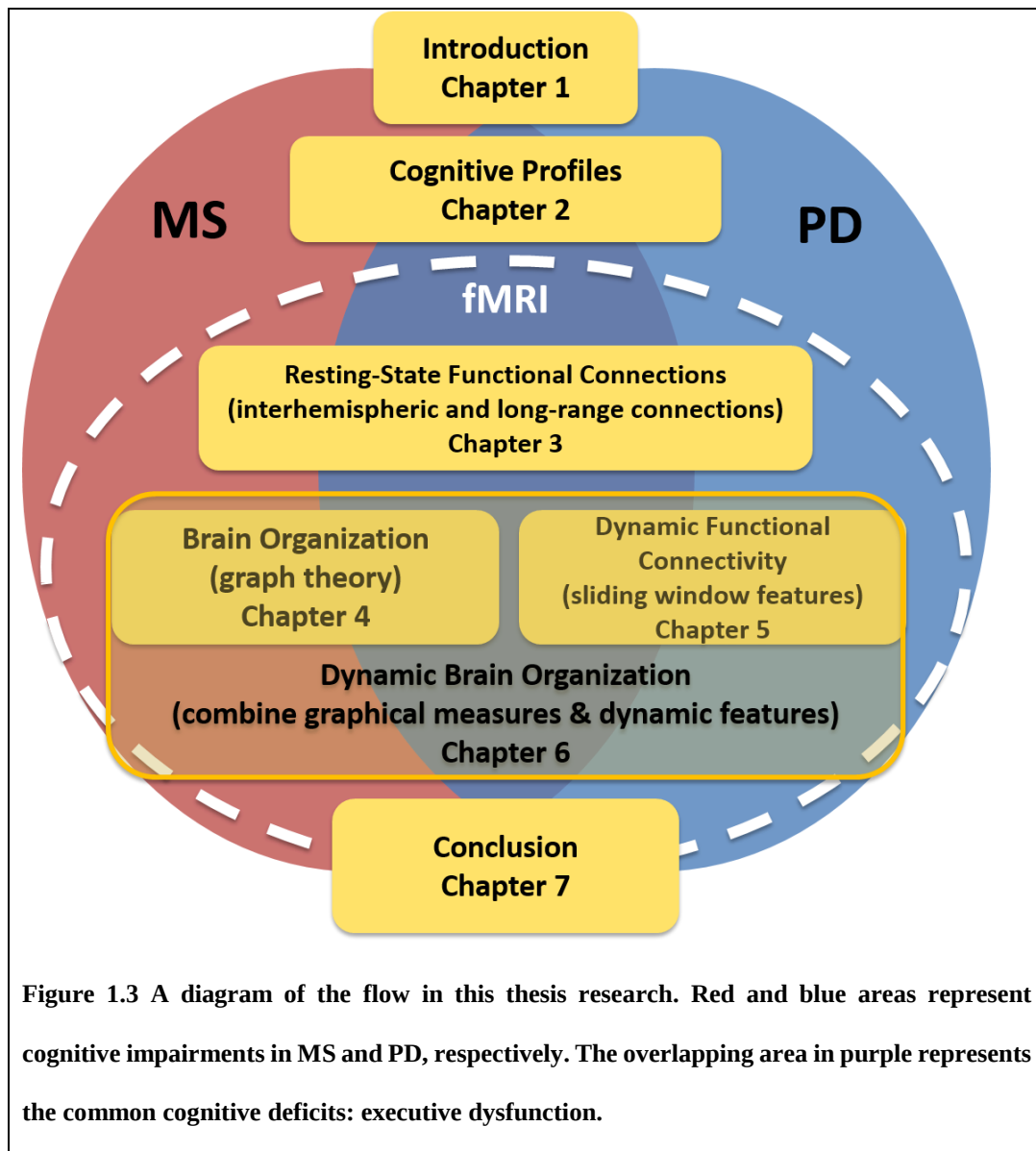
such as decreased dynamic connectivity and hub changes may contribute to executive dysfunction as well.

Taken together, both *hub organization* and *dynamic functional connectivity* are key factors to facilitate higher-order cognition including executive function. Losing dynamic coordination and/or efficiency of information transfer may contribute to clinical deficits including cognitive dysfunction in several brain disorders [Fornito et al., 2015]. Therefore, we argue that *dynamic functional connectivity*, impaired in PD due to neurotransmitter dysregulation, probably causes executive dysfunction; while altered *hub organization* in these two conditions contribute to executive deficits unequally as the affected hubs are not exactly the same.

1.5 Research objectives and thesis organization

Traditional research which investigates functional connectivity and cognitive decline in PD and MS has focused on specific loops and regions. The approaches that have thus far been applied neglect that 1) compensation effects may occur in many locations of the brain, 2) higher-order cognitive function, which appears to impact quality of life the most, requires not only frontostriatal loops but other remote regions, and 3) temporal variation of functional connectivity potentially plays a prominent role in cognition. Several studies utilizing advanced network analyses to investigate brain organization in healthy and disease populations have demonstrated promising preliminary results. These analyses on whole brain rsFC have revealed that functional integration, functional segregation, dynamic functional connectivity, and hub structures are necessary and indispensable to executive functioning. However, clinical research that applies these analyses to study the associations between executive function, clinicopathology, and rsFC remains limited. **In this dissertation, the goal is to highlight the importance of brain organization to executive**

function with the use of advanced network analyses (e.g. graph theoretical theory and time-varying approaches) and explore the relations between cognition, clinicopathology, and brain organization in two representative neurological conditions. Figure 1.3 illustrates the overall flow of the thesis.



In the following chapters, we utilize different data sets:

- **The Parkinson's Progression Marker Initiative (PPMI).** This is a publically-available data set funded by The Michael J. Fox Foundation for Parkinson's Research, containing advanced imaging, biologic sampling, clinical and behavioural assessments with the goal of identifying biomarkers of Parkinson's disease progression. We included one cohort in the PPMI database which contained 31 subjects as all the subjects were scanned in the same medical centre. This data set is included in chapter 2 and 4.

- **The COGMS data set.** This data set was generated from a MS-society grant (awarded to MacKay and McKeown). The original design was to evaluate advanced structural imaging features, resting-state fMRI measures, and cognitive profile in subjects with MS and combine three components together to study the relations between structural integrity, functional connectivity, and cognitive performance (particularly executive function). Forty-six MS subjects were included in chapter 2,4,5, and 6 as well as a subset of age-matched MS and control subjects.

- **The BCT data set.** This was data acquired in Pacific Parkinson's Research Centre (PPRC) and the original design included task-driven fMRI and resting-state fMRI to evaluate the functional connectivity under a motor task and at rest rather than brain-cognitive relations. Therefore, there were limited cognitive measures. Twelve PD subjects and ten healthy controls were included and the data was used in chapter 3.

- **The OPERA data set.** This was a phase III clinical trial conducted in MS clinic at UBC Hospital and supported by F. Hoffmann-La Roche, Ltd. The purpose was to evaluate the effects of Ocrelizumab using both structural and functional MRI. Only the baseline resting-state fMRI data were included in this thesis research (chapter 3, 25 MS and 41 controls); therefore, the results described here were independent to pharmaceutical interventions.

- **The GFM2 data set.** These data were acquired in Pacific Parkinson's Research Centre (PPRC) and the design was to identify biomarkers for PD and evaluate the effects of vestibular stimuli interventions using advanced structural MRI, resting-state fMRI, and task-driven fMRI (with stimulus). Clinical assessments were done in both 24 PD and 15 healthy subjects. The data were included in chapter 5 and 6.

Since this work is from a pooling of different data sets, some of the cognitive tests are not perfectly aligned across studies. However, for the studies which assessed cognitive performance, several domains are commonly evaluated in both disease populations such as executive function, processing speed, working memory, and attention.

Chapter 2: Cognitive profiles in Parkinson's Disease and Multiple Sclerosis

In this chapter, the cognitive profiles in PD and MS are investigated utilizing a machine-learning approach – Canonical Correlation Analysis (CCA), which can be seen as an extension of a multivariate linear regression model. The purpose of the study is to explore the associations between cognitive domains, demographical characteristics, and clinical data such as diseases severity and comorbidity. The results shall help understand how the disease affects cognitive functions in neurological disorders.

2.1 Introduction of cognitive profiles in Parkinson's Disease and Multiple Sclerosis

Parkinson's disease (PD) is a neurodegenerative movement disorder resulting in motor symptoms of tremor, rigidity, bradykinesia, and postural instability. In addition to motor symptoms, non-motor deficits, especially cognitive impairments, have a major impact on quality of life in patients with PD. Patients with PD show cognitive deficits in several common domains such as attention, memory, visuospatial, and executive functions [Pagonabarraga and Kulisevsky, 2012; Poewe, 2008]. These cognitive deficits are typically assessed with such tasks as Digit Span, the Tower of London Test (ToL), the Trail-Making-Test (TMT), and the Verbal Fluency Task [Miller et al., 2013; Williams-Gray et al., 2007]. Older age, non-tremor subtype, and higher Unified Parkinson's Disease Rating Scale (UPDRS) scores are risk factors for the rapid overall cognitive decline [Williams-Gray et al., 2007], and specifically, information retrieval and visuospatial abilities can predict global cognitive impairments in PD. Rather than simply categorising patients into cognition-intact and cognition-impaired subtypes, there is substantial heterogeneity of cognitive

performance in PD, and “frontal”, “posterior”, and “mixed” subtypes have been proposed [Miller et al., 2013]. Related details of cognitive subtypes in PD have been described previously in section 1.1.2. In short, patients with the “frontal subtype” commonly demonstrate executive dysfunction related to decreased dopamine levels in frontostriatal circuits. Patients with the “posterior subtype” constantly show visual-spatial problems related to parietal-temporal deficits as well as degeneration of cholinergic fibers. The disease severity of this subtype can predict dementia and patients often demonstrate symptoms of postural instability and gait disorder (PIGD). Patients with the mixed subtype cannot be easily categorized into the above subtypes. As a result, subtypes proposed in the “dual syndrome hypothesis” are overlapping with the frontal/posterior subtypes [Kehagia et al., 2012; Miller et al., 2013].

Traditional cognitive tests typically attempt to probe one aspect of cognition (e.g. attention), but it is very difficult to test components of cognition in an isolated fashion. Hence performance on different cognitive tests often correlate with each other, and it is likely that novel analyses utilizing machine-learning approaches will be more suitable in establishing overall cognitive profiles in subjects with neurological disorders.

Multiple sclerosis (MS) is a neuroinflammatory disease which causes sensory and motor disturbances, diplopia, ataxia, bladder disturbance, fatigue, and cognitive dysfunction [Gelfand, 2014]. Among these symptoms, cognitive impairments may have a strong impact on subjects’ daily lives as the commonly affected cognitive domains in MS include impaired information processing speed, attention, memory, and executive function [Wallin et al., 2006]. A characteristic feature of MS is that more women are affected than men. In addition to prevalence, gender differences have been addressed in MS with respect to genetic susceptibility, clinical presentation,

effects of sex hormones, immune system, and response to therapy [Harbo et al., 2013]. Previous studies have proposed several links between gender effects and neuroimaging findings such as cortical atrophy, functional connectivity, and white matter changes [Savettieri et al., 2004; Schoonheim et al., 2012a; Schoonheim et al., 2012b]. However, despite the clinical importance of cognition for overall well-being in the MS population, research on the direct association between gender and cognitive dysfunction has not been widely reported in MS.

Schoonheim et al. demonstrated that male subjects with MS showed significantly lower cognitive scores compared to male controls in several cognitive domains such as executive functioning, verbal memory, processing speed, working memory, attention, and psychomotor speed, yet these domains were relatively preserved in female subjects [Schoonheim et al., 2012b]. The authors also found that male subjects had a better correlation between subcortical volume and a crude cognitive marker (the average Z-score of a battery of cognitive tests). In addition, significant white matter changes such as lower fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) in diffusion tensor imaging (DTI) data have been observed in male subjects who had lower cognitive Z scores, but not in female subjects whose cognition was relatively intact [Schoonheim et al., 2014]. In fMRI, male subjects demonstrated decreased resting state functional connectivity as well as lower network efficiency in association with deteriorating cognitive performance [Schoonheim et al., 2012a], especially reduced visuospatial memory. While these studies have focused on the relationship between cognitive dysfunction and functional/structural changes in the brain, less emphasis has been on the characterization of cognitive differences and gender effects in MS.

Several factors appear to be predictors of cognitive dysfunction in MS: early age of onset, male sex, secondary progressive course, neurodegeneration, and low baseline intelligence [Benedict and Zivadinov, 2011]. Male subjects are more likely to develop a severe disease course including physical disability and cognitive impairments. In MS subjects, it appears that cognitive dysfunction in females is less dependent on factors such as physical disability, while cognitive decline in males is correlated with Expanded Disability Status Scale (EDSS), age, disease duration, and education level [Savettieri et al., 2004]. Another study also found that female subjects performed better on the Mini Mental State Examination (MMSE), Wisconsin Card Sorting Test (WCST), language, and memory tests in Repeatable Battery for the Assessment of Neuropsychological Status Update (RBANS) [Beatty and Aupperle, 2002]. Thus, male subjects appear to be particularly cognitively vulnerable in MS.

In this study, eight neuropsychological tests that employed executive function were administered to an MS cohort (13 males, 33 females). Since these tests all probe aspects of executive function, it is likely that performance in these individual tests will be related to (correlated with) one another, yet each test still likely provide unique information. It is therefore desirable to determine if the tests could be judiciously combined in some way and if overall performance across the neuropsychological tests. Specifically, we wanted to establish if there was an established overall pattern of neuropsychological deficits seen in MS, and if this pattern of deficits could be predicted based on disease severity and other demographic factors, including gender. Our implicit hypothesis is that a combination of gender, age, education, and clinical indices will correspond with a combination of results seen in neuropsychological tests. In order to achieve this, we employed canonical-correlation analysis (CCA), a type of machine learning method used to identify patterns

in large data sets. We show that a combination of demographic (i.e., gender, age, education, alone or in combination) and clinical indices (i.e., disease duration, severity of disability, affective states) accurately predicts results of frontal lobe testing. When we then interrogated the particular combination of demographic factors that predicted neuropsychological test performance in MS, we found that gender had the greatest influence.

In the PD cohort, the same method was applied to investigate the cognitive profiles and the relations to demographics in PD, specifically whether gender also contributed to cognitive differences.

2.2 Materials and methods

2.2.1 Subjects

PD data are from the Parkinson's Progression Marker Initiative (PPMI) and MS data are from COGMS project.

Thirty-one subjects with PD who enrolled in the PPMI were included in the study. All subjects underwent neuropsychological assessments and imaging scans with T1-weighted MRI and resting-state fMRI (rsfMRI). All data in this study were acquired at baseline (fMRI results are reported in another chapter). The inclusion criteria required subjects must show at least two of the following: resting tremor, bradykinesia, rigidity or either asymmetric resting tremor or asymmetric bradykinesia. Subjects had a diagnosis of PD for two years or less, Hoehn and Yahr stage I or II, off medication, age 30 years or older at diagnosis, and ability to provide written consent. Exclusion criteria included atypical PD syndromes, taking any PD medication, taking levodopa or dopamine agonists prior to baseline for more than a total of 60 days, dementia (screened by Montreal

Cognitive Assessment (MoCA)), and any other medical or psychiatric condition or lab abnormalities. Demographics were shown in Table 2.1. For the analysis of cognitive profiles, all 31 subjects were included and three of them showed MCI.

Forty-six relapsing-remitting MS subjects (13 males, 33 females) were enrolled in a study examining the relations between results of various MRI sequences (including Diffusion Tensor Imaging, Myelin Water Imaging, lesion load, resting state fMRI functional connectivity, and cortical thickness), cognitive performance, clinical measures and demographics. For the purposes of this chapter, we focus on clinical measures and demographics (Table 2.2) as the imaging will be the subject of another report (in other chapters). All the subjects fulfilled the McDonald criteria for MS diagnosis and were recruited from the MS clinic at the UBC Hospital. Referrals underwent a telephone screen and subjects with significant untreated depression and/or other psychiatric illness, learning disabilities, history of drug or alcohol abuse, had used steroids in the last 3 months or evidence that they were in an active flare were excluded from this study. Subjects were also screened for adequate motor skills for their ability to manipulate a pencil which would have direct impact on some of the tasks (i.e., Coding and Symbol Search). Ethics approval was issued by the University of British Columbia's Research Ethics Board and all subjects provided signed informed consent.

	Parkinson's subject (mean±SD)	
	10 females	21 males
demographics & clinical data		
age	59.85±10.8	61.48±9.4
UPDRS	17.3±7.1	14.67±12.9
depression	4.7±1.2	5.43±0.9
education in years	17.1±2.3	16.67±3.2
cognitive scores		

MOCA	27.8±2.1	27.38±2.1
BJLOTOT	25.2±4.0	25.24±4.0
HVLTTOT	25.2±5.8	22.43±5.2
HVLTDELAY*	9.9±2.4	7.57±2.7
DVT-HVLTOTAL*	53.3±13.3	40.05±13.1
DVT-HVLTDELAY*	57.5±9.1	45.29±17.4
DVT-HVLTRETENTION	56.6±8.7	49.61±16.1
LNS-RAW	11.0±2.5	9.9±2.7
SFCOM	52.1±11.9	45.10±9.8
SFVEG*	15.6±3.9	12.28±3.7
SFANI	21.0±5.5	21.29±4.9
SFFRU*	15.5±4.3	11.52±2.8
SDMT	41.10±9.8	39.67±9.0

Table 2.1 Demographics, clinical data, and cognitive scores in PD subjects.

[UPDRS = Unified Parkinson's Disease Rating Scale, MOCA = Montreal Cognitive Assessment, BJLOTOT = Bento Line Orientation Total Score, HVLTTOT = Hopkins Verbal Learning Test-Revised Total Score, HVLTDELAY = HVL T Delayed Recall Score, DVT-HVLTOTAL = standardized HVL T Total Score, DVT-HVLTDELAY = standardized HVL T Delayed Recall Score, DVT-HVLTRETENTION = standardized HVL T Recognition Trial Score, LNS-RAW = raw Letter-Number Sequencing Test Score, SFCOM = Semantic Fluency Test – combination, SFVEG = Semantic Fluency Test – vegetable trial, SFANI = Semantic Fluency Test – animal trial, SFFRU = Semantic Fluency Test – fruit trial, SDMT = Symbol Digit Modalities Test]

* Differences in two-sample t-test with $p < 0.05$

	Multiple sclerosis subjects (mean±SD)	
	33 females	13 males
Demographics & Clinical measures		
Age	41.1±10.3	45.8±11.6
Education (years) *	15.3±2.2	13.7±2.7
EDSS	2.3±1.6	1.9±1.5
Disease duration (months)	129.0±86.2	128.9± 133.1
Neuropsychological scores		
WAIS Digit Span ScS	9.0±2.5	8.2±2.2
Arithmetic ScS	9.0±2.6	8.9±3.3
Letter Number Sequencing ScS	9.6±2.7	8.8±2.4
Symbol Search ScS	10.4±3.5	9.2±3.2
Coding ScS	10.3±2.6	9.0±2.1

Working Memory Index SS	93.7±12.4	91.0±14.7
Processing Speed Index SS	101.9±16.0	94.5±14.1
FAS ADJ	41.0±10.7	37.4±14.4
WCST Errors SS	93.1±13.7	82.2±19.0
Perseverative Responses SS	92.3±12.6	86.2±23.6
Perseverative Errors SS	91.1±12.9	86.3±23.6
Categories Completed Raw ***	5.5 ±1.1	3.3±1.9
Trials to Complete First Category Raw***	12.7±4.4	38.6±38.3
Failure to Maintain Set Raw	0.5±0.8	1.0±1.6
Learning to Learn Raw	N/A	N/A
TMT A Raw *	30.7±12.3	40.3±13.3
Z	-0.7±1.5	-1.2±1.4
E Raw	0.2 ±0.4	0.1±0.3
TMT B Raw	74.2±61.0	110.7±49.8
Z	-0.5±2.3	-1.5±2.5
E Raw	0.4±1.0	0.6±1.1
MDI Total Score Raw	31.9±22.4	38.3±21.8
T	47.3±8.9	52.7±10.2
STAI State SS	49.8±10.4	50.2±9.7
Trait SS	54.6±12.5	58.5±7.8
FSS Raw	38.2±15.2	35.2±14.8

Table 2.2 Demographics, clinical measures, and neurological scores in MS subjects.
[WAIS: Wechsler Adult Intelligence Scale—Fourth Edition, FAS: Verbal Letter Fluency Test, WCST: Wisconsin Card Sorting Test, TMT A: Trail Making Test A, TMT B: Trial Making Test B, MDI: Multiscore Depression Inventory, STAI: State-Trait Anxiety Inventory, FSS: Fatigue Severity Scale, ScS: scaled score adjusted by age, SS: standardized score, ADJ: adjusted for age/gender/education, Raw: raw score, Z: Z score, E: error, T: t score, N/A: more than 5 missing data sets]

*** Differences in two-sample t-test with $p < 0.05$**

***** Differences in two-sample t-test with $p < 0.001$**

2.2.2 Test battery

The neuropsychological assessments performed on PD subjects have been previously described [Lebedev et al., 2014]. In total, there were 13 scores from the assessments included MoCA, Benton Judgment of Line Orientation (BJLO), raw Hopkins Verbal Learning Test-Revised (HVLRT), raw

HVLT delayed recall, standardized HVLT, standardized HVLT delayed, standardized HVLT recognition trial, raw Letter-Number Sequencing test (LNS), Semantic Fluency Test – combination (SFCOM), Semantic Fluency Test – vegetable trial (SFVEG), Semantic Fluency Test – fruit trial (SFFRU), Semantic Fluency Test – animal trial (SFANI), and Symbol Digit Modalities Test (SDMT) scores (Table 2.1). MoCA screened for overall cognitive functions, BJLO evaluated visuospatial function, HVLT assessed verbal memory, executive functions were evaluated by the Fluency test and MoCA subtests, and SDMT and LNS tested attention. Therefore, memory, visuospatial, and attention/executive functioning domains were measured in this study, which were the most common affected domains in PD. Questionnaires for depression were also administered to measure affective symptoms.

All MS subjects underwent eight psychometric measures assessing processing speed, working memory, executive function, and attention. This battery was selected not for clinical purposes. The tests included WAIS IV (Wechsler Adult Intelligence Scale IV) subtests (Digit Span, Arithmetic, Letter Number Sequencing, Symbol Search, and Coding), Verbal Letter Fluency Test (FAS), Wisconsin Card Sorting Test (WCST), and Trail Making Test A and B (TMT A and B). Composite Index scores from the WAIS IV were also obtained including Working Memory Index (WMI) which utilized scores from Digit Span, Arithmetic, and Letter Number Sequencing subtests. The WAIS IV Processing Speed Index (PSI) is based on the Symbol Search and Coding subtests. Clinical questionnaires were also administered in order to examine affective status, which included Multiscore Depression Inventory (MDI) and State-Trait Anxiety Inventory (STAI). The other measure administered was a widely used fatigue measure in the MS field, the Fatigue Severity Scale (FSS). The duration of the assessment was approximately one hour. Raw cognitive

scores were converted to standardized scores using published normative data that considers psychometric factors such as age, education and gender. The patient's disability rated by the Kurtzke Expanded Disability Status Scale (EDSS) was determined by a neurologist at the time of recruitment or scanning.

Although the test batteries were different between PD and MS groups, some sub-tests were the same. The Letter Number Sequencing (LNS) and the Verbal Fluency Test (SFCOM in PD, FAS in MS) were included in both test batteries. In addition, the Symbol Digit Modality Test (SDMT) in PD was very similar to the Coding sub-test in MS and they both evaluated processing speed.

2.2.3 Analysis

Two-sample t-tests (two-tailed) were carried out with all the scores in male and female groups. Transformed scores were calculated in R (version 3.2.0)- which is a language and environment for statistical computing- if normality did not hold. CCA [Krzanowski, 1988] was done in MATLAB (The MathWorks, Inc.) to determine if demographics were related to cognitive scores. CCA was chosen to study the multivariate data and it can be considered one of the original “machine learning” algorithms that are now used to explore “big data” in many fields [Correa et al., 2008; Donner et al., 2006; Palmer, 1993]. The advantage of the CCA method is that it is an extension of regression that enables additional factors to be included. If we have two sets of correlated variables (e.g the performance on the neuropsychological tests will likely be correlated, and some demographic factors such as disease duration and age will likely be correlated), CCA attempts to find the linear combinations of these two sets of variables that maximally correlate with each other. Note that this will likely be a more powerful approach than regression where one could try and

predict the neuropsychological performance on 1 test – i.e. in regression one only has 1 dependent variable.

In PD, the two sets were the cognitive scores measured by neuropsychological assessments and the demographics of 31 PD subjects. The demographics included gender (encoded as female 2 and male 1), age, UPDRS scores, Depression, and years of education. The cognitive scores included MoCA, BJLO, raw HVLТ, raw HVLТ delayed recall, standardized HVLТ, standardized HVLТ delayed, standardized HVLТ recognition trial, raw LNS, SFCOM, and SDMT scores. As in semantic fluency, the combination trial should represent the performance of semantic fluency in animal, vegetable, and fruit trials, so we only included SFCOM instead of taking all 4 scores. All scores were normalized into z-scores before CCA. We performed CCA in leave-one-out fashion, to ensure robustness of our results, and reported the loadings (i.e. the correlation between transformed CCA data and raw scores) for each variable. Specifically, we excluded one subject at a time and performed the CCA analysis each time. The variability in the weightings/loadings, when each of the subjects was removed, was recorded. This gives an estimate of how much the results could change if more subjects were added. If the 95% confidence intervals based on the cross-validation of each variable did not cross zero, we regarded this variable as a significant contributor to the CCA model.

In MS, in keeping with prior neuropsychological approaches, we analyzed timed and untimed tests separately. We performed CCA on cognitive scores divided into two groups (timed and untimed tests) and demographical variables. The “timed group” included 4 affective variables (Multiscore Depression Inventory Total T scores, State-Trait Anxiety Inventory standardized State scores and Trait scores, and Fatigue Severity Scale Raw scores) and 8 variables from the tests in which

subjects were timed during performance, including 3 scaled scores in WAIS-IV (Arithmetic, Symbol Search, and Coding), Verbal Letter Fluency Test, and 4 measures of Trail-Making Tests (transformed TMT A scores, TMT A Z scores, transformed TMT B scores, and TMT B Z scores). Due to non-normality, raw scores of TMT A and B were transformed by taking the square root of the reciprocal of the raw scores (the transformed score could be expressed as the following: $\sqrt{\frac{1}{TMT\ raw\ scores}}$). In the “untimed group”, 4 affective variables (same as “timed group”) and 8 cognitive variables from the tests in which subjects were not timed were included. The cognitive 8 variables were 2 scaled scores in WAIS-IV (Digit Span and Letter Number Sequencing) and 6 measures in WCST (standard score of Errors, Perseverative Response, Perseverative Errors, raw scores of Categories Completed, Trials to Complete First Category, and Failure to Maintain Set). Age, gender, education, EDSS scores, and disease duration were included as demographical variables in both groups. Of note, due to the data and sample size, we did not perform analysis in different groups in PD.

Calculations were performed in leave-one-out fashion to control for multiple comparisons and ensure the robustness of our results as previously described. The error bars indicated the variability of the results across subjects.

2.3 Results

2.3.1 PD

In PD, CCA revealed that demographics/clinical data were inter-correlated with cognitive scores (Figure 2.1). In the combination of demographics and clinical data, gender, age, depression, and

education all showed significant canonical loadings, but UPDRS scores did not have an impact on this model. In the combination of cognitive scores, all variables demonstrated significant loadings except the standardized HVLT Recognition Trial Score. Variables with loadings the same sign were correlated with each other (i.e. negative loadings in demographics were positively correlated with negative loadings in cognitive scores) and anti-correlated with the variables that demonstrated the opposite sign. The two linear combinations of these two sets of variables were significantly correlated with each other with a correlation coefficient of 0.90 and $p=0.011$.

The model demonstrated gender differences of cognitive performances in PD, where female subjects with more years of education were related to higher scores in almost all cognitive tests as they showed higher performance z-scores than males (Appendix A.1). Further analyses supported this observation, as the mean z-scores of all cognitive tests/variables with significant CCA loadings were higher in female subjects than male subjects except the BJLO test (Appendix A.1). Therefore, the variable gender in the model (shown in Figure 2.1) demonstrated an overall common effect to cognition across tests rather than specific patterns in individual tests. Similarly, education supported overall cognitive functions in PD. Meanwhile, higher age and higher scores in depression scale were anti-correlated with all cognitive scores which showed significant loadings, implying that aging and PD comorbidities such as depression worsened cognitive abilities.

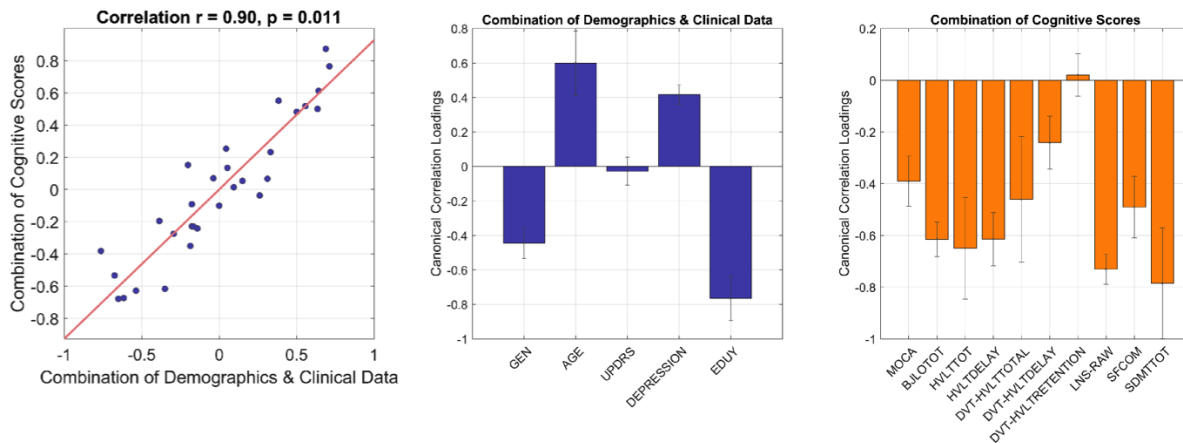


Figure 2.1 The CCA model shows inter-correlated cognitive patterns with demographics and clinical data in PD. The linear combination of demographics/clinical data is significantly correlated with the linear combination of cognitive performances with correlation coefficient 0.90 and p 0.01 (left panel, cross-validation with leave-one-out). Gender, age, depression, and education have significant loadings in the combination of demographics and clinical data (middle panel, i.e. 95% confidence interval does not cross zero as indicated by error bars). In the combination of cognitive scores (right panel), all the variables show significant loadings except standardized HVL T Recognition Trial Score as the 95% confidence interval crosses zero. [GEN: gender, EDUY: education in years, MoCA: Montreal Cognitive Assessment, BJLOTOT = Bento Line Orientation Total Score, HVLTTOT = Hopkins Verbal Learning Test-Revised Total Score, HVLTDLAY = HVL T Delayed Recall Score, DVT-HVLTTOTAL = standardized HVL T Total Score, DVT-HVLTDLAY = standardized HVL T Delayed Recall Score, DVT-HVLTRETENTION = standardized HVL T Recognition Trial Score, LNS-RAW = raw Letter-Number Sequencing Test Score, SFCOM = Sematic Fluency Test – combination, SDMTTOT = Symbol Digit Modalities Test total scores]

2.3.2 MS

In MS, CCA results showed that gender (mean canonical coefficient: timed = 1.01, untimed = 0.94) appears to be an important factor (i.e. weightings can be distinguished from zero) in the combination of demographics for both timed and untimed tests. In the untimed group, EDSS (mean canonical coefficient: 0.26) was influential in addition to gender. Age, education, and disease duration showed limited effects on both timed and untimed tests (mean canonical coefficient: timed/untimed = 0.07/0.00, 0.03/-0.05, -0.02/-0.03, respectively) (Figures 2.2&2.3).

Since we assigned gender male as 1 and female as 0 in the calculation, the variables which showed positive canonical coefficient indicated higher scores in male subjects as long as gender also showed positive weightings. On the other hand, the tests on which female subjects obtained higher scores show negative canonical coefficients. This was because the model treated female gender (0) as “baseline”. The weightings of gender indicate the effects of gender male compared to female in combination of demographics as well as combination of cognitive scores. In the “timed group”, transformed TMT A and B scores showed strongly negative effects compared to other variables (mean canonical coefficient: -28.3 and -31.8, respectively) (Figure 2.2). In contrast, the TMT A Z score demonstrated a positive mean canonical coefficient with 0.64 in the combination of cognitive scores, illustrating that there was a gender-specific pattern in timed cognitive tests where female subjects had higher transformed TMT A and B scores and male subjects had higher TMT A Z scores. In addition, the combination of cognitive scores and demographics were highly correlated with each other (correlation $r = 0.84$, $p\text{-value} < 0.001$, Figure 2.2 right panel), meaning that the linear combination of all the variables in demographics and all the variables in timed cognitive scores forms a significant model to explain and predict the data.

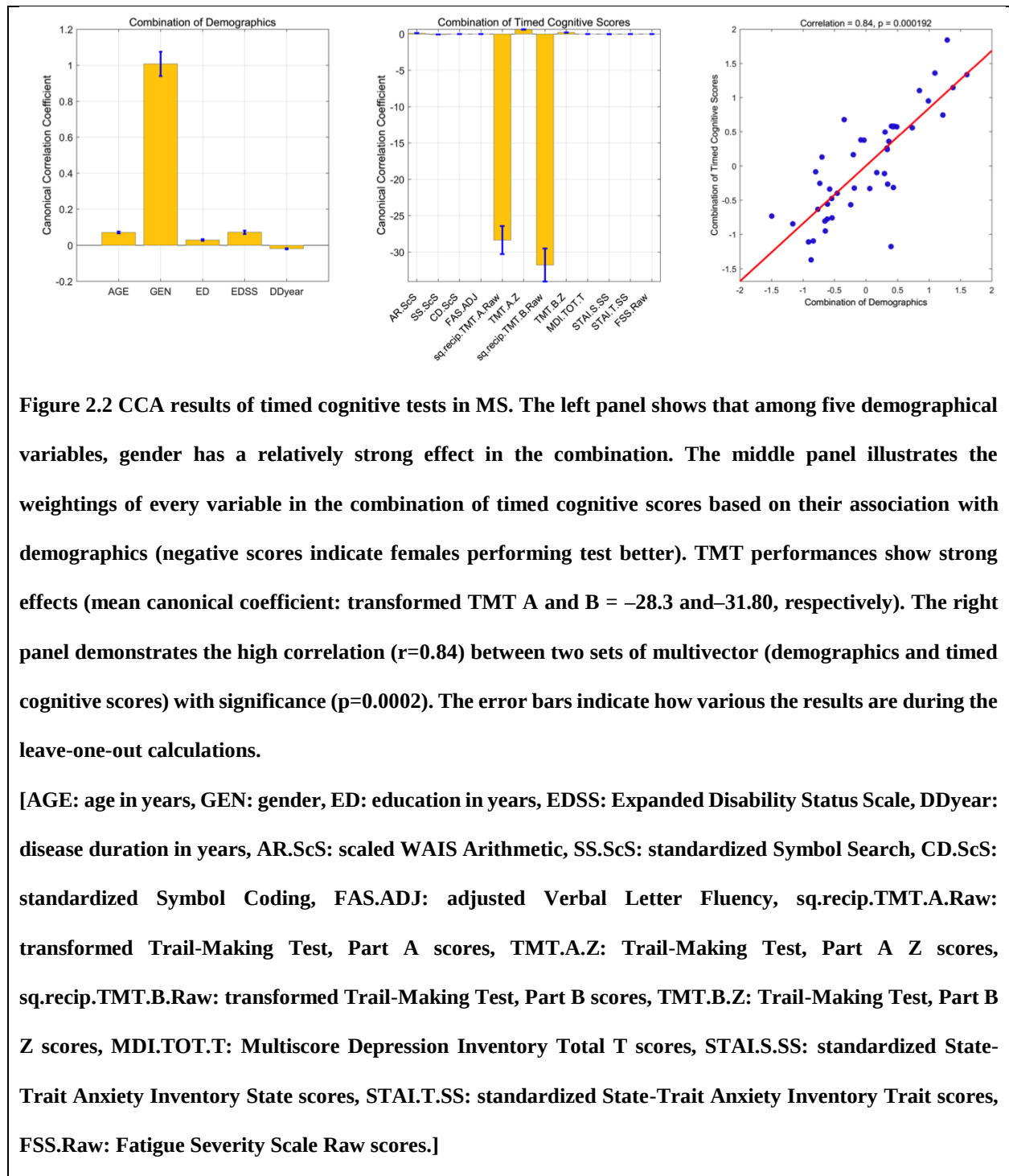


Figure 2.3 shows the results from the “untimed group”. Male subjects had higher scores (i.e. these scores showed higher weightings in male subjects) on WCST Errors, WCST Perseverative Errors, Trials to Complete First Category, Trait anxiety, and fatigue (mean canonical coefficient: 0.03, 0.14, 0.01, 0.02, and 0.01, respectively), while female subjects obtained higher scores (i.e. these scores were more influential on the linear model of all scores in female subjects) on WAIS IV Digit Span, WAIS IV Letter Number Sequencing, WCST Perseverative Responses, WCST Categories Completed, Failure to Maintain Set, and state anxiety (mean canonical coefficient: -0.03, -0.04, -0.14, -0.29, -0.06, and -0.01, respectively). This implied that female subjects completed more categories on the WCST than males, but higher Perseverative Responses also indicated that female subjects were potentially more prone to cognitive inflexibility as they changed strategies less frequently. Moreover, female subjects also did better on the Digit Span and Letter-Numbering Sequencing tasks, meaning that they had better attentional abilities since the scores of these two tests partially form Working Memory Index. Finally, the two sets of variables (combination of cognitive scores and combination of demographics) were highly correlated with each other in untimed group (correlation $r = 0.84$, $p\text{-value} < 0.001$, Figure 2.3 right panel), indicating that the linear combination of all the variables in demographics and untimed cognitive scores forms a model explaining the data.

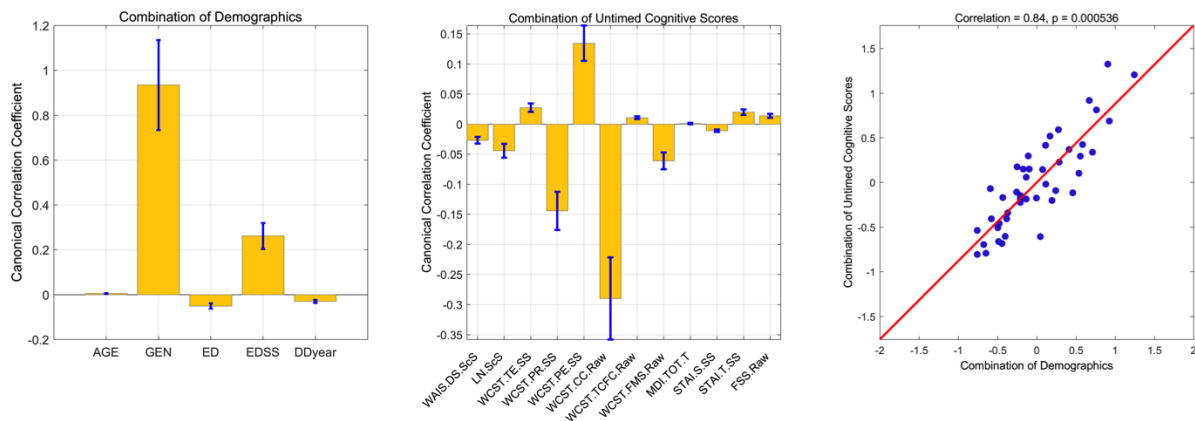


Figure 2.3 CCA results of untimed cognitive tests in MS. The left panel shows that gender and EDSS have strong effects in the combination of demographics compared with other variables. The middle panel illustrates the weightings of every variable in the combination of untimed cognitive scores. WCST Errors showed weightings in male subjects as well as WCST Perseverative Errors, transit anxiety, fatigue, and WCST Trials to Complete First Category (mean canonical coefficient: 0.03, 0.14, 0.02, 0.01, and 0.01, respectively). WAIS IV Digit Span, WAIS IV Letter-Number Sequencing, WCST Perseverative Responses, WCST Categories Completed, Failure to Maintain Set, and state anxiety demonstrated effects in female subjects (mean canonical coefficient: -0.03, -0.04, -0.14, -0.29, -0.06, and -0.01, respectively). The right panel demonstrates that these two sets of multivector (demographics and timed cognitive scores) are significantly correlated with each other ($p=0.001$, $r=0.84$). The errorbars indicate how various the results are during the leave-one-out calculations.

[AGE: age in years, GEN: gender, ED: education in years, EDSS: the Expanded Disability Status Scale, DDyear: disease duration in years, WAIS.DS.ScS: scaled WAIS Digit Span, LN.ScS: scaled WAIS Letter Number Sequencing, WCST.TE.SS: scaled WCST Total Errors, WCST.PR.SS: standardized WCST Perserverative Responses, WCST.PE.SS: standardized WCST Perserverative Errors, WCST.CC.Raw: raw WCST Categories Completed, WCST.TCFC.Raw: raw scores of WCST Trails to Complete First Category, WCST.FMS.Raw: WCST Failure to Maintain Set, MDI.TOT.T: Multiscore Depression Inventory total T scores, STAI.S.SS: standardized State-Trait Anxiety Inventory State scores, STAI.T.SS: standardized State-Trait Anxiety Inventory Trait scores, FSS.Raw: Fatigue Severity Scale Raw scores.]

2.4 Discussion

Several studies have utilized CCA to study inter-correlations between behavioural data, cognition, imaging findings, and daily activity in both healthy subjects and disease populations [Alonso Recio et al., 2013; Davis et al., 2011; Lin et al., 2017; Nilsson et al., 2016; Perry et al., 2017; Smith et al., 2015], indicating that CCA is a useful tool to study relations between two sets of data.

With CCA method, we reported that 1) there were gender specific cognitive patterns in MS and 2) some demographical variables had stronger effects on cognitive performance. More importantly, utilizing a focused test battery of tests sensitive to aspects of executive functioning, there were significant gender differences. The findings from the current study endorse the need for sensitivity to include both untimed and timed tasks in the cognitive assessment of individuals with remitting and relapsing MS. Similarly, CCA models also revealed the inter-correlated behaviour between demographics, clinical measures, and cognitive performances that are commonly impaired in PD including executive function in this study. Interestingly, we also observed gender effects in PD and some demographical data showed stronger impacts than others.

2.4.1 Cognitive profiles in PD: female gender and education support better cognitive function, while comorbidity is related to poor cognition

In PD, a CCA approach found that working memory, attention, planning, and problem solving were inter-correlated with visuospatial memory and episodic memory in early stage PD and executive function (index of working memory, attention, planning) and visuospatial memory contributed the most to cognitive deficits [Alonso Recio et al., 2013]. Although these studies have shown that there are inter-correlations in cognition and disease, gender differences have not been

previously observed in PD with a CCA approach. We found that education supported better cognitive performance in visuospatial, verbal learning, verbal memory, working memory, executive domains as well as information retrieval abilities. Our results are consistent with the concept of *cognitive reserve theory*, whereby education is one of the factors that may enhance neuronal plasticity to maximize/optimize performance or strengthen the ability to engage altered brain networks in the setting of regular aging in healthy individuals and/or neurodegenerative disease [Stern, 2002; Tucker-Drob et al., 2011; Vance et al., 2010]. The enhanced plasticity in a variety of neural circuits includes increased dendritic connections between neurons, an increase in neurotrophic factors, and stronger connections between neurons, which provides more neural resources supporting brain function and increases the capacity to cope with damages due to aging, injury, and diseases [Ansari, 2012; Vance et al., 2010]. Therefore, subjects can tolerate more insults while still being able to perform normally or even more efficiently in cognitive tests before functional impairments are apparent. As a result, the factors which trigger such alterations can be considered protective factors such as education in our study [Stern, 2002]. However, longitudinal studies have suggested that aging may be a stronger factor regarding cognitive changes than education [Tucker-Drob et al., 2011; Zahodne et al., 2011]. This is similar to what we found where both education and age showed strong loadings in the CCA model -- a pattern that has been reported in healthy subjects as well [Perry et al., 2017].

The gender differences that we discovered have been observed previously in PD, but the differences in cognition have not been extensively studied and results of non-motor symptoms have been inconsistent [Augustine et al., 2015; Miller and Cronin-Golomb, 2010]. In general, female subjects tend to perform better on many cognitive tests in older healthy subjects [Smith et

al., 2015]. However, a study with 1700 individuals with PD reported that motor-symptoms were not different between male and female, but female subjects fared better in non-motor aspects which included SDMT performance and daily functioning [Augustine et al., 2015]. Moreover, male subjects have faster decline of cognitive abilities in verbal, letter, and category fluency tests; while females tend to have worse visuospatial abilities [Corkin et al., 2003; Riedel et al., 2008]. Our results also demonstrated that females performed better in SDMT, verbal fluency tests, and overall cognition measured by MoCA, but presented with worse visuospatial function (Appendix A.1), consistent with previous research. Generally, attention, executive functioning, and overall cognitive function is relatively less affected in female PD subjects, which is possibility supported by education. The purported mechanisms of gender differences in cognition are unclear, but it has been postulated that estrogen may impart neuroprotective effects by activating receptors, altering protein expression, and activating kinase on dopaminergic pathways across cortices (e.g. the hippocampus and prefrontal cortex) in several neurodegenerative disorders [Brann et al., 2007; Green and Simpkins, 2000; Miller and Cronin-Golomb, 2010]. Moreover, estrogen therapy may prevent cognitive decline and support the abovementioned viewpoints, but the effects vary across lifetime [Sherwin, 2012].

Unsurprisingly, in PD, we found that depression had a negative effect on cognitive function, consistent with previous research [Starkstein et al., 1989]; however, we did not have evidence to probe whether cognitive decline induced depression or depression manifested cognitive dysfunction in PD – an area of debate [Menza et al., 1993]. We can only interpret that there is a strong association between the co-existence of aging and psychiatric comorbidity and poor cognitive performance that requires attention and executive abilities. Surprisingly, the commonly

used measure of overall disease severity, UPDRS, did not show significant loadings, which implied that overall motor assessment did not directly reflect cognitive decline. Motor deficits and cognitive dysfunction engage partially different pathways and systems [Sawamoto et al., 2002], but there is still a certain degree of association of degeneration as individuals with higher disease severity have a higher chance of developing cognitive impairments.

2.4.2 Cognitive profiles in MS: female gender supports better cognitive function and disease severity is related to worse performance

In MS, gender differences have been reported in previous studies which showed that females perform better than males on memory tasks and the Wisconsin Card Sorting Test [Beatty and Aupperle, 2002; Schoonheim et al., 2012a]. Moreover, male sex has been speculated as a risk factor for development of severe cognitive decline [Benedict and Zivadinov, 2011]. These studies investigated cognitive function based on the responses on cognitive tests in male and female separately. Given that cognition is a complex multi-dimensional entity which can be assessed within different domains [Heyes, 2012], it is reasonable to assume that there are multiple intercorrelated variables modulating cognition. Therefore, we investigated the *intercorrelation* from combinations of demographics and cognitive variables through CCA, determining which linear combination of demographics and cognitive scores best represent the data in two genders as a whole.

As figure 2.2 and 2.3 demonstrate, *gender* was a strong demographic factor in timed tests and both gender and EDSS were influential in untimed tests as the rest of the variables had limited effects. Demographical factors were taken into account in our model, which highlighted the fact that both EDSS and gender were influential factors for cognition in our data especially gender. Our results

were in agreement with previous research showing that gender was a predictor for cognitive dysfunction in MS and male subjects generally showed worse performance [Benedict and Zivadinov, 2011; Schoonheim et al., 2012b]. Education and affective states can directly impact cognition [Bruce and Arnett, 2005]. However, in this study education did not impact cognitive profile even though female subjects had higher education. Moreover, none of the affective variables were significantly different between the two genders and all of them had limited weightings in CCA results. Although there were trends that the females in this study were more educated, it was not a significant difference (Table 2.2). Therefore, we concluded that education and affective status did not significantly influence cognition in our cohort.

However, of note, when rsFC, demographics, and cognitive scores are combined together in another analysis with a similar approach, education appears to be influential. This study is reported in chapter 6.

In our MS data, due to the fact that *transformed* TMT scores were the square roots of ***reciprocal*** TMT raw scores (which had opposite meanings to *raw* TMT scores), our interpretation of high weightings in TMT scores (Figure 2.2) is that female subjects performed better on both TMT A and B tests (i.e. faster responses). We conclude that set-shifting abilities assessed by TMT A/B tests were less impaired in female MS subjects than males. Finally, the high correlation between the combination of demographics and combination of timed cognitive scores illustrated that these linear combinations were significant and robust enough to explain the data. Figure 2.3 demonstrates that gender had strong weightings in the combination of demographics and untimed scores. Among all the untimed scores, male subjects obtained high weightings on WCST Perseverative Errors and Errors, illustrating poor performance in the Wisconsin Card Sorting Test.

In contrast, female subjects tended to perform Wisconsin Card Sorting Test better because they had higher scores on WCST Categories Completed. However, they also had higher scores on WCST Perseverative Responses and Failure to Maintain Set, which possibly indicates an inability to use feedback to modify their response behaviour. It is interesting to know that perseverative behaviour, whether errors or responses, are found in both genders. This is more indicative of the neuropathology (i.e. white matter damages reduce neuronal communication) seen in MS. In addition, female subjects obtained higher scores on WAIS IV Digit Span and Letter-Number Sequencing tests, indicating that, compared to male subjects, their basic ability to sustain attention was less affected. Finally, the untimed group also demonstrated high correlations between the combination of cognitive scores and combination of demographics, and again, gender and a subset of WCST scores were the strong factors which explained cognitive patterns.

Gender differences on cognitive tasks have been long established [Miller and Halpern, 2014]. Separating the timed from non-timed tasks is an important, growing trend in the analysis of neuropsychological test data in multiple sclerosis [Leavitt et al., 2014]. We also analyzed timed and untimed scores together, but the model was not significant. The current results indicate that analyzing timed and untimed scores separately is more capable of distinguishing cognitive profiles between male and female MS subjects.

2.4.3 Commonalities and differences

To conclude, the cognitive profiles in PD and MS shared similar patterns that gender appeared to be an influential factor in cognition. In both cohorts, female subjects performed cognitive tests better, especially tests that required set-shifting abilities. On the other hand, there are several differences in their cognitive profiles. First, some demographical factors showed distinct effects,

whereby age and education were influential on cognition in PD but not in MS, which possibly due to that PD subjects are generally older so aging could impact cognition more than that in MS. Second, disease severity also showed different effects to cognition. UPDRS was not a significant factor in PD, while EDSS was associated with worse performance in MS, which raises debates whether 1) disease severity measured with motor symptoms can represent cognitive impairments or 2) psychological disabilities show certain degree of associations between clinical symptoms and cognitive dysfunction as patients with stronger psychological impairments are more likely to develop cognitive deficits. Further research with a bigger sample size is needed regarding these issues. Finally, psychiatric comorbidity significantly impacted cognition in PD but not in MS. The discrepancies may be related to the neurotransmitter dysregularization as several neurochemistry pathways are altered in PD including serotonin which is highly related to mood disorders [Dauer and Przedborski, 2003], but similar research is relatively limited in MS. A few studies have demonstrated that altered neurotransmitter systems in MS are more related to immune function rather than affective state [Polak et al., 2011], which could be the possible explanation why psychiatric comorbidities were not significantly associated with cognitive performance in our results. However, more research is needed to draw firm conclusions. Finally, as PD subjects are generally older than MS subjects, differences could be partly explained due to age. Aging has been shown to impact several cognitive domains such as processing speed, working memory, and executive function by potentially impairing microstructural changes [Fjell et al., 2017; Murman, 2015]. In addition, age-related diseases accelerate the progression of neural loss, neuronal dysfunction, and cognitive decline [Murman, 2015]. Taken together, the associations between aging and cognitive decline explained why age demonstrated significant effects to cognition in PD, an older population, but not MS, a much younger population.

2.4.4 Limitations

As described roughly in section 2.2, test batteries used in PD and MS were different even though some sub-tests were the same. These test batteries were designed to reflect the cognitive impairments seen in PD and MS. Given that the profiles of cognitive impairments are not exactly the same, test batteries would most likely vary. However, the common affected domain – executive function – was evaluated in both batteries with the Verbal Fluency Test, Wisconsin Card Sorting Test, and Trial-Making-Tests. In addition, as the purpose of the chapter was to explore the cognitive profiles in PD and MS, healthy subjects were not included in the analysis, which may fail to establish whether performance was objectively deficient. Finally, although previous research has implied that the affected neurotransmitter systems in PD are more related to mood disorders and such links are not seen in MS, further investigations are required to study the associations between cognition and psychiatric comorbidities in neurological conditions.

2.5 Conclusion

In this chapter, we applied a machine-learning method to explore the relations between cognitive performance and demographics/clinical data in PD and MS. In PD, the CCA model demonstrates that female sex and education supported the cognitive performance which requires attention and executive functioning. Moreover, age and depression were associated with poorer performance, indicating an association between PD comorbidity and cognitive decline. In MS, we conclude that gender is one of the influential factors on cognitive performances in subjects with MS. There are specific cognitive patterns in MS subjects: First, female subjects performed TMT tests better than males. Second, in untimed tests, male subjects made more errors and female subjects performed better on the Wisconsin Card Sorting Test. Finally, our results imply that with this particular test

battery, female subjects with MS were less cognitively impaired than male subjects. Our study is unique in that we have discovered gender differences exist on selected executive tasks and report a trend that gender differences may also exist on timed tasks vs untimed tasks, which has become an important area of focus in the cognitive assessment of individuals with remitting and relapsing MS.

Taken together, we propose an inter-correlated pattern between cognitive performance, clinical evaluation, and demographical characteristics in PD and MS. Moreover, we conclude that gender is an influential factor to such complex cognitive patterns and female gender shields cognitive functions regardless pathologies, possibly owing to the neuroprotective effects of estrogen. We also revealed differences in the cognitive profiles, whereby demographical characteristics, disease severity, and comorbidities impacted cognition differently in PD and MS.

Chapter 3: Resting-state functional connections and cognition

As Chapter 1 hypothesizes, long-range connections appear to be particularly important for executive function and alterations in these connections might be a common cause of cognitive impairments in both Parkinson's Disease (PD) and Multiple Sclerosis (MS). In this chapter, several strategies are applied to investigate whether neurological diseases demonstrate alterations in long-range connections as well as other important connections such as interhemispheric ones. Regression analyses are also used to explore the associations between rsFC and cognitive scores.

3.1 Introduction

3.1.1 Effects of interhemispheric and long-range connections to cognition

Interhemispheric connectivity appears to be particularly important for performance of information processing and other cognitive functions [Bloom and Hynd, 2005]. Diseases that result in abnormal volumes of the corpus callosum and/or abnormal interhemispheric connectivity show deficits in several cognitive domains, such as memory, speed of processing, and executive function [Bodini et al., 2013; Lee et al., 2010; Mwansisya et al., 2013; Paul et al., 2007; Saar-Ashkenazy et al., 2014]. For instance, patients with agenesis of the corpus callosum (AgCC) have severely impaired high-order cognition (e.g. complex thinking, reasoning and decision making, cognitive flexibility) [Paul et al., 2007]. Decreased interhemispheric connectivity in schizophrenia correlates with negative symptoms and relates to lower information processing speed [Mwansisya et al., 2013]. Moreover, patients with Alzheimer's disease and mild cognitive impairment (MCI) have reduced

volume in corpus callosum [Lee et al., 2010], and impaired interhemispheric connectivity in post-traumatic stress disorder is also highly associated with poor performance in associative memory tasks [Saar-Ashkenazy et al., 2014]. With rsfMRI, patients with major depression disorder (MDD) show negative correlation between rsFC of homotopic regions and the severity of cognitive impairments [Wang et al., 2013]. These regions are located in prefrontal areas and cerebellum. Furthermore, decreased interhemispheric connectivity in stroke patients has been shown to be able to predict behaviour in multiple domains such as verbal and visual memory [Siegel et al., 2016]. However, only a few of these studies specifically target interhemispheric functional connectivity. Most of the studies either assess interhemispheric connections with structural data or simply interpret observed rsFC changes as interhemispheric connectivity.

Long-range connections (i.e. corticocortical connections) have been thought of as supporting diverse cognitive functions, especially higher-order cognition, as well as resting-state patterns [Park and Friston, 2013]. Compared to attention, memory ability engages stronger long-range intrahemispheric connectivity [Hermundstad et al., 2013], showing that higher cognitive load requires stronger long-range connectivity. Language processing is associated with long-range connectivity between the inferior frontal gyrus, posterior middle temporal gyrus, basal temporal cortex, supramarginal gyrus, and superior temporal cortex [Salmelin and Kujala, 2006]. These long-range connections are affected in diseased populations. For example, long-range connectivity between the fusiform gyrus and other remote cortical regions is decreased in autism spectrum disorder (ADS) [Khan et al., 2013]. Decreased connectivity in the fronto-parietal network, perhaps one of the most well-known cognitive networks that also requires long-range connectivity, has been reported in a variety of diseases and associated with cognitive deficits such as schizophrenia,

chronic traumatic brain injury, and Parkinson's disease [Han et al., 2016; Sheffield et al., 2015; Vervoort et al., 2016].

3.1.2 Interhemispheric and long-range connections in Parkinson's Disease and Multiple Sclerosis

We hypothesize that interhemispheric connectivity may also be important in maintaining cognitive performance in MS. Structural research suggests that white matter lesions have a propensity to involve callosal connections [Bodini et al., 2013], and callosal atrophy is related to lower processing speed abilities measured by the Symbol Digit Modalities Test (SDMT) at both baseline and follow-up in MS [Bergendal et al., 2013]. In addition to altered structural interhemispheric connectivity, studies of functional interhemispheric connectivity with other modalities have also been described in MS. Decreased magnetoencephalography (MEG) synchronization between the two hemispheres has been found in MS, suggesting that weakened functional interhemispheric connectivity could be a biomarker for cognitive impairment [Cover et al., 2006]. Therefore, studying the relationship between cognitive performance and interhemispheric connectivity is crucial for further understanding the cognitive profile of MS.

In PD, voxel-mirrored homotopic connectivity (VMHC), which assesses pairwise correlation coefficient between homotopic regions, has been primarily used to evaluate interhemispheric connectivity with fMRI data. PD patients with depression demonstrated lower interhemispheric rsFC in the dorsolateral prefrontal cortex and calcarine, and was associated with overall cognition measured by the Mini Mental State Examination (MMSE) [Zhu et al., 2016]; compared to healthy subjects, lower VMHC values in the putamen, sensorimotor cortex, and supramarginal gyrus in PD subjects are correlated with disease severity and disease duration [Luo et al., 2015b]. In

addition, with diffusion weighted MRI data, which quantifies white matter microstructural integrity, PD subjects exhibited lower white matter integrity of interhemispheric tracts in the somatosensory cortex, primary motor cortex, supplementary motor area (SMA), and pre SMA [Fling et al., 2016]; however, the decreased callosal integrity in PD was only correlated with motor performance rather than cognitive evaluation.

Studies which report the associations between executive function and long-range connections of rsfMRI in PD and MS have been discussed previously (see Section 1.4).

3.1.3 Analyses

Technical issues may complicate interpretation of functional interhemispheric connectivity. For interhemispheric connections, similarity between neural activities in homologous regions may not necessarily be based on transcallosal activity, but rather both hemispheres may be influenced by common brainstem and/or subcortical input. Functional connectivity measures that distinguish between direct and indirect (common) influences between homologous regions are therefore desirable for functional interhemispheric connectivity studies. This can be achieved by partial correlation, whereby the relation between homologous pairs is assessed controlling for the activity in another region. Although the VMHC approach, as discussed previously, specifically examines functional interhemispheric connectivity, pairwise correlation appears to be less robust to noise and possible effects from other regions compared to partial correlation as used here [Smith et al., 2013]. For assessing changes in long-range connections, perhaps exploratory analyses are more suitable given that there is no clear *a priori* knowledge and definition of such connections. Although most studies interpret corticocortical connectivity as long-range connections between

frontal, parietal, and occipital regions [Park and Friston, 2013; Salmelin and Kujala, 2006], other connections may have functional significance.

In this study, we examined functional interhemispheric connectivity in MS and PD during resting-state fMRI using both simple and partial correlations. We then applied elastic net regression models to investigate the relationship between observed functional connectivity changes and performance on cognitive tests. Whole brain connectivity patterns were calculated as well to investigate potential changes in long-range connections. We demonstrate that functional connectivity features are complementarily associated with performance on cognitive tests.

3.2 Materials and methods

3.2.1 Subjects

PD data are from BCT research project and MS data are from OPERA clinical trial, which is different from the previous chapter.

We recruited 25 patients with relapsing-remitting MS (mean age $\pm$ SD = 37.2 ± 9.5 ; 10 male, 15 female) and 41 age-/gender-matched healthy control subjects (HC) (mean age $\pm$ SD = 34.9 ± 10.1 ; 14 male, 27 female) in a Phase III randomized, double-blind, double-dummy trial to evaluate the efficacy and safety of ocrelizumab versus interferon beta-1a in relapsing forms of MS (OPERA II; NCT01412333). The data included in this study (clinical scores and imaging data) were from the baseline time point only. Ethics approval was received from the University of British Columbia's Clinical Research Ethics Board and all subjects provided written, informed consent. HC did not have psychiatric, medical, cognitive, or other conditions that caused an inability to participate in an MRI study. Patients had Expanded Disability Status Scale (EDSS) scores ranging between 0

and 4 (median EDSS = 2). All patients performed the multiple sclerosis functional composite (MSFC) battery including the Paced Auditory Serial Addition Test (PASAT). They also performed a Low Contrast Visual Acuity Test (LCVA), and the Symbol Digit Modalities Test (SDMT) (Table 3.1).

Twelve subjects with idiopathic PD (60.0 ± 9.9 y/o) and 10 age-matched HC were recruited through the movement disorder clinic at UBC hospital. Ethics approval was issued by the University of British Columbia's Clinical Research Ethics Board and all subjects provided written, informed consent. PD subjects were asked not to take their medication one night before the visit (i.e. off medication). After the first MRI scan and clinical examination in the morning, they took medication and underwent the second MRI scan in the afternoon on the same day. In addition to the Unified Parkinson's Disease Rating Scale (UPDRS) part III, questionnaires of apathy and Beck depression scale were administered and overall cognitive function was assessed by Montreal Cognitive Assessment (MoCA). Detailed demographics are shown in Table 3.2.

	HC subjects (mean $\pm$ SD)	MS patients (mean $\pm$ SD)
Age	34.85 ± 10.1	37.20 ± 9.5
Gender	14 males/27 females	10 males/15 females
EDSS	ND	2.14 ± 0.95
Disease duration (months)	ND	67.08 ± 64.85
PASAT	ND	42.44 ± 15.38
SDMT	ND	49.88 ± 11.03
LCVA	ND	40.92 ± 9.65

Table 3.1 Demographics of MS and HC subjects.

[HC: healthy control; MS: multiple sclerosis; EDSS: Expanded Disability Status Scale; LCVA: Low Contrast Visual Acuity; PASAT: Paced Auditory Serial Addition Test-3 seconds; SDMT: Symbol Digit Modalities Test; ND: no data]

	HC subjects (mean $\pm$ SD)	PD subjects (mean $\pm$ SD)
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age	59.4±6.1	60.0±9.9
sex	6 males/4 females	9 males/3 females
UPDRS	ND	29.5±9.6
bradykinesia	ND	10.75±3.7
tremor	ND	5.25±3.5
rigidity	ND	5.92±2.5
PIGD	ND	4.58±2.2
H & Y	ND	2.5±0.4
disease duration	ND	5.92±3.5
medication dosage	ND	625±351.9
apathy+	ND	7.5±5.4
Beck depression scale+	ND	5.75±5.5
MoCA+	ND	27.14±3.4

Table 3.2 Demographics of PD and HC subjects.

[HC: healthy control; PD: Parkinson's disease; UPDRS: Unified Parkinson's Disease Rating Scale; PIGD: Postural Instability and Gait Disorder; H&Y: Hoehn and Yahr scale; MoCA: Montreal Cognitive Assessment; ND: no data]

+ 5 data points missing in apathy, Beck depression scale, and MoCA

3.2.2 Image acquisition

Images of both cohorts were acquired with a Philips Achieva 3.0 Tesla MRI scanner (Best, The Netherlands). 3D T1-weighted images were acquired with CLEAR homogeneity correction with $1 \times 1 \times 1 \text{ mm}^3$ resolution. Eight minutes of resting-state functional MRI (rsfMRI) data were acquired with an echo-planar imaging sequence with $3 \times 3 \times 3 \text{ mm}^3$ resolution, 36 slices, 2000 ms TR, 30 ms TE, and 240 dynamics.

3.2.3 Image preprocessing

Several image preprocessing steps were applied to the fMRI data including slice-timing, isotropic reslicing, and motion correction in MATLAB using SPM8 functions (the Wellcome Trust Centre

for Neuroimaging, UK) and in-house Matlab codes. FLIRT (the FMRIB Centre, UK) was used to register fMRI images and structural images. T1-weighted images were used for cortical and subcortical parcellation, which was carried out using FreeSurfer software 4.5.0 (Massachusetts General Hospital, USA). For MS subjects, thirty-eight cognition-related regions-of-interest (ROIs), which were commonly reported in the MS neuropsychology literature, were chosen (Table 3.3) for connectivity analysis. For PD subjects, fifty-four ROIs that were clinically relevant for PD were chosen (Table 3.4). As the original purpose for the MS project was to evaluate functional connectivity and its relation to cognition, included ROIs were selected based on the neuropsychology literature so these ROIs were supposed to be highly associated with cognition. However, the original purpose for this PD project was to investigate the connectivity among the most clinically affected regions in PD regardless of motor or cognitive syndromes. Therefore, the selected ROIs were not the same, which is one of the limitations in this chapter. The mean time courses over all voxels within one region in fMRI data were extracted from the given ROIs. All calculations were done in the subject's native space. As the processing pipeline was original designed based on common preprocessing steps in SPM package, further steps such as temporal filtering and nuisance signal regression were not applied. However, linear detrending was applied on the extracted time courses and voxel outliers were removed. Typically, we exclude subjects who show higher than 2 mm in translation and/or 2 degrees in rotation, but none of the subjects reached these criteria.

Bilateral ROIs	
frontal pole	parietal and occipital junction areas
superior frontal gyrus	superior occipital gyrus
middle frontal gyrus	anterior cingulate cortex

inferior prefrontal cortex	posterior cingulate cortex
temporal pole, insula cortex, amygdala	precuneus
superior temporal cortex	medial orbitofrontal cortex
posterior parietal cortex	lateral orbitofrontal cortex
post central gyrus	fusiform gyrus
supramarginal gyrus	superior parietal cortex
medial temporal lobe, hippocampus, parahippocampal gyrus	

Table 3.3 The 38 ROIs in the study for MS (19 bilateral regions).

Bilateral ROIs	
middle frontal gyrus	lateral occipital region
ventral lateral prefrontal gyrus	caudal anterior cingulate cortex
insula	posterior cingulate cortex
superior temporal gyrus	precuneus
middle temporal gyrus	ventral medial prefrontal cortex
inferior temporal gyrus	cerebellum
parahippocampal gyrus	primary motor cortex
hippocampus	supplementary motor area
superior parietal gyrus	pre supplementary motor area
inferior parietal lobe	premotor area dorsal part
occipital-parietal area	premotor area ventral part
thalamus	putamen
caudate	pallidum

Table 3.4 The 54 ROIs in the study for PD (27 bilateral regions).

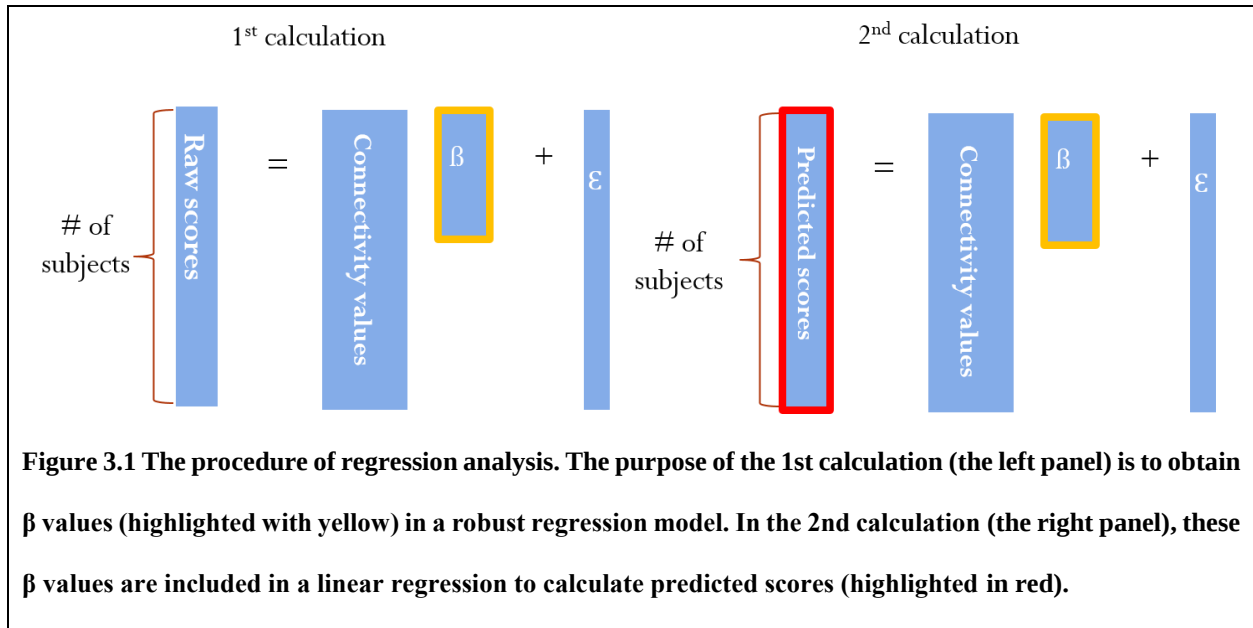
3.2.4 Functional connectivity analysis

For assessing interhemispheric connectivity, we computed correlation coefficients using a combination of two approaches. For each subject, we first divided the time courses from n ROIs

into $n/2$ homologous left, right pairs. For the i^{th} pair, $P_i(L,R)$, we examined the remainder right and left homologous pairs $P_{1 \dots n/2, \neq i}(L,R)$ and computed both the simple correlation (*Pearson's r*) and the partial correlation conditioned on $P_i(L,R)$ (i.e. the rest ROIs). We then computed the difference in the sum of the correlations and partial correlations between each homologous pair, $P_i(L,R)$. The calculation could be expressed as the following mathematical style pseudocode:

$$\sum (| (\text{partial correlation values} - \text{simple correlation values}) |).$$

In order to determine if interhemispheric connectivity was associated with altered performance on cognitive tests, we performed robust regression, which is a common method to predict clinical or behavioural responses using neuroimaging data [Bowman, 2014a]. We took all homologous pair connectivity difference values from every subject as independent variables and behavioural scores as the dependent variable. Age was also included as a nuisance covariate. In MS, the behavioural scores included SDMT, PASAT, EDSS and LCVA scores. In PD, due to small sample size, only the significant connectivity pairs were used for regression analysis as robust regression cannot take more features (connectivity pairs) than observations (sample size). All the clinical scores were included except MoCA, apathy, and Beck depression scale because missing data points resulted in insufficient data to perform robust regression. The first calculation with robust regression obtained β values, which represented the weighting between interhemispheric connectivity and behavioural scores. These values were then included in the second calculation to generate predicted cognitive/clinical scores. Finally, R-squared between raw and predicted scores was reported. Figure 3.1 explains the procedure in a graph fashion.

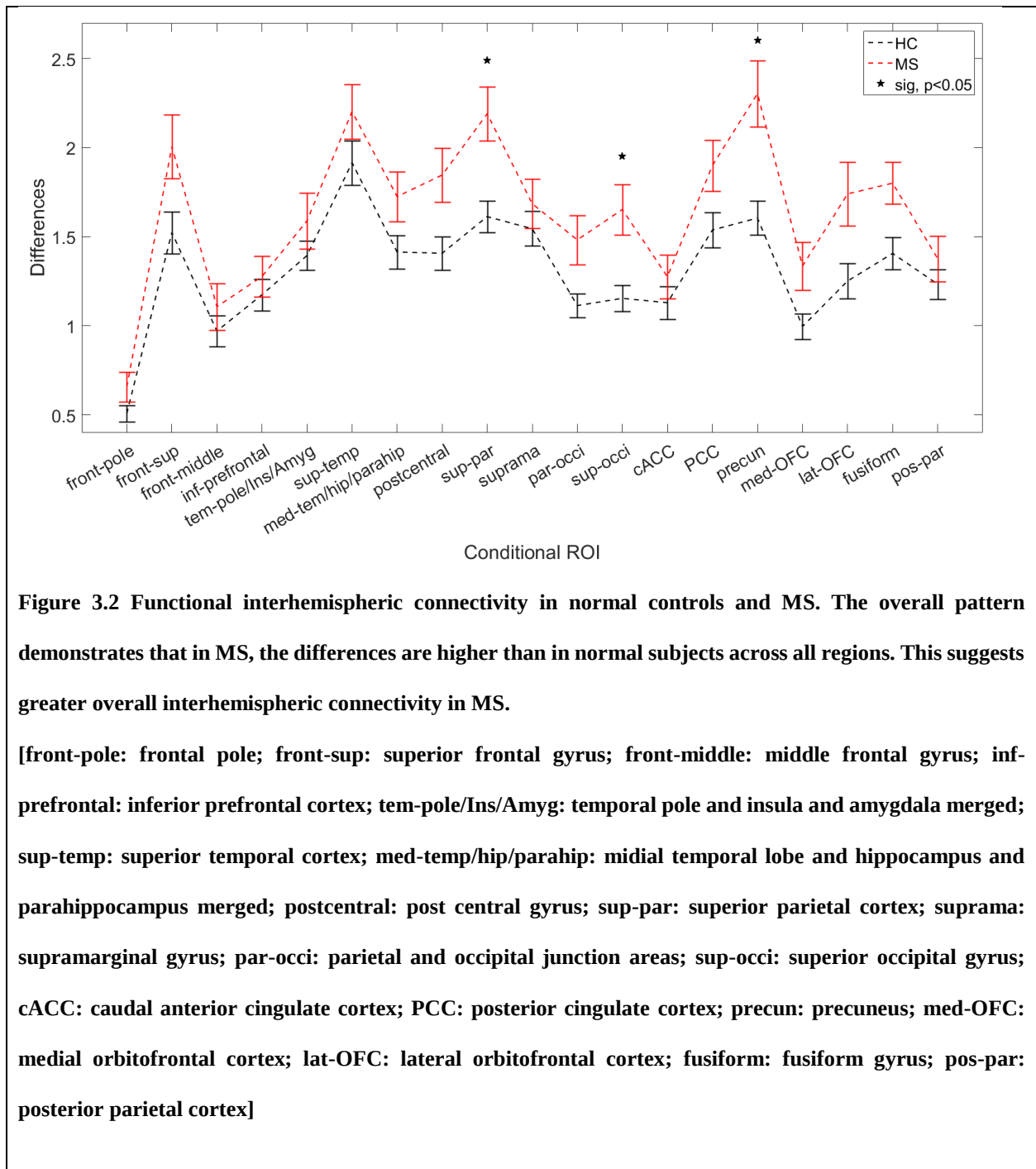


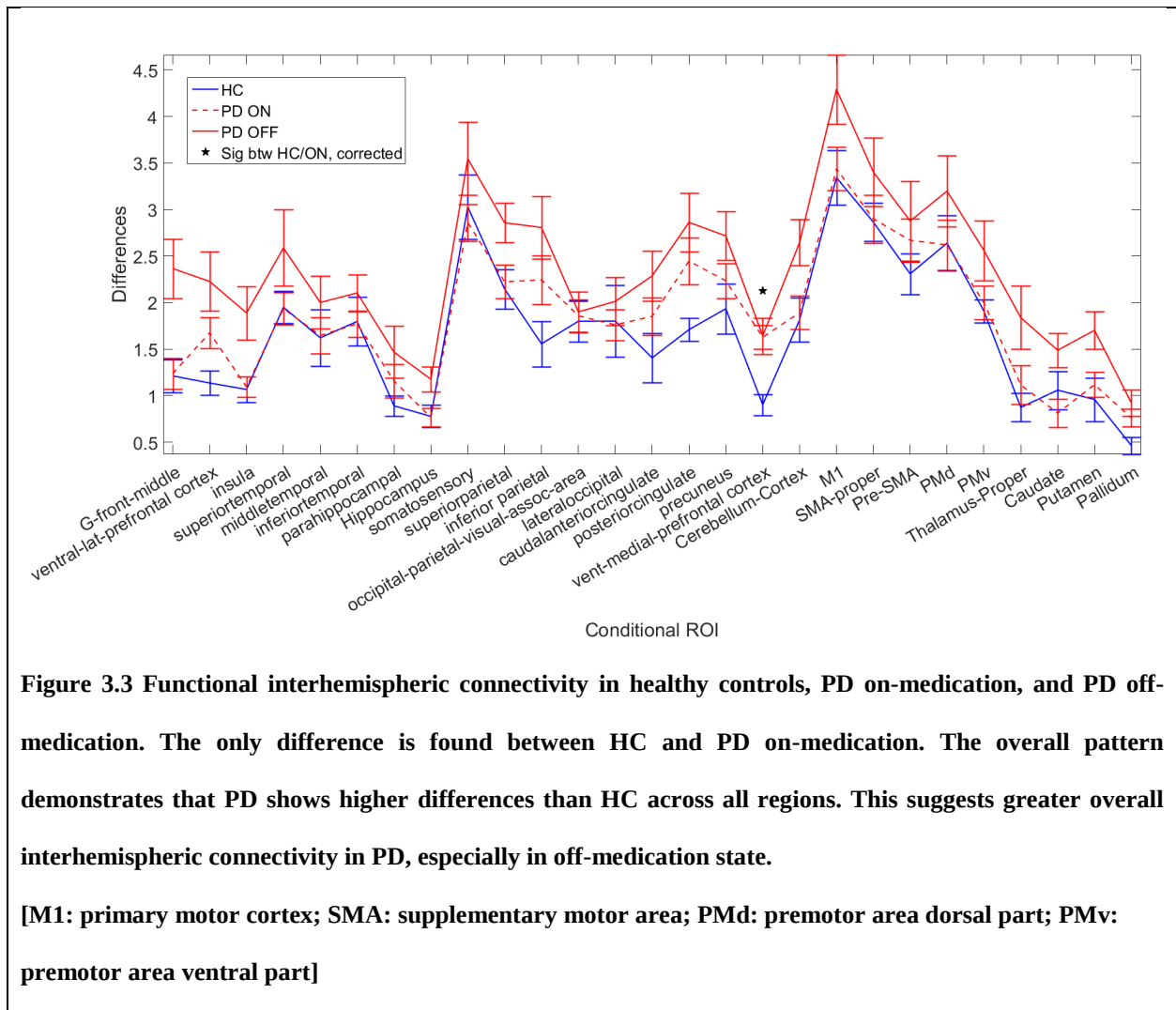
In order to determine if certain homologous pairs had the largest influence on predicting clinical and cognitive scores, we repeated the regression with a sparsity penalty on the regression coefficients by implementing elastic net regression (lasso function in Matlab, with $\alpha = 0.75$) and included age as a covariate. This algorithm attempts to find a balance between predicting cognitive scores and including as few interhemispheric connections as possible to make that prediction. We used a leave-one-out cross validation to determine the optimal shrinkage parameter λ .

For evaluating whether long-range connections were different between patients and HC, we applied an exploratory approach by calculating the whole brain connectivity matrix using *Pearson's r* correlation. The matrix elements were then transformed to Fisher's z values and then converted into a vector for the two-sample t-test with false discovery rate (FDR) corrected. The vectors were reshaped back to matrices and significant differences of connectivity pairs between groups were reported.

3.3 Results

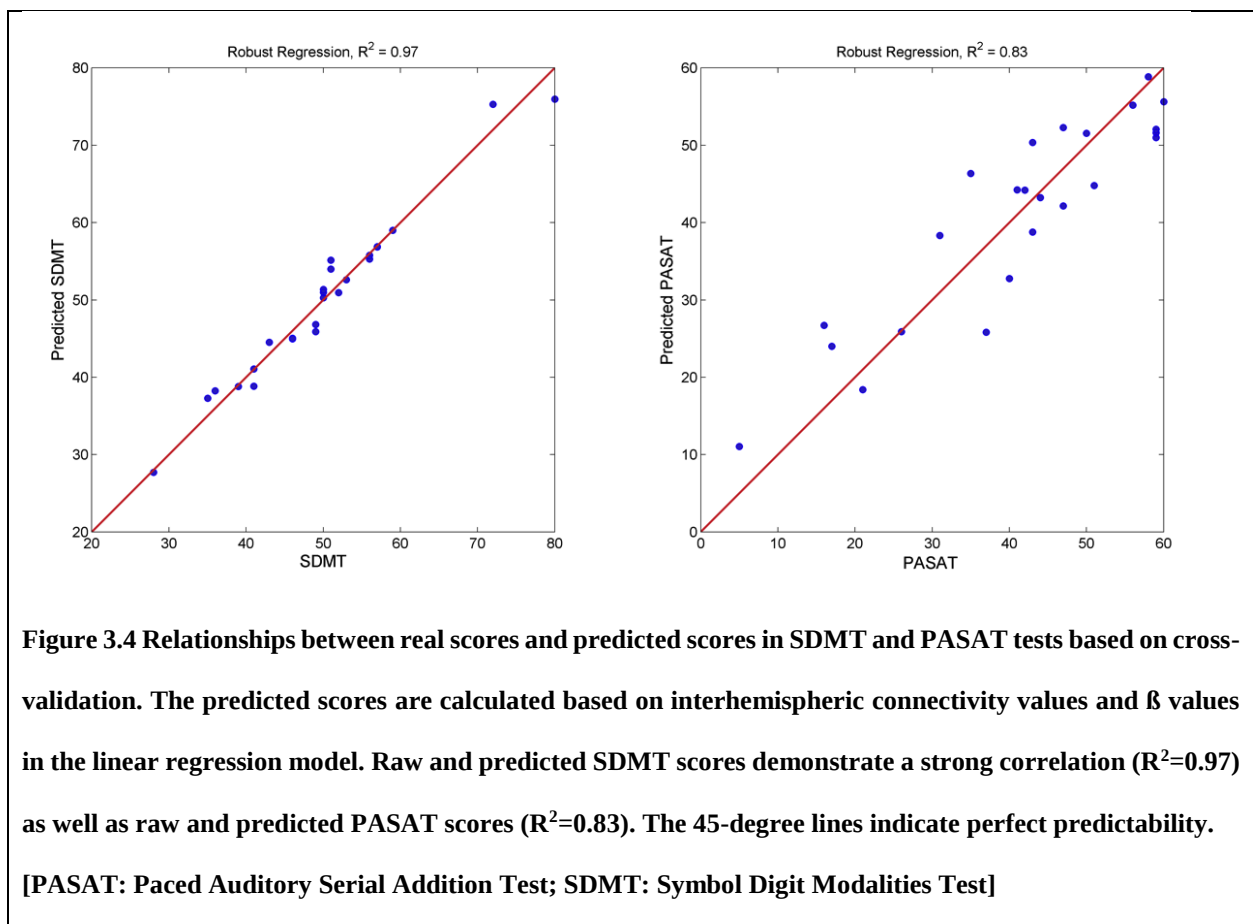
Conditioning on the different left ↔ right ROI pairs resulted in significant differences between partial and simple correlation in MS (Figure 3.2). The changes in overall instantaneous interhemispheric connectivity were significantly different between MS and HC (corrected $p = 0.05$) when the following ROI left ↔ right pairs were used for the partial correlation: the superior parietal cortex, superior occipital gyrus, and precuneus. In addition, the MS group constantly showed higher differences than HC group no matter what pairs were conditioned. In PD, significantly different interhemispheric connectivity was only observed between HC and PD on-medication when the ventral medial prefrontal cortices was used for partial correlation (corrected $p = 0.05$). Similar to MS, PD subjects also showed higher differences than HC regardless which pairs were conditioned (Figure 3.3). The differences represent the relative importance (connectivity values) of the brain regions (conditional ROI) when it is included in the analysis. A larger difference reflects greater importance of that region.





Using robust linear regression, SDMT and PASAT scores could be accurately predicted from the differences between interhemispheric partial and simple correlation (Figure 3.4); while EDSS and LCVA results were insignificant. We performed elastic net regression to detect if only a few of the interhemispheric connections were responsible for prediction (Figure 3.5). However, even with the sparsity constraint (as we set $\alpha = 0.75$, the elastic net regression model was more toward L^1 norm of β (lasso regression) than L^2 norm of β (ridge regression), which sparsity constraint was taken into account.) on the regression coefficients, 18 and 10 ROI pairs respectively were still

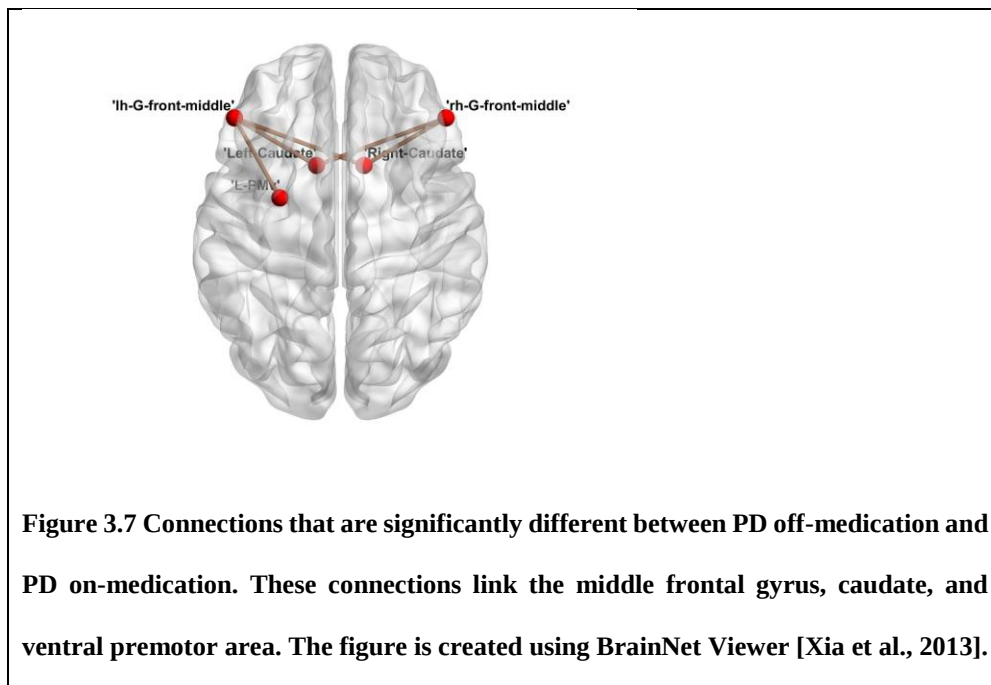
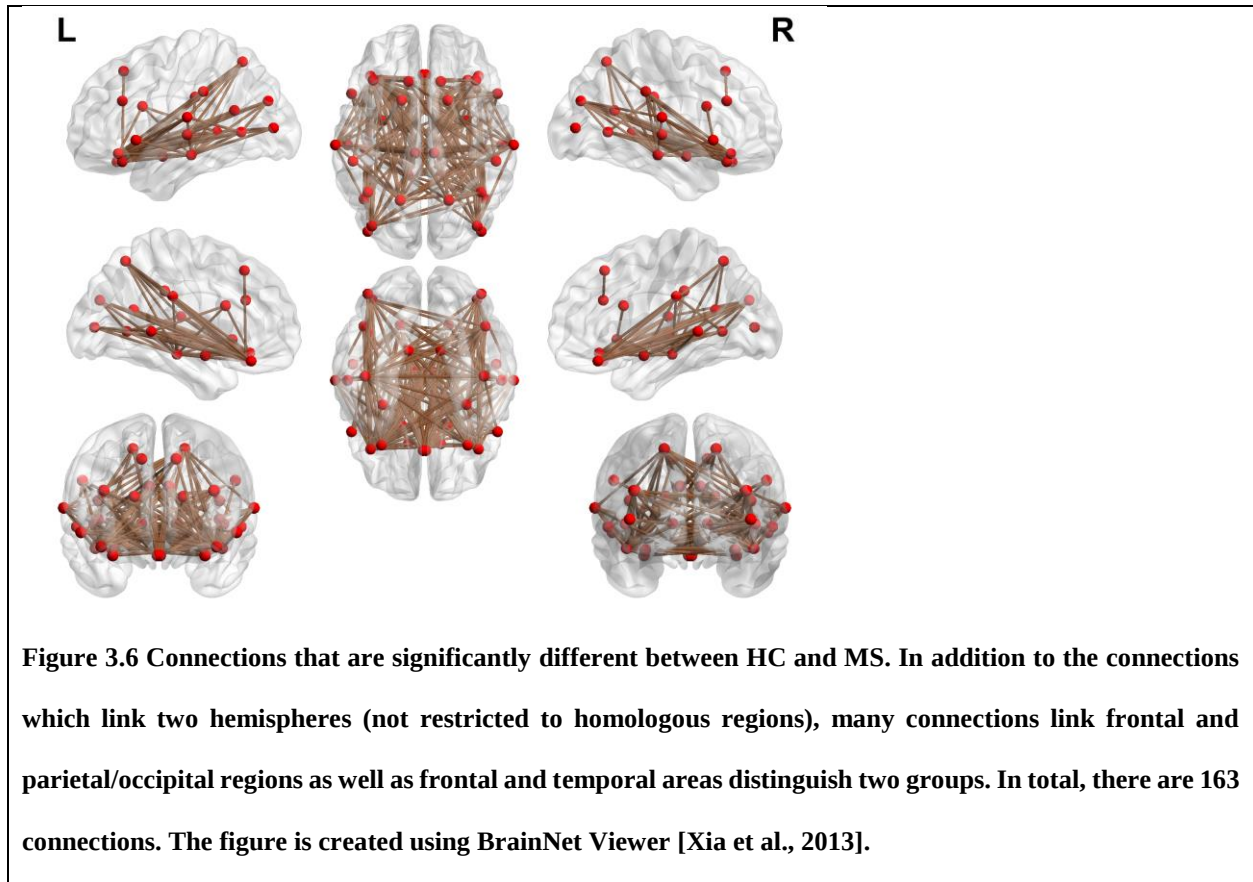
included in the model to predict SDMT and PASAT scores. This method is able to show which linear combination of ROI pairs plus age best predict cognitive performance (i.e. linear combination of positive plus negative weightings). The frontal pole, temporal pole, insula, amygdala regions, superior temporal gyrus, parietal and occipital junction areas, anterior cingulate, and posterior parietal cortex were found to have more positive weights on SDMT performance. In contrast, the superior temporal gyrus, medial temporal gyrus, hippocampal regions, supramarginal areas, superior occipital gyrus, and anterior cingulate cortex impacted PASAT more than other ROI pairs.



[front_pole: frontal pole; front_sup: superior frontal gyrus; front_middle: middle frontal gyrus; inf_prefrontal: inferior prefrontal cortex; tem_pole/Ins/Amyg: temporal pole and insula and amygdala merged; sup_temp: superior temporal cortex; med_temp/hip/parahip: midial temporal lobe and hippocampus and parahippocampus merged; postcentral: post central gyrus; sup_par: superior parietal cortex; suprama: supramarginal gyrus; par_occi: parietal and occipital junction areas; sup_occi: superior occipital gyrus; cACC: caudal anterior cingulate cortex; PCC: posterior cingulate cortex; precun: precuneus; med_OFC: medial orbitofrontal cortex; lat_OFC: lateral orbitofrontal cortex; pos_par: posterior parietal cortex]

In PD, due to insufficient data, we cannot perform elastic net regression and only the significant connectivity pair in the t-test (i.e. ventral medial prefrontal connectivity) was used in robust regression. Only medication dose was predicted with R-square 0.2 in PD on-medication. The other scores were all predicted poorly with R-square lower than 0.2 in both on and off medication status (results are shown in Appendix B.1).

Figure 3.6 shows the connectivity pairs that are significantly different between MS and HC in the connectivity matrices ($p < 0.05$, FDR corrected). Overall, most of the significant connections linked frontal and parietal/occipital regions as well as frontal and temporal areas, which can be seen as long-range connections. The connections that link two hemispheres were also seen. Figure 3.7 demonstrates the significant connections which distinguish PD on-medication and PD off-medication ($p < 0.05$, FDR corrected). These connections linked the caudate, premotor area, and middle frontal gyrus, which is part of the frontostriatal loops and the output component of the executive function model [Miller and Cohen, 2001] (see section 1.4.2). No significant connections were found between HC and PD regardless patients' medication status.



3.4 Discussion

3.4.1 Enhanced interhemispheric connectivity may indicate compensatory mechanisms

Previous fMRI studies have reported decreased functional connectivity in MS [Dogonowski et al., 2013; Kingwell, 2012]; while increased functional connectivity has also been reported during rest as well as during performance of tasks [Janssen et al., 2013; Kingwell, 2012; Specogna et al., 2012], which may reflect compensatory mechanisms. For example, within the default mode network areas, several cortices demonstrate enhanced functional coupling in MS, which is associated with a concomitant loss of cognitive efficiency [Hawellek et al., 2011a]. Consistent with prior studies, we found overall enhanced interhemispheric connectivity in MS subjects as demonstrated in Figure 3.2 where the MS group constantly showed bigger differences. The differences measured alterations between connectivity values derived from two methods (simple correlation and partial correlation). Hence, bigger differences also indicated higher connectivity. In this study, we discovered significantly altered *functional* interhemispheric connectivity in MS through an approach which specifically assessed homologous connections.

In PD, previous studies which specifically measured connectivity between homologous regions all reported decreased functional interhemispheric connectivity [Luo et al., 2015b; Zhu et al., 2016]. However, the approach (i.e. VMHC) utilized in these studies is very different from our approach. Simply calculating *Pearson's r* correlation between homotopic voxels may capture effects from other regions and voxels as simple correlation does not measure “direct correlation”. Moreover, the disease severity in our cohort is different from those studies. If we interpret increased interhemispheric connectivity in this study as a compensatory effect, the disease severity of the study cohort plays an important role and it could be one of the reasons for distinct findings. A

model of network collapse has been proposed in MS, which describes a non-linear relation between functional connectivity, cognitive impairments, and structural damage across disease course [Schoonheim et al., 2015]. Although MS and PD have unique pathologies, we believe that there are certain similarities between them as discussed in Chapter 1 & 2. Therefore, such model may apply to PD as well. A study which recruited PD patients with similar disease severity (based on H & Y scale) also demonstrated increased rsFC as a compensatory mechanism [Simioni et al., 2016]. In addition, this study also observed that patients in an off-medication state showed increased connectivity in the cerebellum, primary motor cortex, and subcortical regions; while in on-medication state, these stronger connections were reduced and both on/off-medication rsFC were correlated with/predicted motor performance, confirming that such increased rsFC pattern reflected a compensatory mechanism. Our results also support that increased rsFC in PD may represent compensation. Similarly to MS, PD also demonstrated higher interhemispheric connectivity than HC especially in off-medication state (Figure 3.3). In fact, not only interhemispheric connections, but the whole brain connectivity in off-medication exhibited higher rsFC than HC (Appendices B.2). Although we did not perform regression analysis to probe whether cognitive performance was related to such compensatory pattern (only medication dose can be roughly predicted, Appendices B.1), our findings still provide insights into the disease affects neuronal networks in PD.

We used both partial and simple correlation to investigate the interhemispheric connectivity. This approach has not been used in the previous research assessing interhemispheric connectivity, which makes the methodology in this study unique. Given that the calculation estimated correlation differences only between homologous brain regions with and without conditioning, it

is more straightforward to interpret the results as *interhemispheric*. Since the correlation differences were robustly larger in MS and PD (Figure 3.2 & 3.3) and the overall interhemispheric connectivity was also larger in the patient groups, there is both enhancement and **homogenisation** of interhemispheric connectivity in neurological disorders, meaning that the interhemispheric connections are more dependent on each other. If one connection is altered, the rest of the connections are more likely to be influenced as well. This also implies that interhemispheric connections in MS and PD lose their ability to independently modulate connectivity. Instead, the homologous regions require further support from other connectivity pairs in order to transfer information across the two hemispheres, which indicates that enhanced interhemispheric communication could be an early compensatory change in MS and PD.

3.4.2 Interhemispheric connectivity predicts cognitive performance

In addition to the finding of overall interhemispheric connectivity, we have also demonstrated that altered functional interhemispheric connectivity closely reflects performance on cognitive tests, namely the SDMT and PASAT in MS (Figures 3.4 & 3.5). Interestingly, even when we used a sparsity constraint on the regression in order to see if only a few interhemispheric connections were important for SDMT and PASAT performance, we still found several ROI pairs were required for accurate prediction of cognitive performance. Thus both SDMT and PASAT performance appear to rely on widespread interhemispheric connectivity. Nevertheless, some cortical regions, which showed positive and high weightings with SDMT and PASAT, had greater influence on predicting cognitive scores such as the insula, frontal areas, temporal areas, anterior cingulate cortex, supramarginal areas, and parietal/occipital regions. Many of these areas are considered “hub” regions in distributed brain networks and reflect critical waypoints for

information transfer [Achard et al., 2006; Hagmann et al., 2008; van den Heuvel and Sporns, 2011], playing an important role in maintaining connectivity and information integration (a key aspect of cognition) in anatomically segregated brain networks. Since hub regions underline numerous aspects of cognition, we believe that these interhemispheric connectivity pairs dramatically influence the cognitive processes which are involved in SDMT and PASAT performance. In addition, it has been suggested that hub regions may be particularly sensitive to functional disruption [Hagmann et al., 2008; van den Heuvel and Sporns, 2011], which is perhaps another reason why both SDMT and PASAT are sensitive measures of cognitive dysfunction in MS. Among the clinical tests, LCVA did not show significant association with interhemispheric connectivity compared to other tests, suggesting that vision problems are less likely to impact interhemispheric connections in our cohort. The results further emphasize the importance of interhemispheric connectivity in cognition.

In PD, unfortunately, due to sample size, we did not have enough results to probe whether interhemispheric connectivity could accurately predict cognitive function, however, we do not necessarily exclude this possibility. In fact, studies which evaluate structural interhemispheric connectivity have shown associations between worsening cognitive function and reduced white matter integrity of interhemispheric fiber tracts in parkinsonism [Fling et al., 2016]. In an MEG study, cognitive symptoms were related to increased interhemispheric connectivity of alpha frequency estimated by synchronization likelihood in newly-diagnosed PD patients [Stoffers et al., 2008]. Taken together, both structural and functional interhemispheric connectivity show relations with cognitive functions in PD and related disorders to certain degree; however, more research on the effects of interhemispheric connections to cognition in PD is needed to draw a firm conclusion.

3.4.3 Sensitivity of interhemispheric connectivity to different cognitive tests

Although both PASAT and SDMT are clinically used for investigating cognitive deficits in MS, numerous studies have reported the SDMT to be a more sensitive, valid and reliable measure than the PASAT [Drake et al., 2010; Langdon et al., 2012; Parmenter et al., 2007; Sonder et al., 2014; Strober et al., 2009]. Indeed, we found a very strong correlation between SDMT and interhemispheric connectivity measures (Figure 3.4), consistent with prior studies suggesting SDMT is more strongly associated with MRI measures [Benedict et al., 2006]. With the elastic net regression, we show that connectivity is important between frontal pole, temporal pole, insula, amygdala, superior temporal cortex, parietal and occipital regions, and posterior parietal cortex for SDMT performance (Figure 3.5), which are partially consistent with previous studies showing that parietal areas play a role in SDMT as well as frontal areas and occipital regions [Forn et al., 2011]. The other regions that we found, such as temporal pole, insula, amygdala, and superior temporal cortex have not been mentioned in previous studies. We suspect that these regions act as mediators in information communication between frontal and parietal areas for a short time, which cannot be observed by the methods used in previous studies. In contrast, performance on PASAT may require information coordination between frontal, parietal regions, and the cerebellum since activation patterns mainly locate within one hemisphere among these regions [Forn et al., 2011], which will not be captured by the interhemispheric connectivity measures examined here but shall be encapsulated in long-range connectivity.

3.4.4 Altered long-range connections

As Chapter 1 hypothesized, cortico-to-cortical long-range connections, which are important for executive function, are impaired in neurological disorders. We have shown that the connections

which significantly distinguish MS and HC were cross hemispheric connections and long-range connections primarily connecting frontal, temporal, parietal, and occipital regions as shown in Figure 3.6. Interestingly, such connectivity pattern was correlated with PSAST but not SDMT performance (Appendices B.3), supporting the idea in the section 3.4.3 that PASAT performance may require coordination between frontal, parietal, cerebellar regions (i.e. long-range connections) more than SDMT performance. On the other hand, in PD, connections which primarily linked the middle frontal gyrus and caudate were significantly different between PD on and off medication states. This connectivity pattern is partially consistent with the output component mentioned in Chapter 1 and the frontostriatal circuits in the PD literature. Due to the fact that the PD subjects we assessed were mild and not cognitively impaired (average MoCA>26), perhaps long-range connections between frontal, parietal, and occipital regions were less impaired compared to the MS cohort. In addition, given that PD patients demonstrate cognitive inflexibility and such deficit has been linked to neuronal activity [Cools et al., 2001; Lange et al., 2017], rsFC might be less flexible as well, which cannot be captured in the current analysis. Instead, time-varying approaches are able to detect temporal changes of rsFC and estimate dynamic functional connectivity. This aspect in PD will be discussed in a later chapter.

3.5 Limitation

We emphasized ROIs associated with higher order cognition based on the previous clinical literature, and thus would not detect other types of connectivity disruption affecting lower cognitive domains such as vision. Moreover, as mentioned in section 3.2, the original study goals of two projects were different so the selected ROIs were not the same, which causes some difficulty in directly comparing results between two disease populations. In a future study, ROI selection

could be more consistent. In addition, here we aimed to study cortical connectivity so some subcortical regions, which might be important for high order cognition, were not included. Therefore, our data were not sufficient to investigate cortico-striatal loops in MS for example. Due to the study design, we did not administer a comprehensive neuropsychological test battery to examine all cognitive domains. Therefore, the results only represent the cognitive tests which have been commonly used in clinical trials and clinical screening. Nonetheless, the PASAT and SDMT are well validated, sensitive and widely used measures of cognition in neurological disorders and inclusion of these measures allows us to compare to previous imaging and cognition studies. Future studies should seek to determine interhemispheric connectivity across a wide range of cognitive domains. While we made attempts to prevent overfitting, including cross-validation, more subjects would enhance the robustness of our results. In addition, the patients were not recruited based on cognitive impairment so our results might not be representative of neurological disease cohorts with severe cognitive problems. Finally, fMRI feature selection for assessing relations between rsFC and cognitive functions remains challenging. Including too few features may lead to insufficient information for brain-behaviour analysis, but having too many features often causes overfitting in neuroimaging research. How to extract informative rsFC characteristics has become an important need. Several methods have been proposed to summarize rsFC patterns such as graph theoretical analysis and other advanced network approaches [Fornito et al., 2013; Rubinov and Sporns, 2010]. These approaches will be discussed in the following chapters.

3.6 Conclusion

This study emphasizes the importance of intact functional interhemispheric connectivity in MS and PD, particularly with respect to cognitive performance. We have demonstrated the

characteristics of interhemispheric connectivity in neurological conditions and healthy controls: these connections are enhanced and become more homogeneous in patients. Furthermore, in MS, SDMT and PASAT scores were robustly correlated with interhemispheric connectivity. Exploratory analysis revealed that long-range connections were altered in MS and such connectivity pattern was related to PASAT performance; while the connections between the frontal and caudate regions distinguished PD on and off medication states but were not related to any clinical scores. The results may potentially benefit the development of novel treatments for cognitive deficits in neurological disorders: targeting interhemispheric connections (as well as long-range connections) and providing cognitive training may help with maintaining normal cognitive functioning.

Chapter 4: Brain organization and executive function

In this chapter, graph theoretical analysis is carried out to investigate the brain organization in PD and MS, which includes functional integration, functional segregation, and hub structures. Moreover, correlation and regression analyses are implemented to explore the relations between brain organization, cognitive performances, and disease severity in both neurological populations. A simple analysis is conducted to test the reproducibility of these graphical measures.

4.1 Introduction

4.1.1 Connections and networks of rsFC and the relations to cognition

Many neuroimaging studies attempt to link cognitive deficits and functional connectivity (FC) at rest. Impaired corticostriatal connectivity resulting in decreased integration among the striatum, mesolimbic cortex, and sensorimotor cortex has been associated with some non-motor symptoms in PD such as mental “rigidity” [Luo et al., 2014]. Overall global cognitive performance in PD is shown to be associated with decreased FC in widespread regions including the paracentral lobe, superior parietal lobe, occipital regions, inferior frontal gyrus, and superior temporal gyrus [Olde et al., 2014]. Weakened FC in the frontoparietal network has been shown to be related to worsening executive function in PD with mild cognitive impairment (MCI) [Amboni et al., 2014a]. Therefore, it is speculated that not only the frontostriatal connections but whole-brain altered connectivity contributes to cognitive deficits in PD.

In MS, decreased connectivity indicates that cortical regions fail to integrate information in resting-state networks (RSNs) derived from independent component analysis (ICA), especially the medial prefrontal cortex and posterior cingulate cortex in the default mode network (DMN), and has been associated with worsening executive function in cognitively impaired patients [Cruz-Gómez et al., 2014; Louapre et al., 2014]; however, another study which calculated whole brain Pearson's r matrices reported that increased functional coupling of rsFC within the DMN regions was related to worsening cognitive efficiency, which was measured by several tests reflecting executive function [Hawellek et al., 2011b]. With a seed-based approach, increased functional connectivity between “cognitive hubs” and the cerebellum, middle temporal gyrus, occipital pole, and angular gyrus was associated with better performance of executive ability, but this study focused on limited brain regions and may neglect ROIs which are not mentioned in the traditional psychology literature [Loitfelder et al., 2012].

4.1.2 Graphical measures and cognition

One of the strategies to characterize the whole brain FC is to apply *graph theory analysis* to summarize the overall network of connections between Regions of Interest (ROIs). These network characteristics summarize the whole brain FC globally and locally in terms of functional integration, segregation, and core/hub structures [Rubinov and Sporns, 2010; Sporns, 2013]. Several network measures have been linked to human intelligence and cognitive functions in healthy subjects [Cohen and D'Esposito, 2016; Pamplona et al., 2015]. In PD, regions in the orbitofrontal regions and occipital pole show decreased node degree (i.e. fewer numbers of connections to/from a given region); while superior parietal, posterior cingulate cortex, supramarginal, and supplementary motor areas have increased node degree [Göttlich et al., 2013].

Baggio et al. [Baggio et al., 2014] discovered reduced FC in long-range connections (i.e. connections between frontal, occipital, and parietal areas) in both PD and PD with MCI; while increased graph theoretical measures such as clustering coefficient, local efficiency, and modularity in the frontal areas were negatively correlated with attention/executive scores in PD with MCI, possibly as compensation/adaptation for impairments in long-range connections. Patients with MS exhibit reduced global efficiency, node degree, centrality, and increased path length on average compared to normal controls, demonstrating altered rsFC in network organization as well as implying inefficient information transfer in the brain in MS [Rocca et al., 2016a]. Another study found that only local measures (local efficiency and clustering coefficient in the left insula, inferior frontal areas, and cuneus) were decreased in MS, but these alterations did not show any associations with cognitive scores in a correlation analysis [Shu et al., 2016]. In addition, an article concluded that increased modularity of rsFC in early stage MS, which represented diminished functional integration, was correlated with worse performance in a dual task [Gamboa et al., 2014]. Overall, although there are minor discrepancies between studies, research with graph theory implies that rsFC in MS is more segregated and may be less efficient to support complex cognitive tasks.

4.1.3 Hub structures and cognition

Previous work has suggested that “hub regions” may be particularly vulnerable to neurodegenerative processes [Crossley et al., 2014]. In healthy subjects, the insula and several frontal regions such as the superior frontal gyrus act as hubs and may facilitate cognitive processes to an even greater extent than the caudate [Baggio et al., 2015; van den Heuvel and Sporns, 2013]. In PD, there is a tendency of failure in hub regions and non-hub regions become more important

than that in healthy subjects [Koshimori et al., 2016]. Reduced importance of normal hubs in the frontal areas and increased importance of non-hub regions in other cortices has been observed in PD with MCI [Baggio et al., 2014]. In PD, the insula may be less likely to act as a hub, but there may be an enhanced role of the caudate as a hub [Koshimori et al., 2016]. This altered brain organization may indicate that the disease first impairs hubs that are important for cognition, resulting in cognitive dysfunction in PD.

On the other hand, in MS, decreased importance in sensorimotor and ventral stream regions has been related to higher disease severity and poor cognition, respectively [Schoonheim et al., 2013]. In MS with MCI, increased connectivity in the DMN and frontoparietal network, which engage many hub regions, is correlated with worse cognitive performance, stating that cognitive impairment affects distributed communication between non-hub regions in “hub-rich” networks [Meijer et al., 2017].

4.1.4 Study aims

In this study, we aimed to investigate 1) functional connectivity changes in PD and MS subjects measured by graph theory analysis, and 2) how cognition is associated with altered graphical measures in PD and MS. Instead of only investigating FC in specific circuits such as the frontostriatal loops, we studied whole-brain connectivity and characterized it by graph theory measures. Finally, we utilized correlation analyses to explore the associations between FC and cognitive profiles and performed regression analyses to predict behavioural outcomes.

Advanced network analyses have been increasingly conducted and applied to clinical neuroimaging research. As there is a growing trend to include these measures in rsfMRI studies,

reproducibility of such features needs to be addressed. Some studies have shown that several graphical measures demonstrate high reliability and reproducibility such as global efficiency, path length, and clustering coefficient among others [Braun et al., 2012; Shah et al., 2016; Telesford et al., 2010]. We also conducted a simple analysis to test whether these graphical measures were reproducible across scans.

4.2 Materials and methods

4.2.1 Subjects and behavioural data

Eleven healthy subjects (mean age: 25.7 ± 3.6 , 4 females, 7 males, all with university education level) were recruited to test the reproducibility of advanced network measures. None of these subjects showed neurological or psychiatric conditions.

The PD data are from the Parkinson's Progression Marker Initiative (PPMI) and MS data are from the COGMS project -- the same as chapter 2. Only a subset of MS subjects were used to ensure that the healthy subjects used for comparison were age-matched healthy subjects.

Thirty-one PD patients who enrolled in the PPMI were included in this study. Detailed descriptions are provided in section 2.2.1. For imaging analysis, twenty-three subjects were included as 8 subjects had excessive imaging and motion artifacts and they were removed from the analysis. Only one subject in the final cohort showed MCI. For comparison, nineteen age-matched healthy subjects (HS) were recruited in this study through Pacific Parkinson's Research Centre at UBC Hospital. None of the HS showed cognitive impairment screened by MoCA. Ethics approval was issued by the University of British Columbia's Research Ethics Board and all subjects provided

written, informed consent. Table 4.1 shows the demographical characteristics of PD and HS subjects.

Forty-six Relapsing-Remitting Multiple Sclerosis (RRMS) patients were included in the study and all the subjects underwent both cognitive testing and MRI scanning. Demographics are shown in Table 4.2. A subset of MS subjects and age-matched normal controls (NC) with university education were included for comparison purposes (18 MS and 15 NC, mean age $\pm$ SD in MS/NC: 32.00 $\pm$ 4.93/28.93 $\pm$ 5.00) (Table 4.2). All patients fulfilled the McDonald 2005 criteria [Polman et al., 2005] for the diagnosis of MS and were recruited from the MS clinic at the University of British Columbia Hospital. Exclusion criteria included: 1) subjects with significant depression and/or other psychiatric illness, 2) history of drug or alcohol abuse, or 3) use of steroids in the last 3 months.

After the exclusions for movements and imaging artifacts, the final PD cohort included 23 subjects and 19 healthy controls. The data were used in both measure comparison and brain-behaviour analysis. The final MS cohort included 46 MS subjects for brain-behaviour analysis. For measure comparison, a subset of the MS subjects were chosen (18 subjects) and 15 healthy controls were included in order to be age-matched.

	Parkinson's subject (mean $\pm$ SD)	healthy subject (mean $\pm$ SD)
demographics & clinical data		
gender	10 females/13 males	9 females/10 males
age ^b	61.04 $\pm$ 9.8	56.12 $\pm$ 16.9
UPDRS ^b	16.96 $\pm$ 11.2	no data
depression ^b	5.17 $\pm$ 1.1	no data
education in years ^b	17.17 $\pm$ 2.8	no data
cognitive scores		
MOCA ^b	27.48 $\pm$ 2.2	27.39 $\pm$ 1.6 ^a
BJLOTOT ^b	25.30 $\pm$ 4.2	no data

HVLTTOT ^b	23.09±5.8	no data
HVLTDELAY ^b	8.39±2.7	no data
DVT-HVLTOTAL ^b	44.70±15.4	no data
DVT-HVLTDELAY ^b	49.00±16.0	no data
DVT-HVLTRETENTION ^b	49.61±13.0	no data
LNS-RAW ^b	10.74±2.6	no data
SFCOM ^b	48.22±10.6	no data
SFVEG	13.74±3.9	no data
SFANI	21.52±4.9	no data
SFFRU	12.96±4.1	no data
SDMT ^b	41.57±9.3	no data

Table 4.1 Demographics, clinical data, and cognitive scores in PD and HS.

[UPDRS = Unified Parkinson's Disease Rating Scale, MOCA = Montreal Cognitive Assessment, BJLOTOT = Bento Line Orientation Total Score, HVLTTOT = Hopkins Verbal Learning Test-Revised Total Score, HVLTDELAY = HVLT Delayed Recall Score, DVT-HVLTOTAL = standardized HVLT Total Score, DVT-HVLTDELAY = standardized HVLT Delayed Recall Score, DVT-HVLTRETENTION = standardized HVLT Recognition Trial Score, LNS-RAW = raw Letter-Number Sequencing Test Score, SFCOM = Semantic Fluency Test – combination, SFVEG = Semantic Fluency Test – vegetable trial, SFANI = Semantic Fluency Test – animal trial, SFFRU = Semantic Fluency Test – fruit trial, SDMT = Symbol Digit Modalities Test]

a: one data point is missing

b: the tests that were included in brain-behaviour analysis

	46 MS subjects	18 MS subjects	15 NC subjects
Age	42.89±10.9	32.00±4.9	28.93±5.0
Gender	13 males/33 females	3 males/15 females	7 males/8 females
EDSS	2.47±1.8	1.63±1.5	no data
Education (years)	14.80±2.5	15.67±2.5	18 ^a
Disease Duration	11.45±8.7	5.46±3.8	no data

Table 4.2 Demographics in MS and NC.

^a Due to many missing data points, 18 is an estimated number.

The neuropsychological assessments in PD and MS have been described in section 2.2.2. Detailed cognitive scores of 46 MS subjects are shown in Table 2.2. Overall, attention, executive function, visuospatial ability, and memory domain were evaluated in PD and 14 behavioural scores were included in brain-behaviour analysis as indicated in Table 4.1. Attention, executive function, processing speed, and working memory domains were assessed in MS and 14 behavioural scores were included in brain behaviour analysis such as age, education, EDSS, disease duration, Working Memory Index (WMI), Processing Speed Index (PSI), Verbal Fluency Test (FAS), Wisconsin Card Sorting Test Complete Categories (WCST-CC), transformed Trail-Making-Test A and B (tTMTA/B), Multiscale Depression Inventory (MDI), State-Trait Anxiety Inventory State (STAI-S), State-Trait Anxiety Inventory Trait (STAI-T), and Fatigue Severity Scale (FSS).

4.2.2 Imaging acquisition

For testing the reproducibility, three resting state fMRI (rsfMRI) sessions were scanned continuously on a Philips Achieva 3.0 Tesla MRI scanner with an echo-planar imaging (EPI) sequence with the following parameters: $3 \times 3 \times 3 \text{ mm}^3$ resolution, 36 slices, 2000 ms Repetition Time (TR), 30 ms Echo Time (TE), 90 degrees flip angle, and 240 volumes/dynamics (8 minutes in total). 3 Dimensional (3D) T1 weighted images were acquired with $1 \times 1 \times 1 \text{ mm}^3$ resolution, 60 slices, 28 ms TR, 4 ms TE and 27 degrees flip angle.

In PD subjects, a standardized MRI protocol on a 3 Tesla Siemens Trio Tim MR system was used. 3D T1-weighted structural images were acquired using MPRAGE GRAPPA sequence with TR 2300 ms, TE 2.98 ms, Field of View (FoV) 256 mm, and resolution $1 \times 1 \times 1 \text{ mm}^3$. RsfMRI images were acquired using echo-planar imaging (EPI) to detect Blood Oxygenation Level Dependent (BOLD) contrast with 212 volumes, 40 slices in ascending direction, TR 2400 ms, TE 25 ms, FoV

222 mm, and resolution $3.3 \times 3.3 \times 3.3 \text{ mm}^3$. All HS subjects underwent imaging scans in MRI research centre at UBC Hospital with a Philips Achieva 3.0 Tesla MRI scanner. 3D T1-weighted images were acquired with TR 8 ms, TE 4 ms, FoV 256 mm, and resolution $1 \times 1 \times 1 \text{ mm}^3$. RsfMRI data were acquired with EPI sequence and the following parameters: 186 volumes/dynamics, 36 slices in interleaved direction, TR 2500 ms, TE 30 ms, FoV 240 mm, and resolution $3 \times 3 \times 3.97 \text{ mm}^3$.

Both MS and NC subjects underwent imaging studies at the University of British Columbia (UBC) MRI Research Centre. Resting-state functional MRI (rsfMRI) data were acquired using an 8 channel head coil and an EPI sequence with the following parameters: $3 \times 3 \times 3 \text{ mm}^3$ resolution, 36 slices, 2000 ms TR, 30 ms TE, 90 degree flip angle, and 240 volumes/dynamics. 3D T1 weighted images were acquired with $1 \times 1 \times 1 \text{ mm}^3$ resolution, 60 slices, 28 ms TR, 4 ms TE and 27 degree flip angle.

During rsfMRI scan, all subjects were instructed to rest quietly with their eyes closed and not to fall asleep.

4.2.3 Preprocessing

The preprocessing steps were the same as chapter 3. Image preprocessing steps were performed in each subject's native space with the functions of slice timing and motion correction from Statistical Parametric Mapping 8 (SPM8, University College London, London) for correcting temporal and spatial differences. For registration, the FMRIB's Linear Image Registration Tool (FLIRT) from the FMRIB Software Library 6.0 (FSL, FMRIB, Oxford) was used and a brain mask was applied to remove non-brain areas before registration. Moreover, fMRI images were rescaled to isotropic

using a self-programmed script in Matlab (The MathWorks, Inc.), so all fMRI data were $3 \times 3 \times 3$ (MS and all healthy subjects) and $3.3 \times 3.3 \times 3.3$ (PD subjects) mm^3 resolution. Cortical parcellation of the high-resolution T1 image was done in Freesurfer (Massachusetts General Hospital, Boston, Boston). Human motor association area template (HMAT) was implemented in order to define the ROIs that are specifically related to human motor function [Mayka et al., 2006]. For the test of reproducibility, thirty-six cortical ROIs were selected as the purpose was to quickly examine network measures initially. For studies in PD and MS, sixty-eight cortical and subcortical ROIs were included for connectivity analysis. We considered as many cortical regions as possible but excluded the ROIs that may have a poor signal-to-noise ratio (SNR) in fMRI due to partial volume effect such as the frontal pole, temporal pole, etc. Table 4.3 lists these 68 ROIs. A brain mask was applied before registration to remove non-brain tissue and we registered the structural image to the mean fMRI image. The same transformation was subsequently applied to the ROI mask in order to obtain the ROIs in fMRI resolution. The ROIs acted as masks to determine the appropriate voxels making up the average ROI time courses. Finally, the fMRI time courses of selected ROIs were extracted using in-house scripts in Matlab and the data were detrended before connectivity analysis. Subjects who had translational and rotational head movements during data acquisition of more than 2 mm and 2 degrees respectively were excluded.

4.2.4 Functional connectivity analysis

In the 11 healthy subjects, binary Pearson's r correlation matrices were created to form the undirected/unweighted "edges" and the 36 ROIs acted as the "nodes". The Brain Connectivity Toolbox (<https://sites.google.com/site/bctnet/>) [Rubinov and Sporns, 2010] was used to calculate graphical measures including global efficiency, assortativity, characteristic path length, density,

information flow coefficient, modularity, and rich-club coefficient, which were commonly used in clinical research. Table 4.4 describes the definition of the graphical measures used in this chapter. Repeated measure ANOVA (rmANOVA) and was applied to test whether these measures were significantly different across three scans and coefficient of variation (COV) (standard deviation divided by the mean) was calculated to evaluate the variance across time.

Bilateral ROIs	
thalamus	middle temporal gyrus
pallidum	superior temporal gyrus
caudate	superior occipital gyrus
hippocampus	fusiform gyrus
amygdala	lingual gyrus
insula	inferior parietal gyrus
accumbens	postcentral gyrus
superior frontal gyrus	posterior cingulate cortex
rostral middle frontal gyrus	precuneus
caudal middle frontal gyrus	superior parietal gyrus
inferior frontal gyrus	angular gyrus
lateral orbitofrontal cortex	supramarginal gyrus
medial orbitofrontal cortex	cerebellum cortex
caudal anterior cingulate cortex	primary motor cortex
rostral anterior cingulate cortex	supplementary motor area
entorhinal	pre supplementary motor area
inferior temporal gyrus	

Table 4.3 68 ROIs are used in the PD and MS studies.

Measures		Definition
global measures	global efficiency	the average inverse shortest path length in the network (measure of integration)
	transitivity	the ratio of triangles to triplets in the network (measure of segregation)
	modularity	it quantifies the degree to which the network may be subdivided into clearly different groups (measure of segregation)

local measures	assortativity	correlation coefficient between the degrees of all nodes on two opposite ends of a link (nodes link to other similar nodes, measure of resilience)
	characteristic path length	the average shortest path length in the network (measure of integration)
	rich club coefficient	the fraction of edges that connect nodes of degree k or higher out of the maximum number of edges that such nodes might share (in this study $k = 6$ in PD & 10 in MS)
	betweenness centrality	the fraction of all shortest paths in the network that contain a given node (measure of centrality/hub)
	local efficiency	the global efficiency computed on the neighborhood of the node (measure of segregation)

Table 4.4 Definitions of the graphical measures used in this study.

In PD and MS studies, partial correlation analysis was conducted to generate a connectivity matrix for each subject, which resulted in a 68-by-68 matrix. The Brain Connectivity Toolbox (BCT) [Rubinov and Sporns, 2010] was used to compute graph theoretical measures. The partial correlation matrix was proportionally thresholded and binarized with the density of 15% to ensure equal density across subjects [van den Heuvel et al., 2017]. For global measures, global efficiency, transitivity, modularity, assortativity, characteristic path length, rich club coefficient (for PD, it was at level 6, which is the highest degree that did not give a Not-a-Number (NaN) across subjects due to matrix sparsity; for MS, it was at level 10) were computed [Fornito et al., 2016; Rubinov and Sporns, 2010]. These global measures summarized network characteristics of the entire brain network. For local measures, betweenness centrality and local efficiency were computed [Fornito et al., 2016; Rubinov and Sporns, 2010], which reported nodal characteristics in the network. Two

sample *t*-tests were carried out to test whether graph theoretical measures were significantly different between patient and control groups.

4.2.5 Brain-behaviour analysis

Several approaches were applied to study the brain-behaviour relationship (i.e. associations between graph theory measures and cognitive scores) in PD and MS studies only.

First, we utilized Spearman's correlation analysis exploring whether individual cognitive tests were correlated with graph theoretical measures in PD and MS. The correlation analyses were carried out on all the global measures against raw cognitive scores from individual tests. For local measures, only ROIs that showed significant differences in *t*-tests were included in the analyses. The local measures of these ROIs were included to correlate with raw cognitive scores. Bonferroni correction was applied to correct for multiple comparisons. Of note, only composite scores were included in the brain-behaviour analysis as these scores were representative for cognitive domains. For example, only WMI and PSI were included rather than all subscores of WAIS IV.

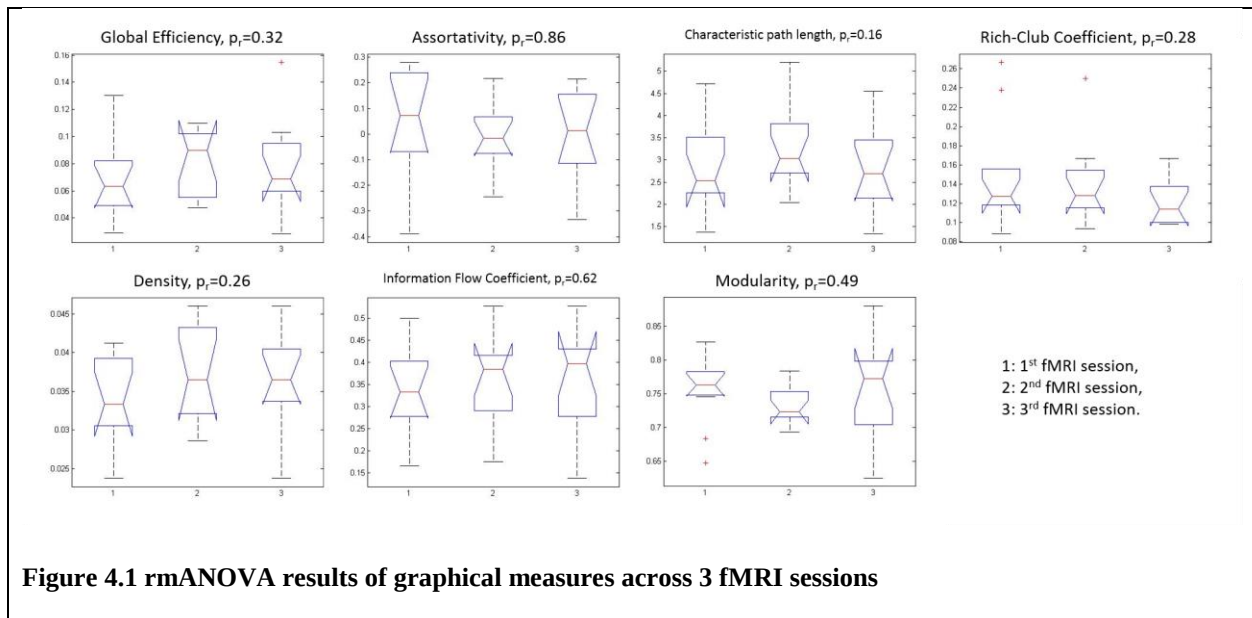
Linear regression was carried out on all global measures against cognitive scores. In other words, all global measures were concatenated in a matrix and acted as predictors, while each cognitive score was the response variable. The *p* values of the linear regression model and R-squared values between real and predicted cognitive scores were reported. Finally, we performed LASSO regression on local measures (predictor data) with 10-fold cross validation to select the nodal values which contributed to individual behavioural scores (the responses). The regression coefficients for such LASSO model were then included in a linear regression to "predict" behavioural scores. At this stage, all calculations were done with all the subjects as a whole without

separating data into training and testing data sets; therefore, we referred the findings as “regression results”. Results with R-squared higher than 0.5 were considered good results and p values were reported. This preliminary approach allowed selection of variables between graphical measures and cognitive scores. Finally, we repeated such processes with training and testing data sets to precisely predict the behavioural outcomes in a leave-one-out fashion, which were referred as “prediction results”.

4.3 Results

4.3.1 Reproducibility

None of the graphical measures showed significant differences among the three fMRI sessions ($p_r > 0.05$ in all measures, Figure 4.1). Moreover, COV of most of the measures derived from three fMRI sessions demonstrated similar values except the measures that were non-Gaussian distributed (Table 4.5). The results indicate that these measures are reproducible across scans.



Graphical Measures	1st fMRI	2nd fMRI	3rd fMRI
global efficiency	42.7%	29.4%	43.2%
assortativity	70.3% #	70.3% #	61.6% #
characteristic path length	33.4%	29.4%	32.3%
density	17.8%	16.2%	16.5%
information flow coefficient	31.5%	28.4%	30.2%
modularity	6.8%	3.9%	9.6%
rich club coefficient	36.4% *	31.1% *	18.8%

Table 4.5 COV of all graphical measures across fMRI sessions.

*** not Gaussian**

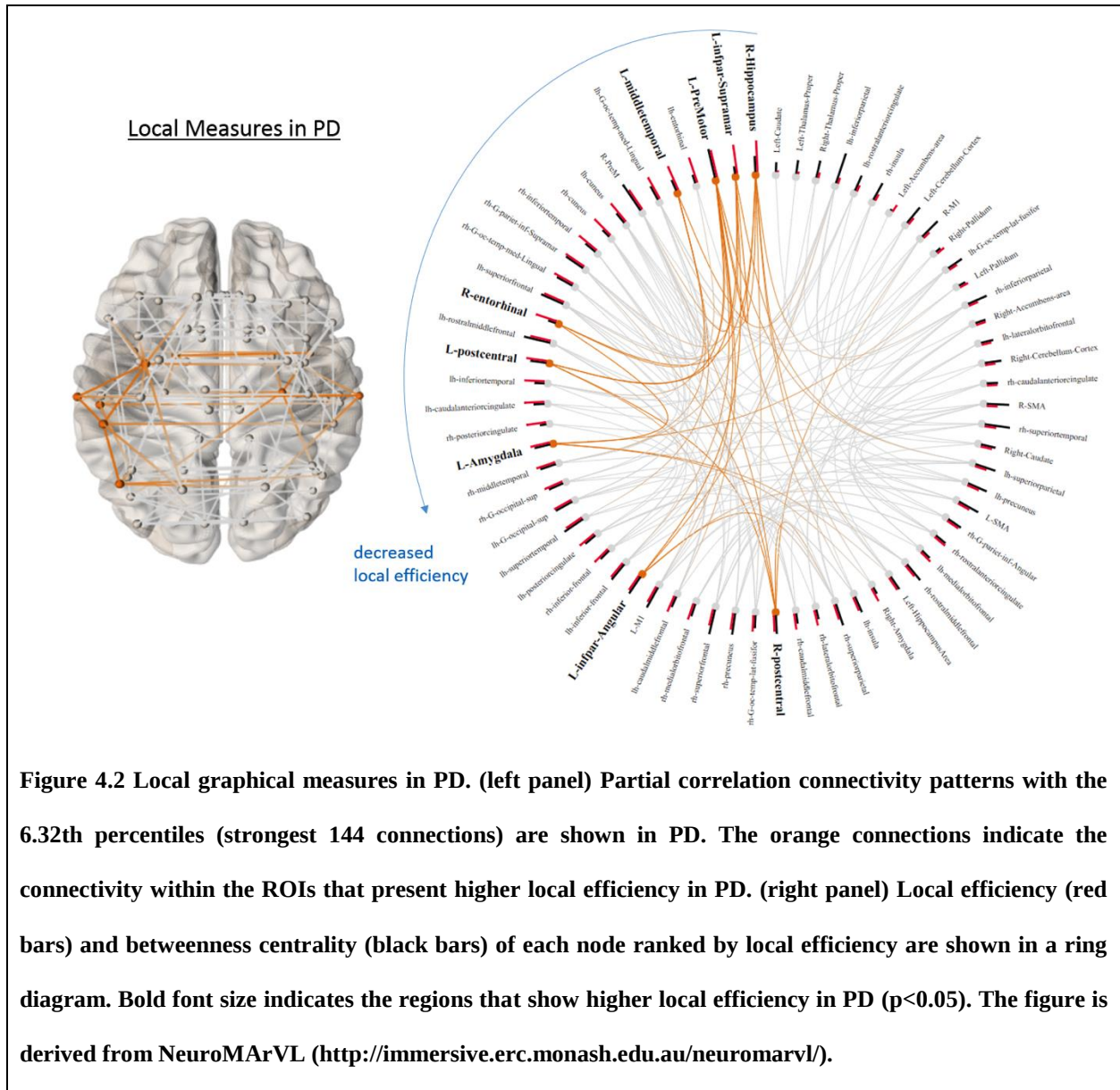
take absolute values

4.3.2 Parkinson's Disease

4.3.2.1 Graphical measures

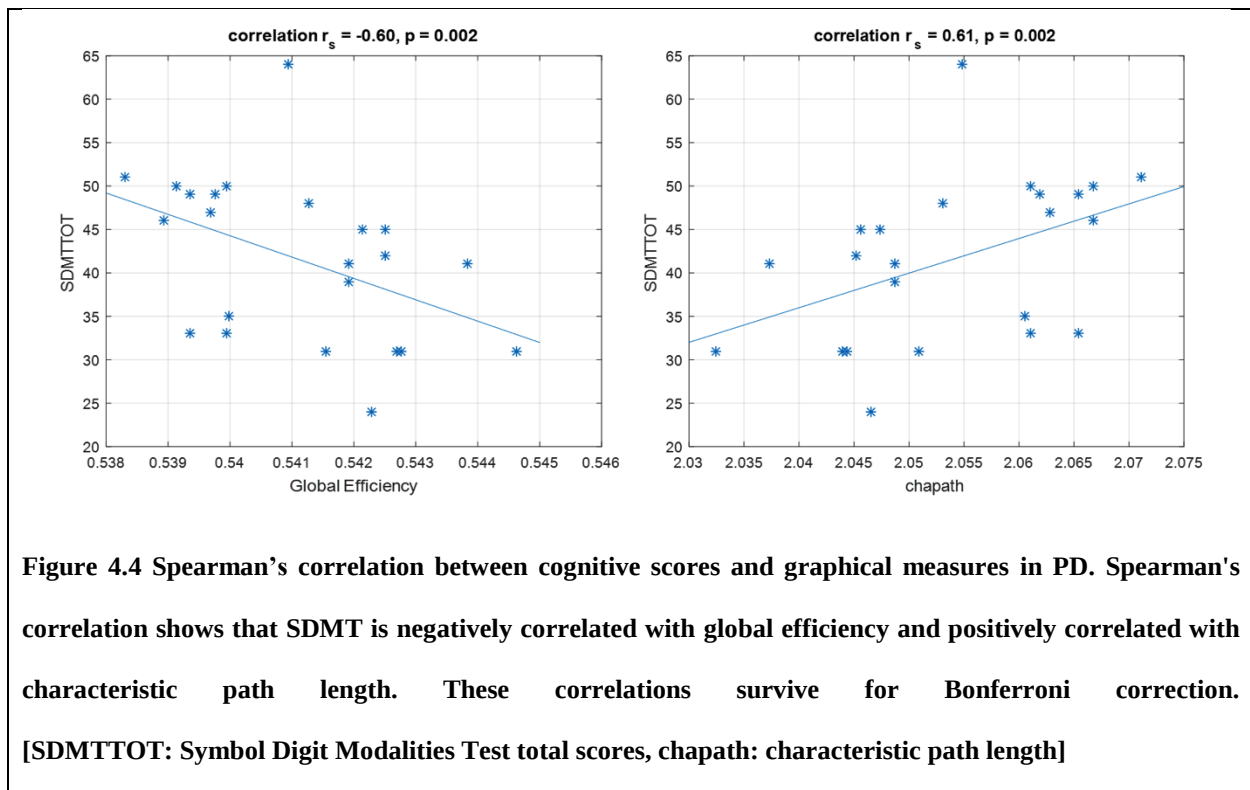
None of the global graph theoretical measures were different between PD and HS, however, several ROIs showed altered local efficiency and betweenness centrality. Figure 4.2 left panel shows the average connectivity patterns in PD on a brain template. Color-coded connections indicated the connectivity within the ROIs that distinguish PD and HS. Figure 4.2 right panel presents the local measures in PD on a ring diagram. The right hippocampus, left supramarginal gyrus, left pre-motor cortex, left middle temporal gyrus, right entorhinal cortex, left postcentral gyrus, left amygdala, left angular gyrus, and right postcentral gyrus demonstrated higher local efficiency in PD ($p < 0.05$, uncorrected) (Figure 4.2, Appendices C.1), indicating that functional connectivity was more segregated in PD. Figure 4.3 left panel highlights the connections that differentiate PD and HS. Figure 4.3 right panel demonstrates local measures in HS ranked by betweenness centrality in a ring diagram and color-coded the ROIs that were significantly different

between two groups. These ROIs showed lower betweenness centrality in PD such as the left superior frontal gyrus, bilateral superior parietal cortices, left middle temporal gyrus, and right inferior frontal gyrus; while the right accumbens area and right pallidum exhibited higher betweenness centrality in PD (Figure 4.3, Appendices C.1). The changes of betweenness centrality in PD indicated an altered hub organization, where important nodes lost significance and the nodes with a less central role have become more important. However, the results did not survive for multiple comparison. Appendices C.2 shows another analysis with logistic LASSO to indicate that graphical measures can be clearly separated into PD and HS groups.



4.3.2.2 Brain-behaviour association

In the Spearman's rank correlation analysis, only raw Symbol Digit Modality Test (SDMT) scores were significantly correlated with global efficiency and characteristic path length ($p = 0.002$ and $r_s = -0.6$, $p = 0.002$ and $r_s = 0.61$, respectively, survive for Bonferroni correction with 14 tests were run) (Figure 4.4). Higher global efficiency was related to lower SDMT scores; while higher characteristic path length (which is the inverse measure of global efficiency) was associated with better performance. Overall, correlation results indicated that only specific network measures were correlated with the performance of certain cognitive tests. No significant associations were found in local measures.



With all global measures as predictors and individual behavioural scores as responses, linear regression did not reveal any significant models for PD. While performing LASSO on local measures to predict behavioural outcomes, the models were over-fitted as there were 23 observations but 68 features in one model even the processes were carried out in leave-one-out fashion. Therefore, we were unable to report results for regression and prediction analysis in PD. However, with a multivariate approach, better cognitive performance was related to higher modularity and transitivity. The analysis and details are shown in Appendices C.4.

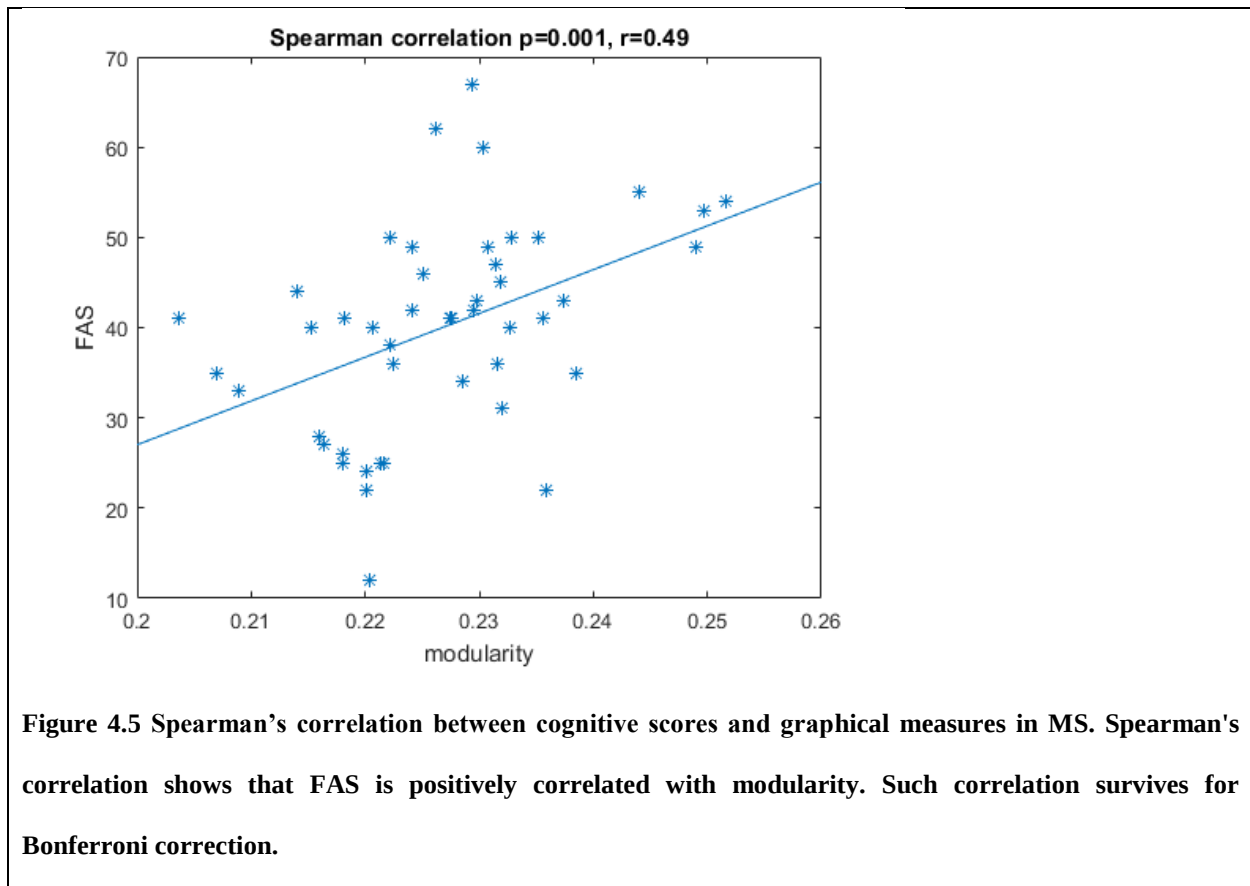
4.3.3 Multiple Sclerosis

4.3.3.1 Graphical measures

None of the global and local measures showed significant differences between MS and NC.

4.3.3.2 Brain-behaviour association

In the Spearman's rank correlation analysis, only the performance of the Verbal Fluency Test (FAS) was significantly correlated with modularity in MS ($r = 0.49$, $p = 0.001$, survived for Bonferroni correction with 14 tests as indicated in section 4.2.1) (Figure 4.5). Higher FAS score (better performance) was related to higher modularity (i.e. more segregated networks).



As none of the local measures demonstrate differences, we did not included either betweenness centrality or local efficiency in the Spearman's rank correlation analysis. In linear regression, the model of all global measures against FAS appeared significant ($p=0.04$); however, only modularity demonstrated significant weighting ($p=0.0038$) and the predictability of this model was small ($R\text{-squared}=0.16$). In other words, FAS was correlated with modularity, but modularity cannot accurately predict FAS in a linear regression.

In the regression results of local measures, we discovered 6 models that demonstrated significant relations between LASSO-selected nodal measures and behavioural outcomes. Selected betweenness centrality exhibited significant relations with EDSS ($p<0.001$, $R\text{-squared}=0.66$),

MDITOT ($p < 0.001$, $R\text{-squared} = 0.65$), and transformed TMTB ($p < 0.001$, $R\text{-squared} = 0.82$) (Figure 4.6, Table 4.5). Selected local efficiency showed significant relations with DD ($p < 0.001$, $R\text{-squared} = 0.77$), PSI ($p < 0.001$, $R\text{-squared} = 0.89$), and STAIS ($p < 0.001$, $R\text{-squared} = 0.77$) (Figure 4.6, Table 4.5). Furthermore, in the prediction results, whereby 23 training and 23 testing data sets were applied, 8 nodal measures of local efficiency accurately predicted EDSS with $p = 0.0078$ and $R\text{-squared} = 0.55$ (Figure 4.7). These 8 nodal measures were the local efficiency of the following ROIs: left thalamus, left inferior frontal gyrus, left lateral orbitofrontal gyrus, left entorhinal cortex, right accumbens area, right lateral orbitofrontal gyrus, right primary motor cortex, and right supplementary motor area.

Local measures	LASSO-selected ROI (gyrus/cortex)	Behavioural score	Statistics
betweenness centrality	L caudal middle frontal, L rostral anterior cingulate, L inferior temporal, L middle temporal, L inferior parietal, L M1, R caudate, R lateral orbitofrontal, R middle temporal, R superior occipital, R superior parietal	EDSS	$R^2 = 0.66$ $p = 3.0 \times 10^{-7}$
	L inferior frontal, L lateral orbitofrontal, L superior temporal, L Lingual, L Angular, M1, R thalamus, R rostral middle frontal, R medial orbitofrontal, R inferior temporal, R superior occipital, R cuneus, R superior parietal, R supramarginal, R preSMA	MDITOT	$R^2 = 0.65$ $p = 7.7 \times 10^{-6}$

betweenness centrality	L Hippocampus, L rostral middle frontal, L lateral orbitofrontal, L middle temporal, L superior temporal, L cerebellum, L preSMA, R hippocampus, R superior frontal, R rostral middle frontal, R inferior frontal, R lateral orbitofrontal, R inferior temporal, R supramarginal	transformed TMTB	R ² = 0.82 p=7.3e-10
	L thalamus, L hippocampus, L inferior frontal, L entorhinal, L cerebellum, L M1, R hippocampus, R accumbens, R superior frontal, R caudal middle frontal, R lateral orbitofrontal, R medial orbitofrontal, R rostral anterior cingulate, R entorhinal, R superior temporal, R lingual, R M1, R SMA		
local efficiency	L hippocampus, L inferior frontal, L medial orbitofrontal, L caudal anterior cingulate, L rostral anterior cingulate, L inferior temporal, L fusiform, L inferior parietal, L postcentral, L post cingulate, L angular, L supramarginal, L M1, L SMA, L preSMA, R caudate, R insula, R accumbens, R superior frontal, R lateral orbitofrontal, R rostral anterior cingulate, R fusiform, R lingual, R inferior parietal, R postcentral, R cuneus, R cerebellum	disease duration	R ² = 0.77 p=2.1e-07
local efficiency	L hippocampus, L caudal middle frontal, L entorhinal, L superior temporal, L superior occipital, L fusiform, L angular, R thalamus, R pallidum, R caudate, R hippocampus, R amygdala, R superior frontal, R rostral middle frontal, R caudal anterior cingulate, R entorhinal, R middle temporal, R superior temporal, R inferior parietal, R postcentral, R preSMA	PSI	R ² = 0.89 p=1.6e-07
local efficiency		STAIS	R ² = 0.77 p=3.3e-06

Table 4.6 Regression results of local measures in MS. The table shows the statistical power to predict behavioural scores using the nodal measures selected by Lasso regression.

[L: left hemisphere, R: right hemisphere, M1: primary motor cortex, preSMA: pre supplementary motor area, SMA: supplementary motor area, EDSS: Expanded Disability Status Scale, MDITOT: Multiscore Depression Inventory Total Scores, TMTB: Trail Making Test B, PSI: Processing Speed Index, STAIS: State-Trait Anxiety Inventory State]

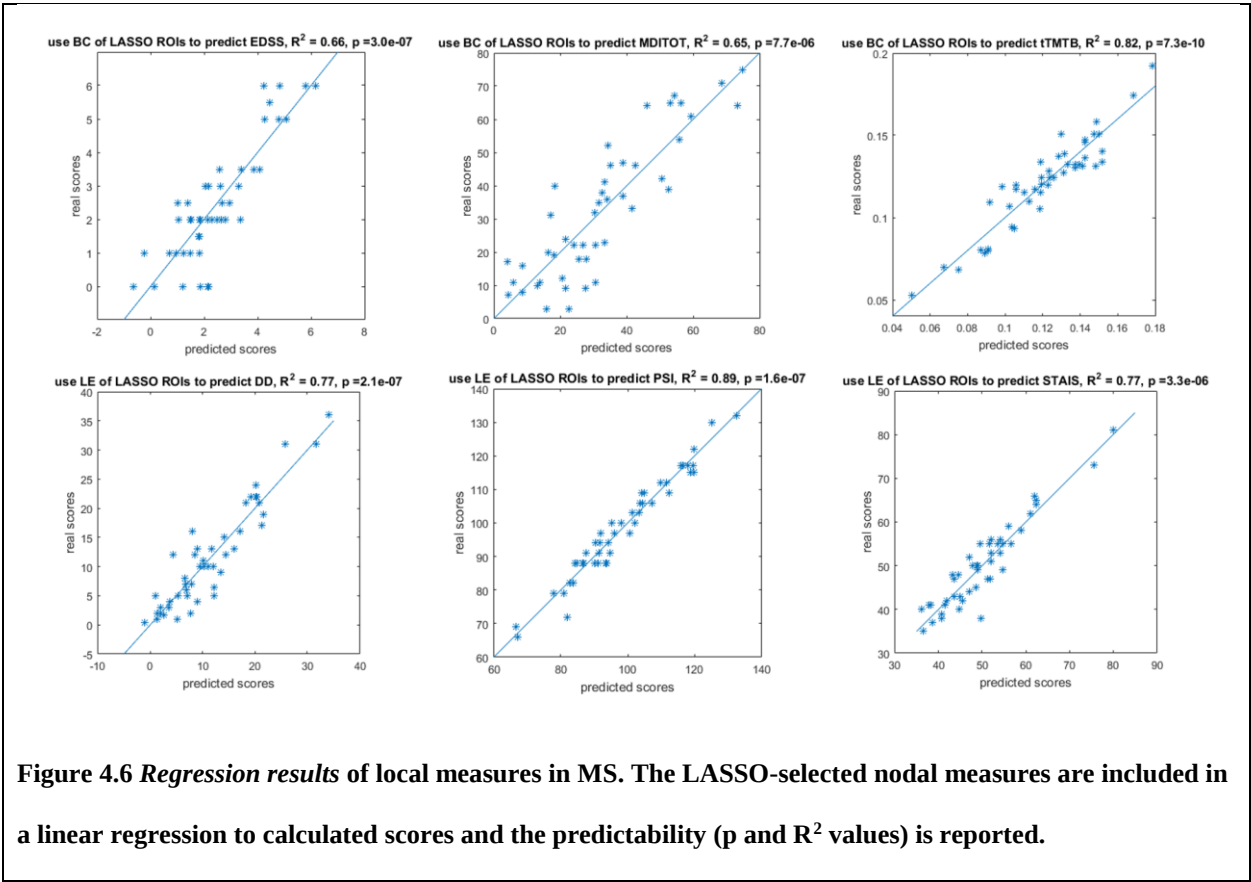
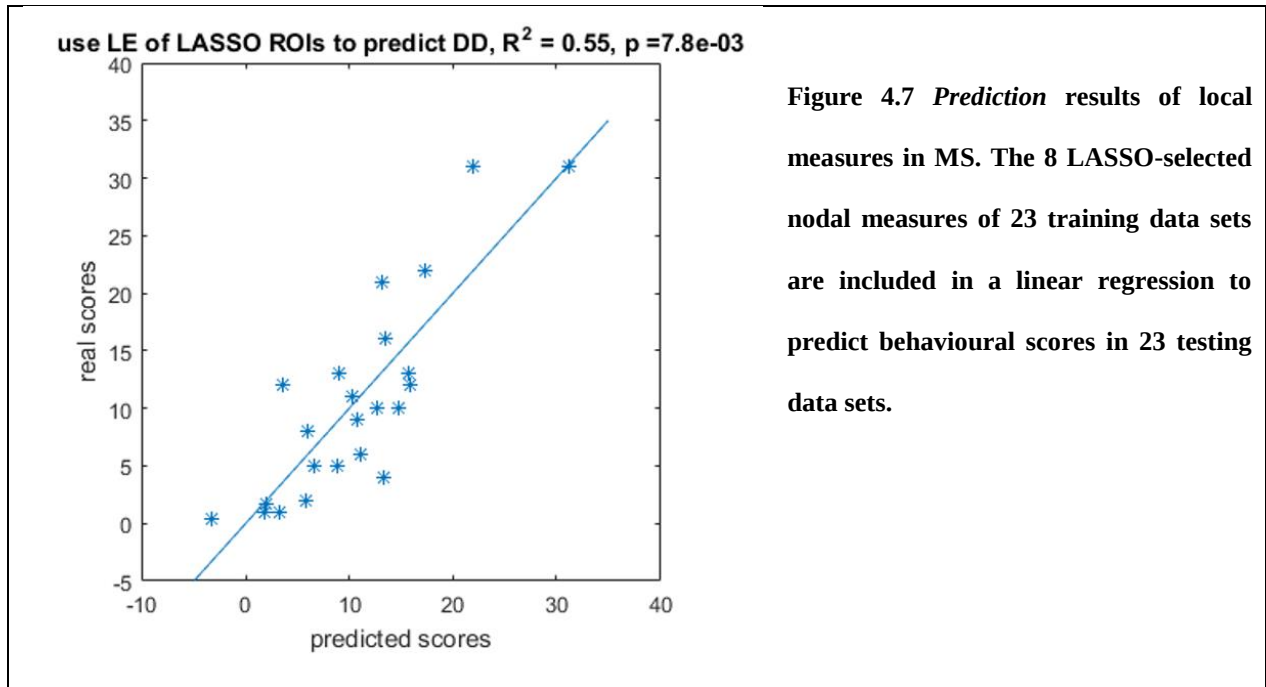


Figure 4.6 Regression results of local measures in MS. The LASSO-selected nodal measures are included in a linear regression to calculated scores and the predictability (p and R² values) is reported.



4.4 Discussion

Our results of reproducibility further support previous studies that have shown that graphical measures are robust observations for resting state functional connectivity. Although sophisticated statistical methods shall be implemented such Inter Class Correlation (ICC), our preliminary results reinforced the rationale of using graphical measures to study brain organization.

4.4.1 Changes of brain organization

Overall brain organization can be thought of as a balance between integration and segregation, in which the former facilitates information integration across the whole brain; while the latter enables information transfer within individual networks [Sporns, 2013]. This organization allows the brain to function in an economical way by reducing the wiring cost of linking anatomically segregated regions [Bullmore and Sporns, 2012]. In addition, hub regions – the cortical areas that play a

central role in the networks – support information integration in many cognitive functions as well as neuronal coupling between networks [van den Heuvel and Sporns, 2013]. These principles together maintain brain function and support cognition in healthy subjects; in the diseased brain, this delicate balance is altered and fails to sustain normal functioning [Crossley et al., 2014; Fornito et al., 2015; Stam, 2014].

Some studies have reported altered functional organization measured by graph theory in PD. For example, PD with MCI presented increased measures of segregation such as modularity and clustering coefficient and these measures in the frontal areas were both negatively and positively correlated with cognition, meaning that functional connectivity in the frontal regions has become more segregated and failed to support cognitive functions [Baggio et al., 2014]. Although other studies reported decreased clustering coefficient and local efficiency [Luo et al., 2015a], which implied that FC might be less segregated, differences in methodology should be taken into account. Increased local efficiency has been observed in PD in another study, further suggesting that information transfer in PD is better within local sub-networks than at the global network level [Berman et al., 2016]. Furthermore, hub reorganization has been described, in which PD lost hubs but other non-hub regions became more important as compensation [Koshimori et al., 2016].

Our results of local graph theoretical measures indicated increased segregation of rsFC in PD, consistent with the previous studies utilizing graph theory. As ROIs across temporal, occipital, parietal, motor association and sensory regions presented higher local efficiency in PD, we propose that functional connectivity of multiple regions in PD has become more segregated than that in HS. Interestingly, most of the ROIs that showed significant differences also had higher local efficiency in PD (Figure 4.2), implying that these regions played important roles in local networks

rather than global connectivity. We also observed hub changes in this cohort, which demonstrated decreased betweenness centrality (i.e. an index of hub and measures how important a given node is) in the ROIs that showed higher values than other regions. These ROIs have been previously defined as functional hubs, such as the superior frontal gyrus, superior parietal gyrus, middle temporal gyrus, and inferior frontal gyrus [van den Heuvel and Sporns, 2013] (Figure 4.3). Although the results were not apparent after controlling for multiple comparison, there was still a trend that these hub regions were affected compared to non-hub regions. In addition, as shown in Appendices C.3, with a more nuanced approach (i.e. Logistic LASSO), local measures can be clearly categorized into PD and HS groups, implying that collectively these nodal measures provide a robust way to distinguish between groups. Thus our findings are consistent with the *vulnerability of hubs* in neurological disease populations [Crossley et al., 2014; Stam, 2014]. Only two ROIs (the right accumbens and pallidum) in this PD population demonstrated increased betweenness centrality and these ROIs in HS showed the smallest values (Figure 4.3).

The increase in connectivity in the right accumbens and pallidum that we observed is intriguing. The nucleus accumbens (NAc) receives dopaminergic projections from the ventral tegmental area (VTA) and substantia nigra (SN) regions and projects to several deep grey matter areas which include globus pallidus; therefore, the NAc has been hypothesized to be associated with the nigrostriatal and mesolimbic systems [Salgado and Kaplitt, 2015] and linked to reward behaviour [Knutson et al., 2007]. In PD, the NAc receives less dopamine projection from the VTA and SN and the globus pallidus receives output from the NAc, so the increased FC is perhaps surprising. The PD patients in this study were relatively mildly affected, and likely capable of a significant

amount of compensation. Thus NAc and pallidum may up-regulate their overall connectivity to maintain function.

Unlike previous studies which reported changes in global measures such as modularity [Baggio et al., 2014], we did not observe differences in global indices. Again, as our cohort was relatively mildly affected, the limited damages in local regions might not be severe enough to impact global measures. Local FC might be more sensitive to pathological and physiological features and potentially serve as biomarkers than global measures at early disease stages.

In our MS cohort, we did not find any graphical measures which were significantly altered. Although the sample size was relatively larger than that in our PD cohort, none of the MS subjects demonstrated cognitive impairments at the time of examination. Therefore, we suspected that the pathological damages were not severe enough to impact functional connectivity measured by graph theory. However, brain-behaviour analysis revealed some promising results (discussed in the following sections), which implied that even though there were no significant changes of brain organization, subtle alterations of graphical measures were informative of cognitive decline and disease severity.

4.4.2 Reduced functional integration and increased functional segregation correlated with better cognitive performance

The relations between FC, graph theoretical measures, and cognition have gained attention lately in network neuroscience and clinical studies. Several graphical measures have been associated with intelligence, working memory, and executive functions in healthy subjects [Cohen and D'Esposito, 2016; Pamplona et al., 2015; Reineberg and Banich, 2016], yet research in

neurological disorders has been limited to a few studies. With a correlation approach, a study reported that hub organization in PD was more related to dopaminergic medication dosage rather than cognitive functions [Koshimori et al., 2016]. Although the study did not rule out the associations between hubs and cognitive functions that a simple correlation method might not be able to catch, more sensitive statistical analyses are required to explore complex relations between cognition and FC. With a linear regression analysis, Baggio et al. discovered that increased local measures in PD with MCI, such as clustering coefficient, local efficiency, and modularity in the frontal areas, were correlated with worse attention and executive function [Baggio et al., 2014]. As previously mentioned in the introduction (section 4.1.2), some studies have proposed that function connectivity in MS is more segregated (i.e. reduced integration) compared to healthy subjects [Gamboa et al., 2014; Liu et al., 2017; Rocca et al., 2016a]; however, whether such segregated brain organization is related to any cognitive function remains unclear. Overall, in both PD and MS, more evidence of the associations between cognitive functions and FC is needed to underline the neural mechanism of cognition and how the disease affects behaviour.

In this study, we only observed strong correlations between measures of integration (i.e. global efficiency and characteristic path length) and SDMT scores in PD with a correlation analysis. The performance of SDMT requires attention, processing speed, scanning abilities, and engages several brain regions including the occipital cortex, middle frontal gyrus, precuneus, superior parietal lobes, and cerebellum [Forn et al., 2011] and has been proven as a robust tool to detect cognitive impairments in healthy aging and neurological disorders [Alamri et al., 2017; Parmenter et al., 2007; Sheridan et al., 2006]. Therefore, it would be reasonable to assume that higher functional integration is related to better SDMT performance. In fact, our results demonstrated the opposite

trend, whereby higher functional integration (i.e. higher global efficiency and lower characteristic path length, as they are inversely related) was related to poor performance of SDMT. Furthermore, as shown in Appendices C.3, with a multivariate approach we revealed that better cognitive function in several domains was associated with higher measures of functional segregation, supporting the results with the univariate method (i.e. correlation). Such paradoxical relations may be potentially due to disease effects, leading toward a more segregation-oriented brain organization in order to respond to cognitive demand. This is consistent with prior reports, demonstrating more segregated FC in frontal areas related to attention/executive function in PD [Baggio et al., 2014]. We suggest that “pathological resonance” in the basal ganglia–cortical network, previously described in PD [Eusebio et al., 2009], may result in excessive *regional* integration but overall *global* segregation.

Although increased modularity in MS has been related to worse dual task performance [Gamboa et al., 2014], we, in fact, observed the opposite relation. Higher modularity, which implies a stronger subdivision into segregated groups of nodes, was correlated with better performance of verbal fluency test in our cohort. Such association asserted that the executive skills of spontaneously generating information according to rules are associated with brain regions subdividing into segregated groups in mild MS. Patient demographics could be a factor to explain these discrepancies between studies. First, the previous study [Gamboa et al., 2014] included both RRMS and clinically isolated syndrome (CIS) patients as they counted for “early stage of MS”. On the other hand, we only included RRMS in the study. Moreover, the sample size in our study is almost 6 times bigger (46 RRMS in our study, 8 RRMS in the previous study) than that in the previous research, which provides stronger statistical power to obtain robust results. Finally,

although the dual task included PASAT and a maze test, subjects were instructed to give priority to the PASAT. The cognitive performance of the previous study required different skills compared to the Verbal Fluency Test. Presumably, such dual task requires more attention, calculation, processing speed, and visuospatial orientation abilities; while the Verbal Fluency Test measures higher-order skills which is more goal-oriented. Therefore, we concluded that better executive functioning is associated with more segregated rsFC in MS. Such segregated rsFC, which represents a reduction of network efficiency, could be a result of compensating for tissue damage before network collapse [Fleischer et al., 2017].

The optimal balance between brain segregation and integration for higher-order cognitive function remains a source of debate, with previous research arguing for more of one or the other [Cohen and D’Esposito, 2016; Reineberg and Banich, 2016]. Between-network communication (i.e. integration) may be important for working memory [Cohen and D’Esposito, 2016], but executive functions may require more nodal FC (i.e. segregation) [Reineberg and Banich, 2016]. The delicate balance of segregation/integration may relate to the balance between focusing on internal brain states versus external sensory input [Miller and Cohen, 2001]. Sensory input from several cortices can send signals to the prefrontal cortex, which integrates this information with internal brain states, with the resultant output transferred to subcortical and motor association areas to execute the action. Presumably, during processing of input and output in the prefrontal regions, integration is required in order to communicate with different brain regions; while processing internal states, redundant and unnecessary regions are excluded in order to focus on the processes within the prefrontal cortex. We propose that the disease may have preferentially affected integration between remote regions rather than internal processing, consistent with the “pathological resonance”

concept alluded to above in PD. Moreover, in MS, segregated brain organization may represent a compensatory mechanism before network collapse.

4.4.3 Predictability of graphical measures to behaviour

One of the challenges to predict behavioural outcome using imaging data is sample size. Unfortunately, due to small sample size, we were unable to perform LASSO analysis on local measures in PD as there were too many features and not enough observations. The linear regression model did not show significant relation between global measures and behavioural outcome in PD. Therefore, this section mainly discusses the findings in MS.

Although correlation analysis showed the associations between individual graphical measures and behavioural scores, further analyses can be done to investigate whether any of the features were jointly related to any behavioural outcome. In this study, with linear regression, only modularity was related to verbal fluency performance, further supporting the relation between segregated brain organization and executive skills. However, the predictability of such altered rsFC to executive skills was not promising in linear regression as R-squared value between real and predicted FAS was only 0.16. Taken together, certain executive skills were indeed related to segregated brain networks (i.e. brain networks have more modules rather than working as a whole), but the association was not strong enough for brain connectivity to accurately predict behaviour.

For local measures, as there were too many features for linear regression and caused insufficient observations, we decided to perform LASSO first as a step of feature selection. The selected nodal graphical measures were included as predictor data in linear regression and individual scores acted as responses. This process revealed which nodal measures were influential to behavioural

outcomes and whether such influence was strong enough to predict individual scores. For EDSS, the betweenness centrality (indicate the importance of a given node) across frontal, temporal, parietal, and occipital regions as well as motor areas demonstrated strong impacts to predict disease severity measured by physical disability. For depression symptoms, interestingly, most of the influential nodes were located in the frontal regions and a subset were in the occipital, parietal, and subcortical areas. For TMTB performance, the importance of several frontal and temporal nodes were significantly influential as well as the inferior parietal region and cerebellum. These nodal measures together highly predicted TMTB performance, which requires task switching ability. Therefore, we propose that 1) the disease severity was related to distributed regions in MS, 2) the importance of frontal regions was largely related to depression symptoms in MS, and 3) executive function (i.e. task switching ability) was significantly associated with the coordination between not only frontal, temporal, and parietal regions but also the cerebellum, supporting the “cognitive role” of cerebellum in neurological diseases [Buckner, 2013].

Local efficiency (i.e. network efficiency in nodal level) of frontal, subcortical, and motor-associated regions highly predicted disease duration. Of note, this was the only model that could predict disease duration in the testing data. In the prediction results, even though fewer nodes were selected, these regions still covered frontal, subcortical, and motor association regions, which further emphasized the role of these regions regarding disease duration. The longer the disease duration, the higher nodal efficiency in these regions. For processing speed ability, highly distributed regions were included, highlighting that processing speed requires distributed regions across whole brain (include cerebellum) to coordinate together. Finally, unlike depression, state anxiety was more related to nodal efficiency in subcortical and temporal regions rather than the

frontal cortex, suggesting a different mechanism compared to depression even though both symptoms are affective. To conclude, pathology-related scores were more associated with nodal efficiency in frontal, subcortical, and motor areas; while cognition-related scores were more associated with connectivity across whole brain. Anxiety, on the other hand, involved different mechanism opposite to other affective disorders.

4.4.4 Limitations

First, due to motion and image artifacts, eight PD subjects had to be removed from the connectivity analysis and the sample size was relatively small. For advanced statistical approaches, including machine learning methods, a bigger sample size will likely be needed. Although the sample size of MS cohort seemed to be sufficient to perform LASSO regression and leave-one-out cross validation was applied, a bigger sample size would still be required to maximize the advantages of machine learning approaches and avoid over-fitting. Moreover, subjects in both study cohorts tended to be mild and were in the early stages of the disease. This could be the reason why we did not observe significant differences between patients and HS after correcting for multiple comparison and why we found few associations between graphical measures and cognitive scores in correlation and regression analyses.

4.5 Conclusion

In this study, with a graph theoretical approach, we demonstrated that rsFC was more segregated in PD across regions and PD subjects demonstrated hub vulnerability. Increased connectivity in the nucleus accumbens and pallidum suggested possible compensation for PD pathologies in mildly-affected individuals. With a correlation analysis, we concluded that attention and

processing speed abilities were associated with segregated FC in PD, possibly related to pathological synchrony in basal ganglia structures. This conclusion was further supported by the results of multivariate analyses. In MS, the ability of generating information based on rules was also correlated with segregation rsFC, possibility representing a compensatory effect before network collapse. Furthermore, nodal graphical measures across frontal, subcortical, and motor association areas can predict disease progression; while nodal measures across cortices in cerebrum and cerebellum predicted executive skills. Finally, different affective disorders in MS may involve different mechanisms.

Chapter 5: Dynamic functional connectivity and executive function

This chapter investigates whether time-varying dynamic functional connectivity (dFC) at rest can be used as a biomarker for neurological disorders (i.e. PD and MS). Several dynamic features are calculated to summarize how connectivity changed over time. Moreover, how dynamic features of rsFC are related to cognition, especially executive function, and reproducibility of these dynamic features is also investigated.

5.1 Introduction

5.1.1 Dynamic functional connectivity

Recent evidence has shown that connectivity fluctuates across time from seconds to minutes even in the resting state, which can be estimated by models of dynamic functional connectivity (dFC) [Allen et al., 2014; Betzel et al., 2016; Chang and Glover, 2010; Handwerker et al., 2012; Hutchison et al., 2013a; Jones et al., 2012]. The simplest, and perhaps most common time-varying approach to assess dFC is to estimate correlations between brain regions within a fixed-length, sliding window, with the (possibly overlapping) windows ultimately moved over the entire data. Nevertheless, there are potential pitfalls with such an approach [Hindriks et al., 2016; Hutchison et al., 2013b]; if the window is too long, then important dynamic changes may be missed. If the window is too short, the connectivity estimates may be unstable as too few samples are available for the statistical inferences. A window length of 30-60 seconds for fMRI data has been heuristically suggested [Leonardi and Van De Ville, 2015; Zalesky and Breakspear, 2015]

5.1.2 Dynamic functional connectivity and cognition

Dynamic functional connectivity (dFC), also referred to as network dynamics and assessed by time-varying approaches, appears to be particularly pertinent to several cognitive processes including memory, language, attention, and executive functions [Braun et al., 2015; Bressler and Scott Kelso, 2001; Kucyi et al., 2016; Mattar et al., 2015; McIntosh et al., 2008; Nomi et al., 2017; Shafto and Tyler, 2014; Thompson et al., 2013]. Increased dynamical variability in the EEG was found to be correlated with better performance (i.e. shorter reaction time and higher accuracy) in a memory task, emphasizing the importance of brain complexity in cognitive development [McIntosh et al., 2008]. There are associations between dynamic changes in frontoparietal/frontotemporal networks and neuropsychological measures, showing that the flexibility of neuronal activity in the frontal regions is cognitively beneficial for working memory performance and executive functioning [Braun et al., 2015]. This has led to a proposed “functional cartography” of the cognitive system, based on the estimated amount of *integration* and *recruitment* of brain regions during different cognitive processes [Mattar et al., 2015]. In addition, cognitive flexibility, which is an important part of executive function, has been associated with greater variability of resting-state connectivity [Nomi et al., 2017]. Network dynamics may also be important for language function in an aging population [Shafto and Tyler, 2014]. Measures of dFC have been recently applied to understand how the human brain is affected by diseases such as Parkinson’s disease, Schizophrenia, Alzheimer’s disease, and major depression [Damaraju et al., 2014; Kaiser et al., 2015; Madhyastha et al., 2014; Sakoglu et al., 2010; Wee et al., 2013].

5.1.3 Dynamic functional connectivity in diseased populations

A sliding window approach combined with *k*-means clustering, demonstrated that patients with schizophrenia have shorter “dwell time” in metastable states [Damaraju et al., 2014], implying an unstable connectivity pattern. In schizophrenia, decreased connectivity between subcortical regions and sensory networks were only observed in dynamic networks, suggesting that static connectivity was less sensitive to functional abnormalities. Research in major depression has revealed decreased dynamic resting-state functional connectivity (drsFC) between the medial prefrontal cortex and parahippocampus, and increased dynamic connectivity between the medial prefrontal cortex and dorsolateral prefrontal cortex [Kaiser et al., 2015]. These distinct patterns could be the results of positive and negative correlations in activity across sliding windows, which would not have been captured in static functional connectivity analysis alone. Alzheimer’s disease patients with mild cognitive impairment (MCI) exhibit altered graphical measures such as decreased small-world coefficients and smaller clustering coefficients in some temporal networks [Wee et al., 2013], indicating a failure to maintain a small-world brain connectivity compared to healthy subjects.

In Parkinson’s disease, with a sliding window approach, altered dFC in the dorsal attention and frontoparietal network was related to performance in an attention task [Madhyastha et al., 2014]. With a sliding window approach combined with Hilbert transform, deep-brain stimulation (DBS) has been shown to “rebalance” the global dynamics in PD towards a healthy regime in the thalamus, globus pallidus, and right orbitofrontal regions judged by “phase consistency” [Saenger et al., 2017]. Although this study did not investigate the relations between DBS-altered dFC and cognitive function, the findings showed that dFC can be an index of disease progression.

Combining graph theory, independent component analysis, the sliding window approach, and clustering methods together, PD subjects have shown altered rsFC states, whereby networks were more strongly interconnected between each other rather than sparsely connected, indicating that connections were stronger but less dynamic in PD [Kim et al., 2017]. Such connectivity pattern caused abnormal functional integration with higher variability, indicating an inefficiency of information transfer in PD [Kim et al., 2017]. A similar approach was applied to PD patients with MCI and without MCI. Only patients with MCI demonstrated altered dFC, whereby PD-MCI spent less time in the “*hypo-connectivity*” state and showed more state transitions, implying that PD-MCI actually presented weaker but more dynamic rsFC than PD and normal subjects [Díez-Cirarda et al., 2018]. Perhaps, taken together, stronger rsFC becomes more rigid but weaker rsFC becomes more dynamic in PD. On the other hand, with a similar approach, patients with MS demonstrated the opposite trend compared to PD.

MS patients with MCI spent less time in a “*high-connectivity*” state and demonstrated less switches between state transitions (i.e. lower dynamic fluidity) [D’Ambrosio et al., 2018]. Another study applied principal component analysis (PCA) to identify “eigenconnectivity” after data were processed in the sliding window approach [Leonardi et al., 2013]. People with MS showed reduced strength of drsFC in distributed regions including the amygdala, occipital, parietal, middle and posterior cingulate, and superior frontal regions. Moreover, two of the eigenconnectivity components demonstrated differences between MS and healthy subjects, whereby MS had stronger contributions than controls (i.e. the connectivity patterns were more obvious in MS). One component showed stronger mean drsFC in the posterior part of the default mode network (DMN), while the weaker mean drsFC in anterior and middle temporal regions. The other component

demonstrated stronger mean drsFC in temporal and angular areas; while weaker mean drsFC was found in fronto-parietal, right amygdala, and motor regions [Leonardi et al., 2013]. Although the study revealed that dFC can be a functional biomarker for MS, no correlations were reported between connectivity patterns and clinical data. To conclude, these studies have concluded that dFC has functional relevance and provides further insights into how brain networks are affected in neurological disorders. However, robust associations between dFC and cognitive domains, especially executive functioning, rather than cognitive states (i.e. cognitive impaired vs cognitive intact) remain absent.

In this study, we utilize a sliding window approach to calculate connectivity differences across time and quantify these changes by estimating dynamic features. Furthermore, methods of correlation and regression are implemented to explore the relations between dFC and cognitive function in PD and MS. In addition, similar to the last chapter, we carry out an analysis to test whether the dynamic features are reproducible across time.

5.2 Materials and methods

5.2.1 Subjects and behavioural data

Eleven healthy subjects (mean age: 25.7 ± 3.6 , 4 females, 7 males, all with university education level) were recruited for the test of reproducibility as section 4.2.1.

PD data are from research project GFM2 and MS data are from COGMS project. The MS cohort is the same as chapter 2 and 4, but PD cohort is different from the previous chapters. A subset of MS subjects are used for comparison with age-matched healthy subjects as previous chapter.

The same groups of MS subjects and normal control subjects (NC) as the last chapter were included (46 MS for correlation and regression, 18 MS and 15 NC for comparison; details are shown in section 4.2.1). The same neuropsychological scores were included as well (Table 2.2).

Twenty-four PD (mean age: 68.38 ± 4.73 , 6 females, 18 males) and fifteen age-matched NC subjects were recruited through the movement disorder clinic at UBC Hospital. All subjects went through cognitive assessment with Montreal Cognitive Assessment (MoCA) and questionnaire evaluations for depression scale, apathy, and fatigue with BECK Depression Inventory II, Apathy Scale (SAS), the Lille Apathy Rating Scale (LARS), and Fatigue Severity Scale (FSS). In addition to full score, sub-scores in MoCA were reported as well, which evaluated cognitive functions in multiple domains: visuospatial and executive functions, rapid naming and lexical retrieval ability, concentration, attention, language ability, abstraction, memory, calculation, and orientation skills [Julayanont and Nasreddine, 2017]. PD subjects also went through clinical evaluations with MDS-UPDRS Part I, II, III, and IV for motor and non-motor experience, motor examination, and motor complications (Table 5.1). Both image scans and clinical evaluations were done in on medication state. Ethics approval was issued by the University of British Columbia's Research Ethics Board and all subjects provided signed consent forms.

	PD subjects (mean $\pm$ SD)	NC subjects (mean $\pm$ SD)
demographics		
age	68.38 $\pm$ 4.73	69.4 $\pm$ 4.76
gender	6 females/18 males	5 females/10 males
disease duration	9.92 $\pm$ 5.86	no data
UPDRS I	9.33 $\pm$ 5.97	no data
UPDRS II	10.92 $\pm$ 6.51	no data
UPDRS III	27.25 $\pm$ 8.67	no data
UPDRS IV	1.29 $\pm$ 0.91	no data
HY	2.13 $\pm$ 0.61	no data
cognitive & affective scores		

MoCA full score	26.08±2.24	26.93±1.96
MoCA visuospatial/executive	4.63±0.71	4.53±0.64
MoCA picture naming	3±0	3±0
MoCA attention	5.25±0.85	5.6±0.51
MoCA language	2.38±0.64	2.33±0.62
MoCA abstraction	1.96±0.20	1.87±0.35
MoCA memory-delay recall	3±0.38	3.67±1.18
MoCA orientation	5.92±0.28	5.87±0.35
BECK depression scale	7.92±5.02	3.07±3.90
SAS	11.53±5.03	8.07±5.51
LARS	-24.75±5.41	-28.8±4.04
FSS	3.93±1.53	2.36±1.32

Table 5.1 Clinical, demographical, and cognitive assessment scores in PD and NC. Bold font indicates significant differences between two groups in t-tests with $p < 0.05$.

[UPDRS: the Unified Parkinson's Disease Rating Scale, HY: Hoehn and Yahr scale, MoCA: Montreal

Cognitive Assessment, SAS: apathy scale, LARS: the Lille Apathy Rating Scale, FSS: Fatigue Severity Scale]

5.2.2 Imaging acquisition

All subjects underwent imaging studies at the University of British Columbia (UBC) MRI Research Centre with a Philips Achieva 3.0 Tesla MRI scanner. Resting-state functional MRI (rsfMRI) data were acquired using an 8 channel head coil and an echo-planar imaging sequence with the following parameters: $3 \times 3 \times 3 \text{ mm}^3$ resolution, 36 slices, 2000 ms TR, 30 ms TE, 90 degree flip angle, and 240 volumes/dynamics. 3 Dimensional (3D) T1 weighted images were acquired with $1 \times 1 \times 1 \text{ mm}^3$ resolution, 60 slices, 28 ms TR, 4 ms TE and 27 degree flip angle.

5.2.3 Preprocessing

For the studies of reproducibility and MS subjects, preprocessing was the same as previous chapters. Image preprocessing steps were performed in each subject's native space with the functions of slice timing and motion correction from Statistical Parametric Mapping 8 (SPM8,

University College London, London) for correcting temporal and spatial differences. For registration, the FMRIB's Linear Image Registration Tool (FLIRT) from the FMRIB Software Library 6.0 (FSL, FMRIB, Oxford) was used and a brain mask was applied to remove non-brain areas before registration. Cortical parcellation was done on the T1-weighted images in Freesurfer version 4.5.0 (Massachusetts General Hospital, Boston) and thirty-six cognition-associated regions-of-interest (ROIs) were selected (Table 5.2). These ROIs have been commonly reported in the neuropsychological literature and frequently used to investigate the relations between cognition and resting-state functional connectivity (rsFC). Finally, the average fMRI time courses among voxels within individual ROIs were extracted using self-programmed scripts in Matlab (The MathWorks, Inc.) and the data were detrended before connectivity analyses.

Bilateral ROIs
superior frontal gyrus
medial frontal gyrus
inferior prefrontal cortex
temporal pole, insula, and amygdala merged
superior temporal cortex
posterior parietal cortex
post central cortex
supramarginal region
middle temporal lobe, hippocampus, hippocampal gyrus merged
occipital-parietal area
lateral occipital lobe
anterior cingulate cortex
posterior cingulate cortex
precuneus
medial orbitofrontal cortex
lateral orbitofrontal cortex
fusiform gyrus
superior parietal cortex

Table 5.2 Eighteen bilateral regions-of-interest (ROIs) in the connectivity analysis in MS study and healthy subjects for reproducibility. Some ROIs are merged as one because these ROIs are anatomically small and geographically close.

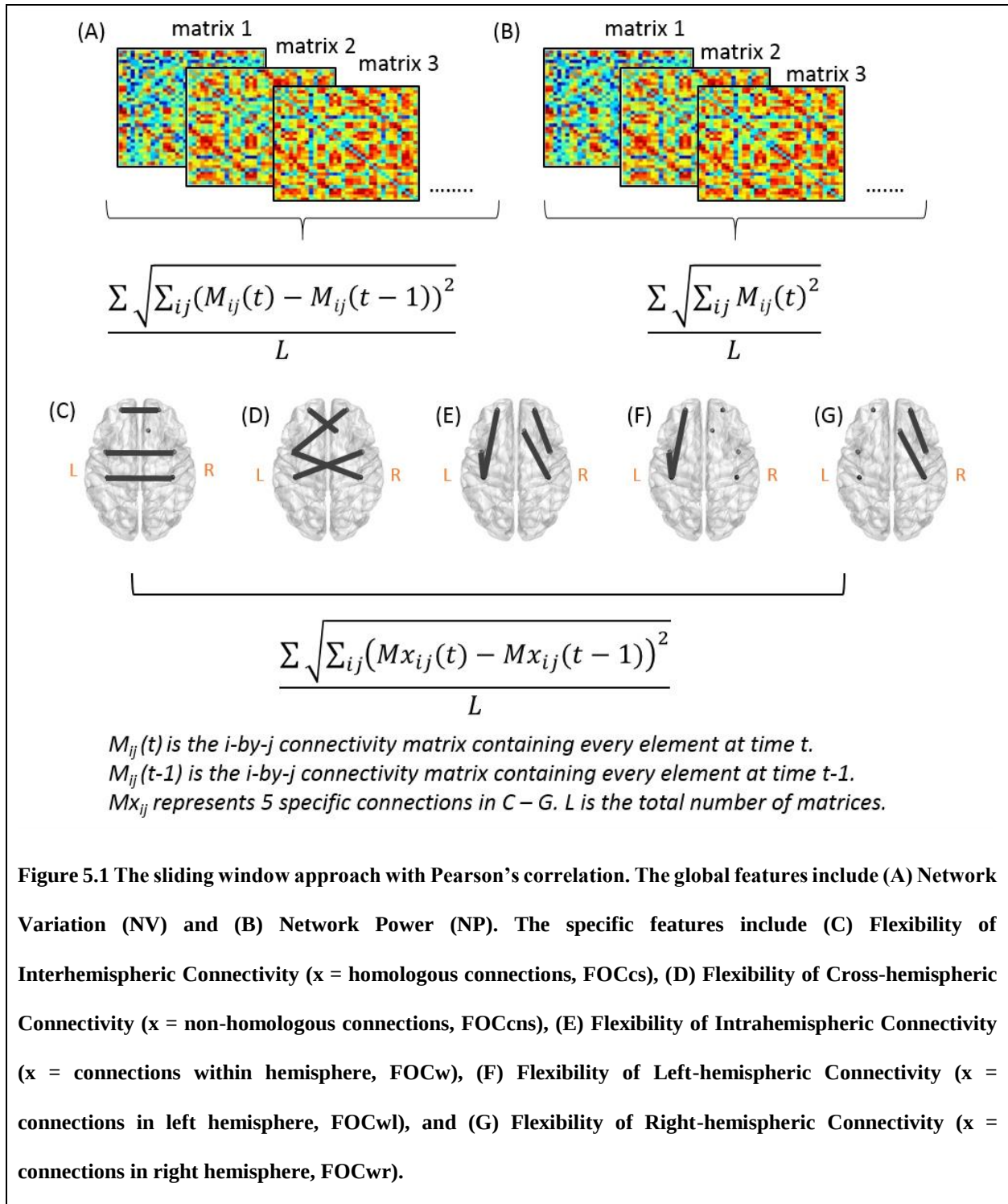
In PD and age-matched control subjects, AFNI (NIMH, Bethesda) software package was used for fMRI preprocesses, including despiking, slice timing correction, 3D isotropic correction (3x3x3 mm³ resolution), and motion correction with rigid body alignment. Whole brain parcellation was done in FreeSurfer 6.0 on the T1-weighted images and the structural images were then registered to the fMRI images using rigid registration. This registration step provided the FreeSurfer segmented ROI mask in the fMRI space. All analyses were done in the native fMRI space rather than transforming all fMRI data to a common template, which was designed to prevent introducing any unwanted distortions to fMRI. In the next step, several sources of variance such as head-motion parameters, white-matter, and CSF signals were removed using linear regression. The fMRI signals of the same ROIs were extracted and detrended to remove any linear or quadratic trends and smoothed with 6 FWHM Gaussian kernels. Finally, bandpass filtering was performed to retain the signal between the recommended frequencies of interest for resting state activity (0.01 Hz to 0.08Hz).

5.2.4 Dynamic functional connectivity analysis

For testing reproducibility, a sliding window with Pearson's correlation, which is the most common approach in the literature, was applied to calculate the windowed correlation matrices in 11 subjects with a window length of 20-time points. The window was moved 1-time point forward in each Pearson's r calculation, resulting in 221 correlation matrices for each subject. Seven network features were acquired based on learned dynamic connectivity: Network Variation (NV), Network Power (NP), Flexibility of Interhemispheric Connectivity (homologous connections, FOCcs), Flexibility of Cross-hemispheric Connectivity (non-homologous connections, FOCcns), Flexibility of Intrahemispheric Connectivity (within hemisphere, FOCw), Flexibility of Left-

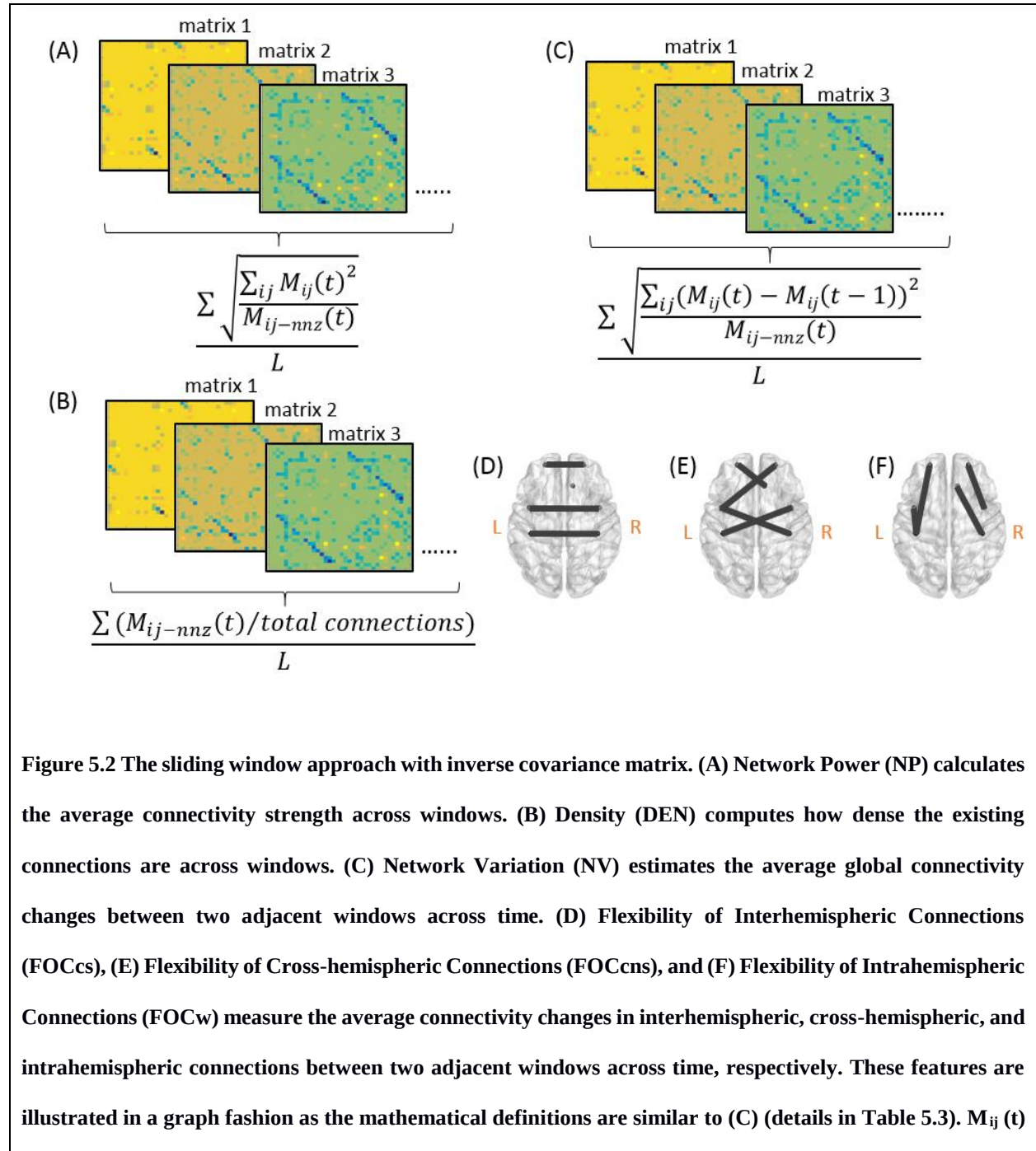
hemispheric Connectivity (within left hemisphere, FOCwl), and Flexibility of Right-hemispheric Connectivity (within right hemisphere, FOCwr). These features summarized how connectivity patterns change between two correlation matrices (Figure 5.1, Table 5.3). *Network power* (NP) measured the summed values of the dynamic functional connectivity pairs in all the windows and the values were divided by the number of non-zero elements in each window. *Network variation* (NV) calculated the differences of connectivity values between two adjacent windows and the differences of each connectivity pairs were summed up and divided by the number of non-zero elements in each window. *Flexibility of interhemispheric connections* (FOCcs) calculated the connectivity differences of homologous connections only between two windows and then the values were summed up to form one measure. *Flexibility of cross-hemispheric connections* (non-homologous regions, FOCcns) was the measure of summed connectivity differences of non-homologues connections between two windows. *Flexibility of intrahemispheric connections* (within hemisphere, FOCw) measured the connectivity differences of connections within left and right hemisphere between two windows and all the values were then summed up to form one value, which can be further divided into *Flexibility of right hemispheric connections* (FOCwr) and *Flexibility of left hemispheric connections* (FOCwl)

Repeated measure ANOVA (rmANOVA) and coefficient of variation (COV) (standard deviation divided by the mean) were calculated to test reproducibility across time.



For the analysis in both MS and PD data sets, a sliding window approach (with a window length of 20 time points) and the *inverse covariance matrix* of the ROI time courses was used to estimate connectivity. Such a sliding window and inverse covariance matrix approach has been applied to capture dynamic functional connectivity and accurately estimate direct connections between brain regions in fMRI [Hutchison et al., 2013a; Smith et al., 2013]. Since the TR was 2 seconds, the 20-point window length (WL) was 40 seconds in length, consistent with previous recommendations [Zalesky and Breakspear, 2015]. The window was shifted one time point at a time, resulting in 221 windowed inverse covariance matrices in total for each subject. Afterwards, 6 network features were acquired based on the learned dynamic functional connectivity. In addition to the features mentioned in the last paragraph, another feature was calculated only based on regularized matrices. *Density* (DEN) estimated how dense the connections were by taking all non-zero connectivity values and divided by all possible connections. In short, DEN and NP measured how dense and strong the overall connectivity was, while NV and flexibility measures calculated global and specific network dynamics, respectively. All the connectivity values in every measure (except DEN, as DEN focused on quality rather than quantity) were squared first, summed and then the square root of the sum was taken. All values (the square root of the sum) across windows were summed and then divided by the total number of windows. Therefore we did not take into account the effects of positive and negative correlation between two ROIs in our analyses, and instead, considered how connectivity strength changed. Although these network features were all calculated based on learned dynamic connectivity matrices, we considered DEN and NP as stationary network features as they did not calculate the *differences* between two matrices. Rather, they represented the average values across the scanning time. Figure 5.2 demonstrates these network features in a graph fashion. Table 5.3 describes the mathematical definitions of each

measure. In MS, due to the sparsity of connectivity matrices, FOCw was not divided into FOCwl and FOCwr. Therefore, in total, there were 6 dynamic features in MS and 8 features in PD.



is the i-by-j inverse covariance matrix containing every element at time t, $M_{ij}(t-1)$ is the i-by-j inverse covariance matrix containing every element at time t-1. $M_{ij-nnz}(t)$ is the i-by-j inverse covariance matrix containing non-zero values at time t. L represents the total number of windowed matrices.

Network Features	Definitions
Density (DEN)	$\frac{\sum(M_{ij-nnz}(t)/totcon)}{L}$
Network power (NP)	$\frac{\sum \sqrt{\frac{\sum_{ij} M_{ij}(t)^2}{M_{ij-nnz}(t)}}}{L}$
Network variation (NV)	$\frac{\sum \sqrt{\frac{\sum_{ij} (M_{ij}(t) - M_{ij}(t-1))^2}{M_{ij-nnz}(t)}}}{L}$
Flexibility of interhemispheric connections (FOCcs)	$\frac{\sum \sqrt{\sum_{ij} (Mh_{ij}(t) - Mh_{ij}(t-1))^2}}{L}$
Flexibility of cross-hemispheric connections (FOCns)	$\frac{\sum \sqrt{\sum_{ij} (Mn_{ij}(t) - Mn_{ij}(t-1))^2}}{L}$
Flexibility of intrahemispheric connections (FOCw)	$\frac{\sum \sqrt{\sum_{ij} (Mw_{ij}(t) - Mw_{ij}(t-1))^2}}{L}$

Table 5.3 Mathematical definitions of network features learned in the sliding window approach

[$M_{ij}(t)$ is the i-by-j connectivity matrix containing every element at time t, $M_{ij-nnz}(t)$ contains all the non-zero connectivity values in the matrix $M_{ij}(t)$, totcon is the total possible connections in the matrix, which is the number of ROI times the same number, $M_{ij}(t-1)$ is the i-by-j connectivity matrix containing every element at time t-1, Mh_{ij} represents all homologous connections in matrix M_{ij} , Mn_{ij} represents all interhemispheric connections except homologous elements in matrix M_{ij} , Mw_{ij} represents all intrahemispheric connections in matrix M_{ij} , L represents the total number of windowed correlation matrices]

Two sample *t*-tests were carried out to investigate significant differences of all network features between patient and healthy subject groups. False-discovery rate control (FDR) was applied as a method to correct for multiple comparisons.

5.2.5 Correlation and regression analyses

Correlations between individual dynamic features and behavioural scores were evaluated by Pearson correlation. Only the correlations that survived for Bonferroni correction were reported. In addition, a principal component analysis (PCA) was carried out to remove the inter-correlations between dynamic features before linear regression. The PCA scores of components (explaining > 90% of the variance) were included in the linear regression model as predictors and age was also included as covariance. Individual behavioural measures were included in the regression model as response variables.

In the MS data set, composite and transformed/standardized scores were included such as the Verbal Fluency Test (FAS), Working Memory Index (WMI), Processing Speed Index (PSI), transformed Trail Making Test Part A and B (transformedTMTA/B), the Wisconsin Card Sorting Test Complete Categories (WCSTCC), Multiscore Depression Inventory Total T Scores (MDITOTT), State-Trait Anxiety Inventory: Trait (STAIT), State-Trait Anxiety Inventory: State (STAIS), and Fatigue Severity Scale (FSS). In addition, age, education, EDSS, and disease duration were included as well.

In the PD data set, demographical and clinical measures were included in the analysis such as disease duration, gender, UPDRS scores of 4 parts, MoCA full scores, H&Y stage, apathy scores, fatigue scales, and BECK depression scale scores. Moreover, the sub-scores of MoCA were further

included to evaluate functions in multiple cognitive domains: visuospatial and executive functions, rapid naming and lexical retrieval ability, concentration, attention, language ability, abstraction, memory, calculation, and orientation skills.

5.3 Results

5.3.1 Reproducibility

None of the network features showed significant differences among the three fMRI sessions ($p_r > 0.05$ in all measures, Figure 5.3). Similarly, COV of most of the measures derived from three fMRI sessions demonstrated similar values (Table 5.4). The results indicate that these measures are reproducible across scans.

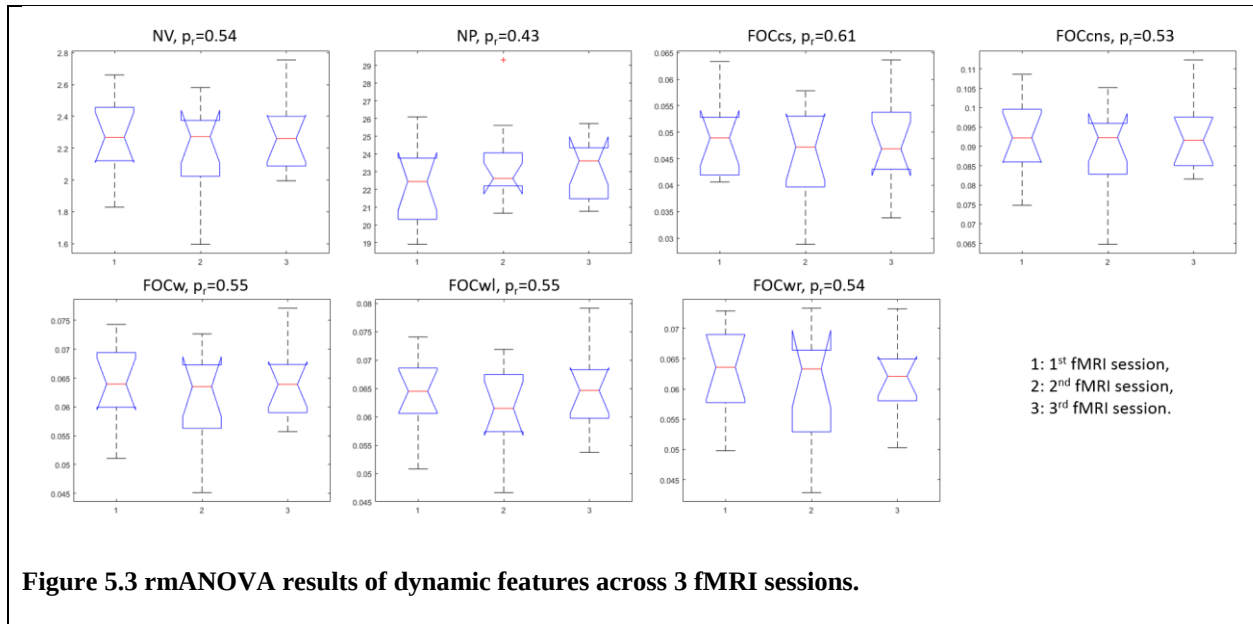


Figure 5.3 rmANOVA results of dynamic features across 3 fMRI sessions.

Dynamic network features	1 st fMRI	2 nd fMRI	3 rd fMRI
NV	10.5%	12.9%	9.7%
NP	10.3% *	10.2% *	7.3% *
FOCcs	14.7%	19.1%	18.2%

FOC _{cns}	10.3%	12.8%	9.6%
FOC _w	10.6%	13.0%	9.9%
FOC _{wl}	10.4%	11.9%	10.6%
FOC _{wr}	11.4%	15.1%	10.1%

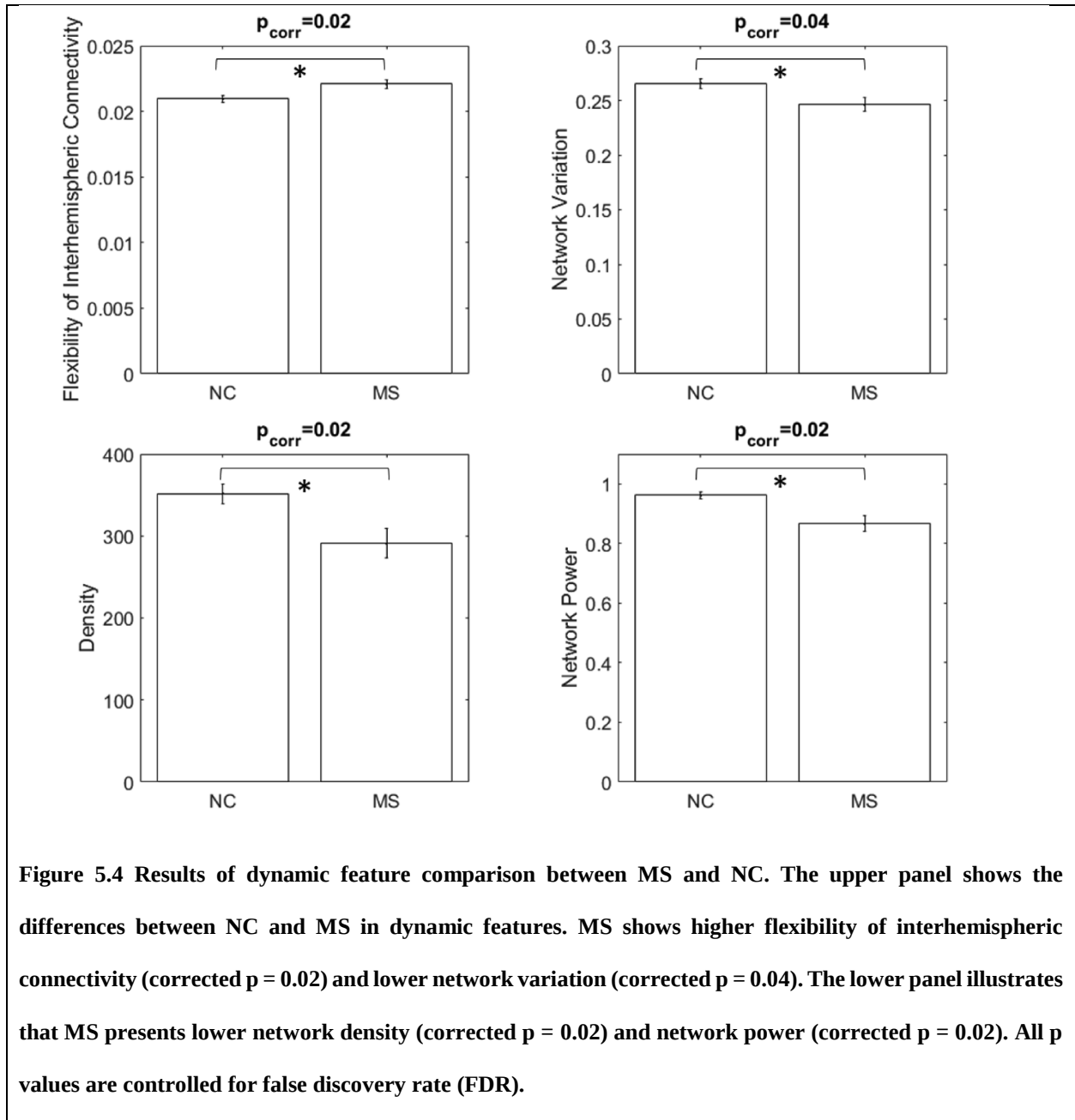
Table 5.4 COV results of dynamic features across 3 fMRI sessions.

[* not Gaussian]

5.3.2 Multiple Sclerosis

5.3.2.1 Feature comparison

MS subjects showed lower network variation (NV) and higher flexibility of interhemispheric connections (FOC_{cns}) than NC while controlling for a false discovery rate (FDR) (corrected p values: 0.02 and 0.04, respectively, Figure 5.4 upper panel). Moreover, MS subjects also demonstrated lower density (DEN) and network power (NP) with FDR correction (corrected p values: 0.02 and 0.02, Figure 5.4 lower panel). These results indicated that MS subjects had overall weaker connectivity, fewer connections, less dynamic overall connectivity, but more flexible interhemispheric connections in MS subjects. In other words, there is a loss of dynamic coordination in global connectivity and increased interhemispheric connectivity fluctuations in MS subjects compared to NC.



5.3.2.2 Correlation and regression

Among all the correlation pairs, only disease duration showed significant correlations with dynamic features FOCns ($r=-0.55$, $p<0.001$), FOCcs ($r=-0.56$, $p<0.001$), and FOCw ($r=-0.54$, $p<0.001$) in MS after corrections for multiple comparisons with 14 tests were run (Figure 5.5).

The first two PCA components of dynamic features in MS explained > 90% of the variance and therefore they were included in the linear regression model. These two components represented different aspects of dFC. The first component, explaining 79% of the variance, showed similar and positive coefficients of all features (except DEN); therefore, this component mostly represented global dynamics (Figure 5.6). The second component, explaining 11% of the variance, had NV and NP loading negatively while the rest features loaded positively, and thus represented connection density and the effects from dFC in specific connections rather than global dynamics (Figure 5.6). Among all the demographical, clinical, and cognitive scores, only disease duration appeared to be significantly modulated by these two components of dynamic features and age ($p < 0.001$). The loadings on both the 1st and 2nd components were negatively correlated with disease duration, with significant p values of 0.00088 and 0.03705, respectively. Table 5.5 and Figure 5.7 illustrate the results of linear regression analysis.

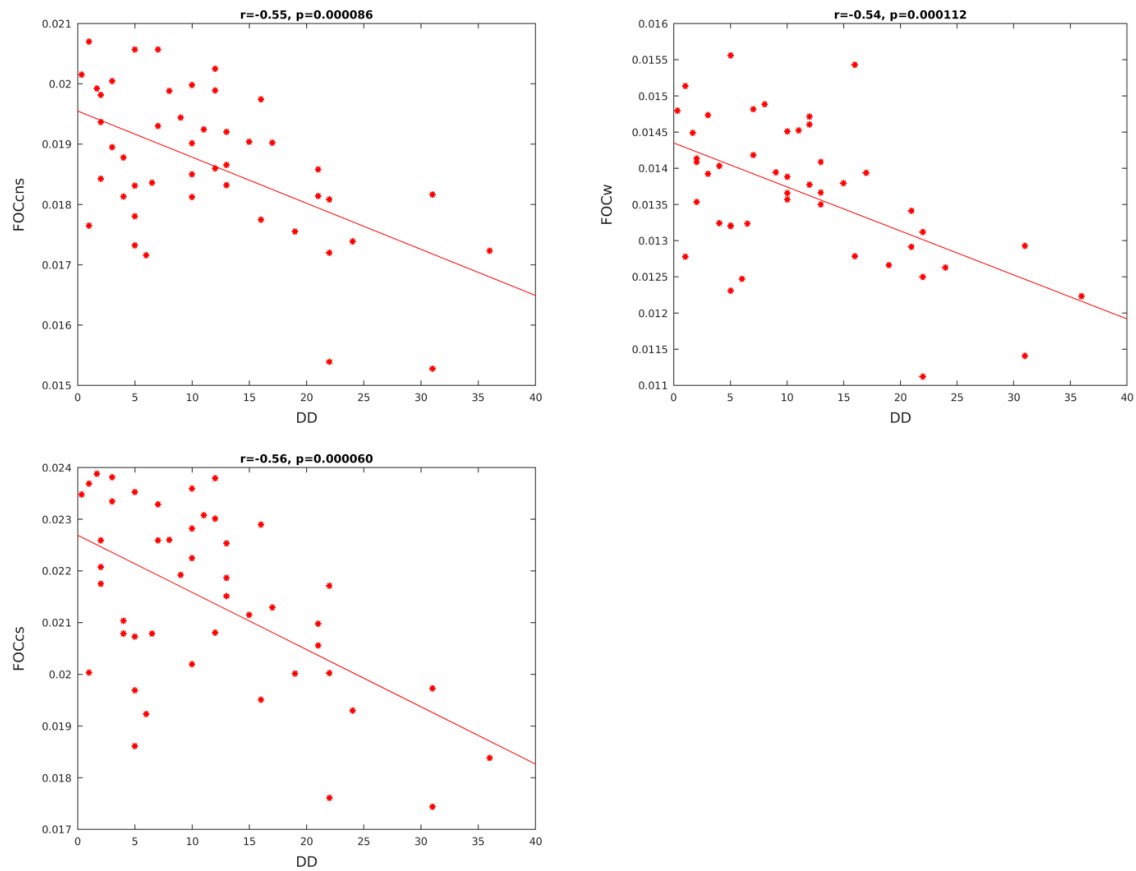


Figure 5.5 Significant correlations between disease duration and dynamic features in MS. All correlation pairs survive for Bonferroni correction.

[FOCns: flexibility of cross-hemispheric connectivity, FOCcs: flexibility of interhemispheric connectivity, FOCw: flexibility of intrahemispheric connectivity, DD: disease duration]

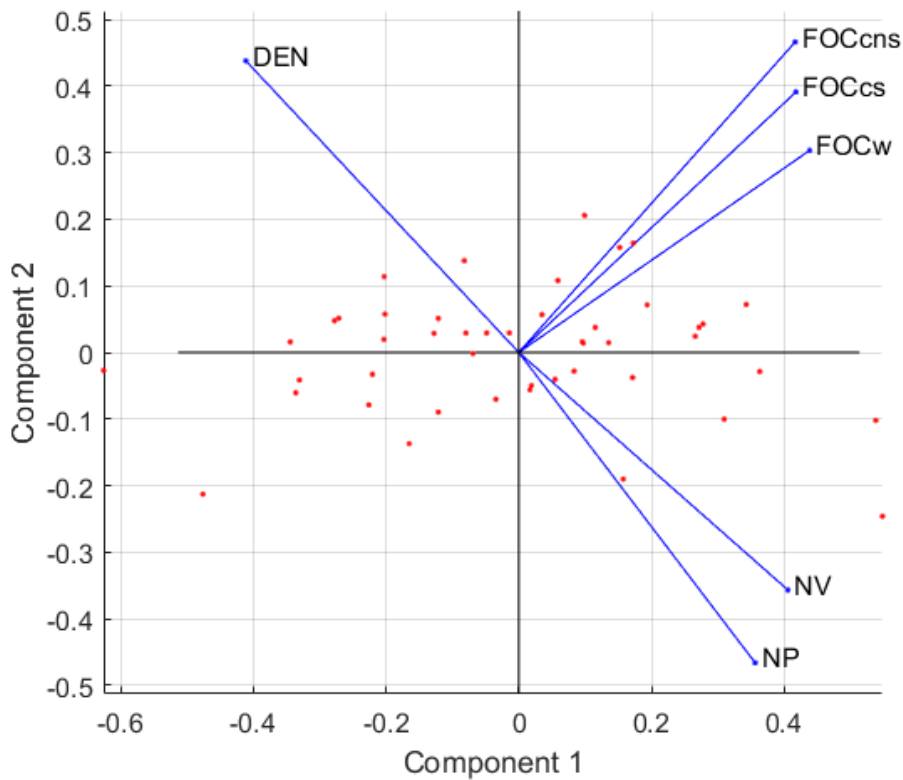


Figure 5.6 PCA results of dynamic features in MS. These two components explain 90% of the variance and are included in the linear regression analysis as predictor data.

[FOCcns: flexibility of cross-hemispheric connectivity, FOCcs: flexibility of interhemispheric connectivity, FOCw: flexibility of intrahemispheric connectivity, NV: network variation, NP: network power, DEN: density]

For individual predictors

response/	predictors /PCA components	estimate in	standard	p
disease duration	component 1	-1.56	0.43	0.00088
	component 2	-2.50	1.16	0.03705
	age (covariate)	0.37	0.09	0.00015

For the whole model

Number of observations: 46, Error degrees of freedom: 43

Root Mean Squared Error: 6.25

R-squared: 0.523, Adjusted R-Squared 0.489
p-value = 6.81e-07

Table 5.5 Significant linear regression model in MS.

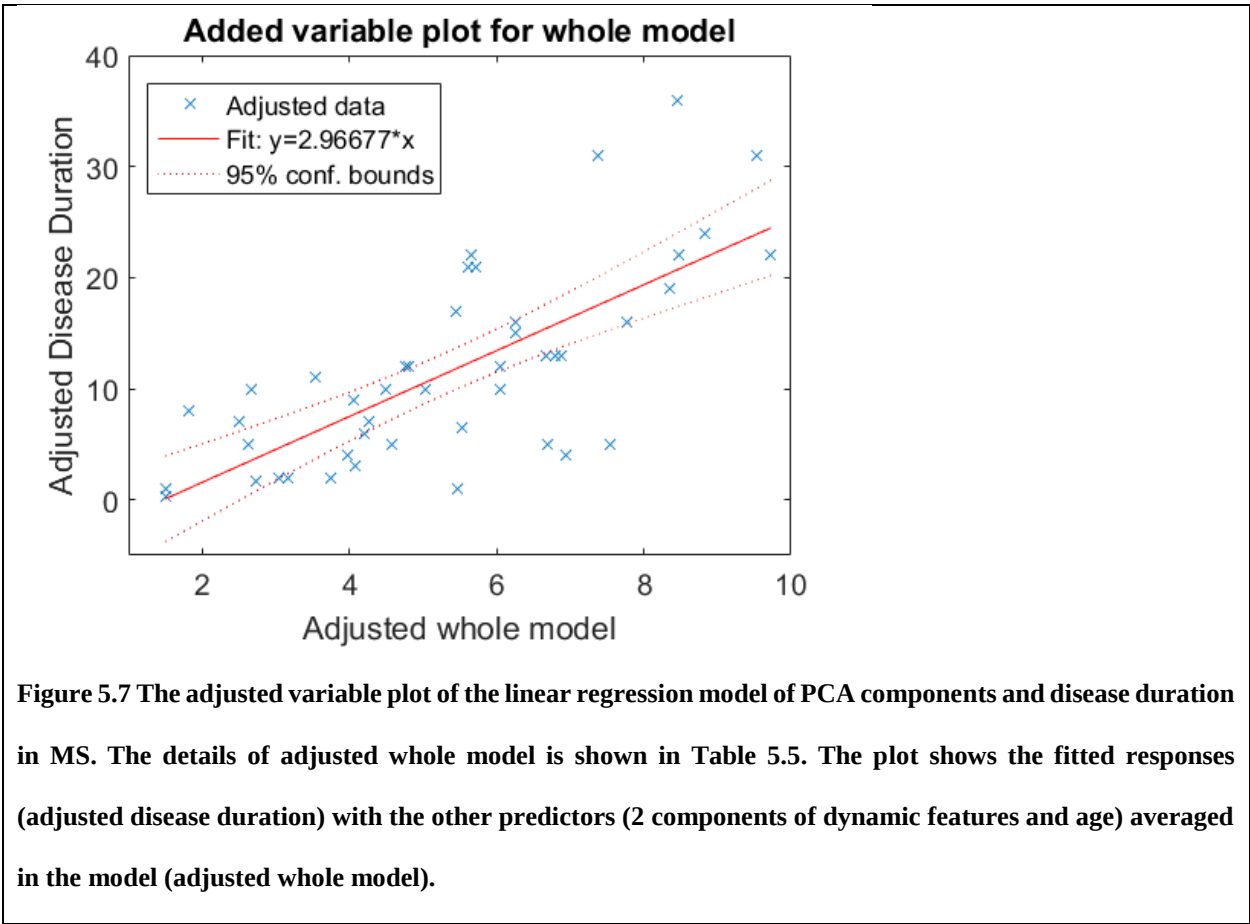


Figure 5.7 The adjusted variable plot of the linear regression model of PCA components and disease duration in MS. The details of adjusted whole model is shown in Table 5.5. The plot shows the fitted responses (adjusted disease duration) with the other predictors (2 components of dynamic features and age) averaged in the model (adjusted whole model).

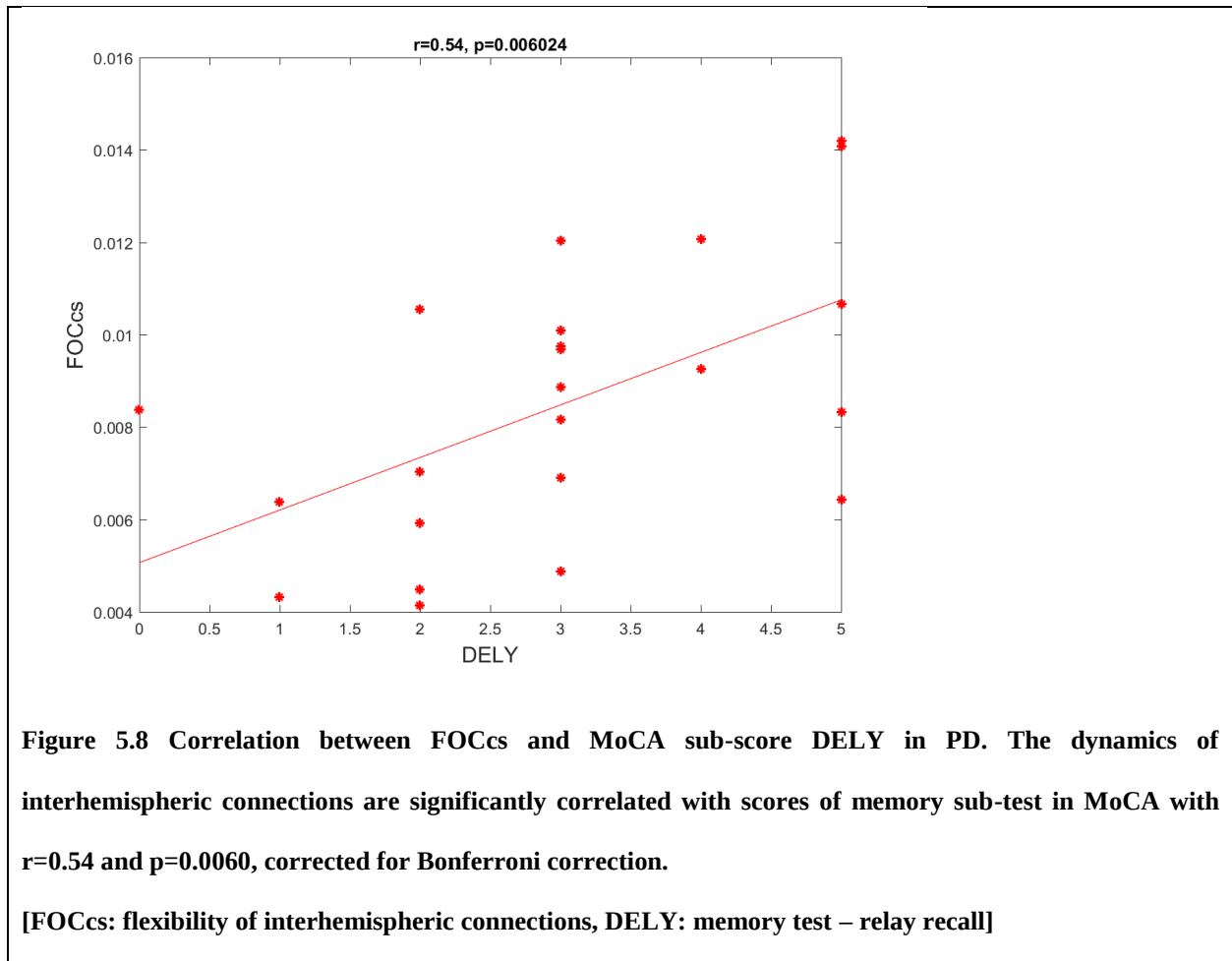
5.3.3 Parkinson’s Disease

5.3.3.1 Feature comparison

PD subjects did not show any significant differences of dynamic features compared to NC.

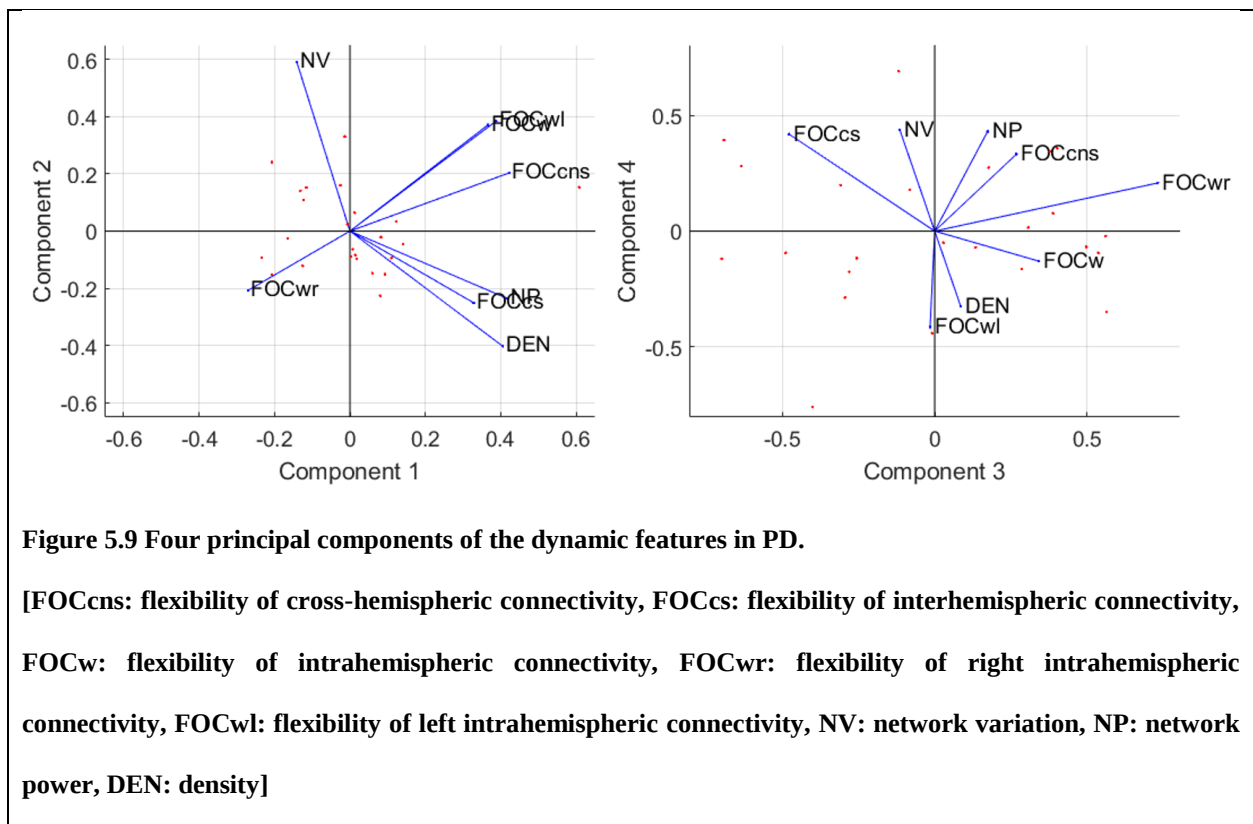
5.3.3.2 Correlation and regression

None of the clinical measures were significantly correlated with dynamic features. However, FOCcs was correlated with MOCA sub-score delayed recall ($r=0.54$, $p=0.006$, Bonferroni correction corrected with 7 tests of MoCA sub-scores were run).



The first four PCA components of dynamic features explained $> 90\%$ of the variance and they were included in the linear regression analysis (Figure 5.9). The 1st component explained 42 % of the variance and mostly represented overall dFC, while the 2nd component explained 29 % of the variance, in which non-interhemispheric dynamics and interhemispheric dynamics/connectivity

strength loaded heavily. Hence, this component expressed interhemispheric vs non-interhemispheric dFC. The 3rd component explained 13% of the variance and represented interhemispheric vs non-interhemispheric dFC but with less effects from overall connectivity as NP and DEN both showed limited loadings. The 4th component, explaining 7% of the variance, loaded on all dynamic features equally except FOCw, which implied that this component represented overall dynamics with less effects from the variation of intra-hemispheric connectivity.

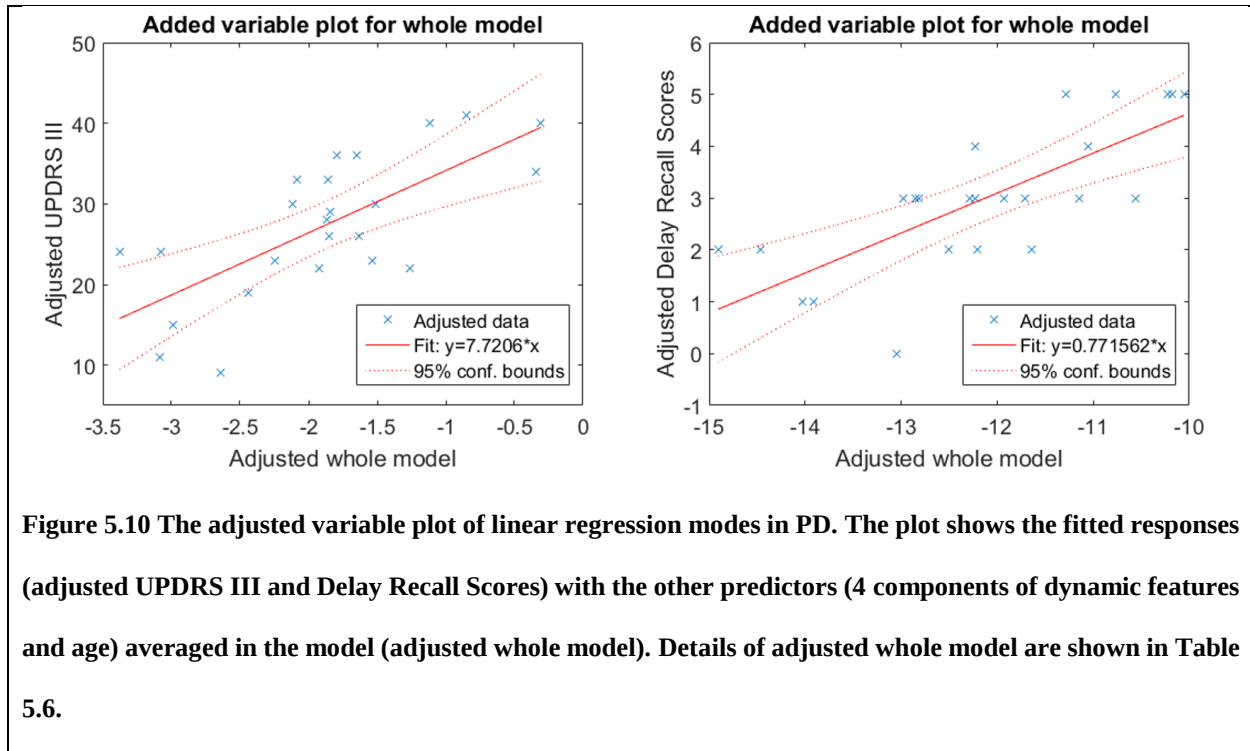


In the linear regression analysis, UPDRS III and memory sub-score of MoCA were predicted by components of dynamic features with $p=0.0177$ and 0.006 , respectively. In the model of UPDRS III against components of dynamic features, component 4 demonstrated significant effects

($p=0.001$) with a negative estimate. On the other hand, in the model of MoCA memory scores against components of dynamic features, component 3 and age both showed significant contributions with $p=0.047$ and 0.02 with negative estimates, respectively (Table 5.6, Figure 5.10).

Model 1				
For individual predictors				
response/	predictors / PCA components	estimate in	standard	p
UPDRS III	component 1	0.80	0.92	0.39394
	component 2	0.81	0.95	0.40680
	component 3	-1.02	1.46	0.49399
	component 4	-7.56	1.94	0.00106
	age (covariate)	-0.21	0.36	0.56314
For the whole model				
Number of observations: 24, Error degrees of freedom: 18				
Root Mean Squared Error: 6.88				
R-squared: 0.507, Adjusted R-Squared 0.37				
p-value = 0.0177				
Model 2				
For individual predictors				
response/	predictors / PCA components	estimate in	standard	p
MoCA sub-score:	component 1	0.02	0.14	0.89292
	component 2	-0.18	0.14	0.22987
Delay recall	component 3	-0.47	0.22	0.04703
	component 4	0.57	0.29	0.06325
	age (covariate)	-0.14	0.05	0.02096
For the whole model				
Number of observations: 24, Error degrees of freedom: 18				
Root Mean Squared Error: 1.03				
R-squared: 0.569, Adjusted R-Squared 0.449				
p-value = 0.00608				

Table 5.6 Two significant linear regression modes in PD.



5.4 Discussion

Our results of reproducibility demonstrated that even though dynamic functional connectivity underlined how neural patterns change temporally, the dynamic network features were still quite reproducible across scans in this study. As section 4.4 stated, advanced statistical methods can be used to ensure the robustness of reproducibility, but our preliminary results justified the use of dynamic network features to study brain organization.

5.4.1 Changes in dynamic functional connectivity may indicate compensation in MS

In this study, we observed that average connectivity strength (i.e. network power) and density were both reduced in MS, and that MS subjects had overall reduced dynamic functional connectivity. Interestingly, interhemispheric connectivity was more variable compared to NC, possibly to

compensate for overall decreased global connectivity. Our results are consistent with previous dFC studies in MS [D'Ambrosio et al., 2018]. Previous research had concluded that MS subjects spent less time in “high-connectivity” states, which means that networks were more often to be weakly connected than strongly connected. This phenomenon was similar to our findings that average connectivity strength was reduced and connectivity was less dense in MS. Moreover, fewer switches were observed in the previous study in MS [D'Ambrosio et al., 2018], which indicates a reduction of dynamics in MS. Similarly, we observed reduced network variation in MS, suggesting that global connectivity did not change as much as in normal subjects across time. This finding also supports previously-reported dynamic connectivity reduction in MS subjects. However, as previous studies did not target specific connections, the dynamic balance between different connections was not captured. Our results demonstrated that while global connectivity in MS subjects lost dynamic coordination, interhemispheric connections became more dynamic, possibly demonstrating a compensatory effect to overcome the functional disruption elsewhere and structural damage (i.e. demyelination) in the corpus callosum [Bodini et al., 2013]. Such compensatory effect in dFC is also supported by the results in Chapter 3. In Chapter 3, we discovered that stronger interhemispheric connections in MS are homogenized and associated with better cognitive performance, representing compensatory effects. Therefore, we concluded that when structural damages impact information transfer across hemispheres via the corpus callosum, the interhemispheric connections become stronger as well as more dynamic (i.e. fluctuate more) in order to maintain brain function. Taken together, we propose that *global rsFC in MS is weaker, sparser, and more rigid*; on the other hand, *other specific connections such as interhemispheric connections may be stronger and more dynamic to compensate for functional disruption elsewhere and structural damage in callosal connections*.

In PD, we did not observe any differences of dynamic features between PD and NC, which is possibly due to the relatively mild disease severity in this cohort. However, the index of overall disease severity (i.e. UPDRS III score) was related to dynamic features, which is discussed in the following section.

5.4.2 Disease duration is robustly modulated by dynamic functional features in MS

In both correlation and regression analyses, only disease duration exhibited association with dynamic connectivity features. Longer disease duration was associated with decreased dynamics in interhemispheric, intra-hemispheric, and cross-hemispheric connectivity, implying that as disease progressed, functional connectivity lost dynamic coordination of distributed brain regions connecting the two hemispheres and regions within the same hemisphere. In the linear regression model, different aspects of dynamic patterns were affected by disease duration. The loadings on both components were negatively correlated with disease duration, supporting the conclusion that disease progression is associated with the loss of dynamic coordination across the brain in MS. Previous studies of dFC in MS subjects have conjectured that decreased dynamics served as biomarkers [D'Ambrosio et al., 2018; Leonardi et al., 2013], yet the relations between dFC and clinical data remain unclear; similarly, whether clinical presentation and cognitive function can be predicted by dFC requires further investigation. In this study, we partially addressed this question by showing that disease duration is significantly associated with dynamic features in a linear regression model. Although advanced statistical methods are required to predict disease progression and any other behavioural outcomes, our findings shed light on exploring dynamic connectivity and disease effects.

Interestingly, EDSS did not show any significant relations to dynamic features but disease duration did. Based on the current literature, we assume that dFC is more related to cognitive function rather than motor and physical ability. As EDSS mainly evaluates disease severity based on physical disabilities, it is possibly that this disease index is less related to dFC. Rather, a more general index, such as disease duration, contains information of cognitive decline along disease course and exhibits relations to dFC.

We did not observe any associations between cognitive performance and dynamic features in the correlation analysis. Similarly, none of the cognitive scores was modulated by the components of dynamic features. However, when more PCA components were included in a linear regression model (i.e. data explained almost 100% of the variance), component 4 appeared to be significantly related to the Wisconsin Card Sorting Test Complete Categories (WCSTCC) ($p=0.011$, Appendices D.1). In this cognitive task, the ability to switch strategies based on rules is required (i.e. cognitive flexibility), which has been shown to be related to dynamic functional connectivity [Douw et al., 2016]. Yet this component only explained 1.8% of the variance and flexibility of interhemispheric connections (FOCs) loaded positively and heavily onto this component (Appendices D.2). Therefore, this regression pattern implied that the dynamic fashion of interhemispheric connections might support the performance of strategy switching, but such pattern may not be representative enough in our data as the component explained a limited amount of variance.

We conclude that drsFC can be indicative of disease progression, which could serve as a biomarker, and dynamic coordination of homologous regions might be supportive of strategy switching ability, but such brain-behavioural association is very mild in our cohort.

5.4.3 Disease severity can be predicted by dynamic features in PD

In the linear regression model, the UPDRS III score could be significantly predicted by the 4th component of dynamic features. This component only explained 7% of the total variance in dynamic features and represented overall dynamics with fewer effects from intra-hemispheric connectivity. As this component was negatively weighted in the regression model, it was interpreted that higher overall dynamics was associated with lower UPDRS III scores, implying that higher disease severity was related to reduced dFC in PD. Previous research has shown that weaker connections were more dynamic but stronger connections lost dynamic coordination in PD [Díez-Cirarda et al., 2018; Kim et al., 2017]. As we did not observe differences in dynamic features, it is hard to conclude whether such dynamic balance between strong and weak connections exist in our data. However, we do show that higher disease severity is related to decreased dFC in PD, which is partially consistent with previous studies. One possible explanation for this is that different sub-types of motor symptoms in PD have been linked to different types of cognitive deficits [Kehagia et al., 2012; Miller et al., 2013; Thenganatt and Jankovic, 2014]. Tremor-dominant PD subjects often demonstrate disabilities in planning, working memory, and executive functions; therefore, this subtype has been associated with the cognitive “frontal subtype” and dopamine depletion. The other subtype is associated with pronounced gait disturbance and often shows deficits in visuospatial function and semantic fluency, which has been related to the cognitive “posterior subtype” and cholinergic deficits in PD. Therefore, although UPDRS III is assessed based on motor symptoms, dopamine depletion not only impairs motor loops but also frontal-striatal circuits which are important for many cognitive functions [Kehagia

et al., 2012]. Therefore, the relations between UPDRS score and dynamic features in this study may be an indirect indicator of the relations between frontal subtype and dFC in PD.

5.4.4 Memory function is robustly associated with dynamics in PD

The MoCA sub-score of memory delayed recall screens deficits in retrieval memory, and was the only MoCA sub-score that demonstrated associations in both correlation and linear regression analyses. With correlation analysis, FOCcs was positively correlated with scores of delayed recall, suggesting that higher dynamics of interhemispheric connections were related to better retrieval memory function in PD. In the linear regression model, delayed recall performance was modulated by component 3 of dynamic features and age. Component 3 explained 13 % of the variance and mainly represented interhemispheric dFC with negative loadings and intra-hemispheric dFC with positive loadings as other features showed limited loadings. Because component 3 showed a negative regression coefficient, higher FOCcs and lower intra-hemispheric dFC predicted better delayed recall performance as they loaded positively and negatively, respectively. Therefore, taken together, both correlation and linear regression suggest that better retrieval memory was not only correlated with, but also could be predicted by, higher dynamics in interhemispheric connectivity in PD, strengthening the important role of dynamic coordination between two hemispheres on cognitive process.

Delayed recall scores were also modulated by age, which acted as covariate in the regression model. As age had a negative regression coefficient, the model also reinforced the links between aging and decreased cognitive ability in the memory domain. Finally, we also propose that memory function might be strongly related to dynamics of interhemispheric connections, but it might be

more influenced by aging than dynamic features when they were jointly assessed together, given that component 3 was almost not significant in the linear regression model.

In this study, we did not evaluate cognitive functions in PD subjects with a comprehensive neuropsychological battery other than MoCA. Therefore, although we only observed relations between memory function and dFC, it did not mean other cognitive domains, especially executive function, are unrelated to dFC. In fact, as the sub-tests in MoCA which evaluate attention/executive function are relatively easy for subjects without dementia or MCI, using only MoCA might be insensitive to mild executive dysfunction in the early stage. Further test batteries which specifically evaluate set-shifting, mental calculation, and other executive skills are needed to explore brain-behaviour associations in PD, which may provide further information to understand the disease and develop cognitive training as a treatment for cognitive impairments.

5.4.5 Limitations

Choosing ROIs for connectivity analysis is always challenging. As the focus of the study is to explore the relations between dFC and cognition in neurological disorders, we selected the cognition-related ROIs that are commonly reported in the literature as described in previous chapters. Furthermore, in order to reduce the computational demand of calculating inverse covariance matrix in the sliding window approach, only a relatively fewer ROIs associated with cognition were included in the analysis. For future research, more regions should be included regardless whether they are related to cognition or not from a traditional point of view.

5.5 Conclusion

In this chapter, the goal was to investigate 1) whether dFC features can serve as biomarkers for neurological diseases and 2) how dFC features are related to cognitive functions in PD and MS – two distinct diseases with similar cognitive impairments such as executive dysfunction. In MS, average connection density, strength, and global dynamics were all decreased, but interhemispheric connections became more variable, possibly compensating for structural damage in the corpus callosum and other regions. In PD, we did not observe differences of any dynamic features compared to control subjects, which might be due to the relatively mild disease severity in our cohort. In the MS subjects, the brain-behaviour analyses revealed that higher disease duration was associated with decreased dFC and such association could be predicted by the principal components of dynamic features. Set-shifting abilities measured in WCST were predicted by the component representing dFC in interhemispheric connections; however, this relation did not explain a significant proportion of the variance in the functional connectivity data. In PD, better performance of memory tests was robustly related to/predicted by higher dynamics in interhemispheric connectivity, while overall disease severity was modulated by global dynamics with fewer effects from intra-hemispheric connectivity. Taken together, these brain-behaviour associations provide insights into understanding the disease effects in different neurological conditions.

Chapter 6: Dynamic brain organization, disease severity, and executive function

In this chapter, different aspects of functional connectivity are integrated to study the relations between stationary, dynamic functional connectivity, cognitive functions, disease severity, and demographical factors. By combining stationary and dynamic functional connectivity, dynamic brain organization can be assessed, which provides a more comprehensive approach to investigate the relations between functional connectivity, disease progression, and cognitive function as well as compensatory effects.

6.1 Introduction

6.1.1 Stationary and dynamic functional connectivity

Functional connectivity in human brain networks is usually estimated by calculating the temporal correlation (e.g. Pearson's r correlation) or neural influence (estimated by e.g. conditional dependence) between brain signals among anatomically-segregated brain regions [Friston, 1994; Friston, 2011]. These methods usually assume that the estimated functional connectivity is temporally stationary, i.e. does not change over time. However, connectivity fluctuates across time from seconds to minutes even in the resting state, which can be estimated by models of dynamic functional connectivity [Allen et al., 2014; Betzel et al., 2016; Chang and Glover, 2010; Handwerker et al., 2012; Hutchison et al., 2013a; Jones et al., 2012]. The simplest, and perhaps most common time-varying approach to assess dynamic functional connectivity is to estimate

correlations between brain regions within a fixed-length, sliding window, with the (possibly overlapping) windows ultimately moved over the entire data. Details regarding this method has been discussed in sections 1.2.2 and 5.1.1. The time-varying approach can capture the temporal variability of functional connectivity, but the spatial network characteristics cannot be estimated with this method. A graph theoretical approach appears to be a powerful technique to obtain topological information of networks, which quantifies information flow in stationary functional connectivity globally and locally.

6.1.1.1 Cognition and stationary functional connectivity: graph theoretical analysis

Graph theoretical analysis summarizes network characteristics and can represent how efficiently the networks propagate information globally and locally [Sporns, 2013]. Global efficiency, a measure of integration, has been related to working memory and verbal comprehension; while modularity, a measure of segregation, correlates with motor task performance [Cohen and D'Esposito, 2016; Pamplona et al., 2015]. Hub structures are related to higher-order cognitive functions such as executive function [Reineberg and Banich, 2016]. With graphical metrics, the brain can be divided into modules, with each module related to an individual cognitive component [Bertolero et al., 2015]. These “cognitive brain modules” are linked by hub structures and the hubs with higher connectivity engage more cognitive modules. Alterations in graphic theoretical measures of the computed brain stationary connectivity networks have been associated with a variety of cognitive abilities and disease populations. Altered hub structure has been demonstrated in people with Parkinson's disease with attention/executive deficits, with hub nodes having reduced importance [Baggio et al., 2014]. Global network measures cannot significantly distinguish depressed subjects from healthy controls; however, with a support vector machine

approach, individuals have been accurately classified with network measures [Lord et al., 2012], suggesting that a combination of machine learning methods and connectivity features is beneficial to assist diagnosis.

6.1.1.2 Cognition and dynamic functional connectivity: time-varying approach

Dynamic functional connectivity, as also referred to network dynamics and assessed by time-varying approaches, appears to be particularly pertinent to several cognitive processes including memory, language, attention, and executive functions [Braun et al., 2015; Bressler and Scott Kelso, 2001; Kucyi et al., 2016; Mattar et al., 2015; McIntosh et al., 2008; Shafto and Tyler, 2014; Thompson et al., 2013]. Increased dynamical variability in the EEG was found to be correlated with better performance (i.e. shorter reaction time and higher accuracy) in a memory task, emphasizing the importance of brain complexity in cognitive development [McIntosh et al., 2008]. There are associations between dynamic changes in frontoparietal/frontotemporal networks and neuropsychological measures, showing that the flexibility of neuronal activity in the frontal regions is cognitively beneficial for working memory performance and executive functioning [Braun et al., 2015]. This has led to a proposed “functional cartography” of the cognitive system, based on the estimated amount of *integration* and *recruitment* of brain regions during different cognitive processes [Mattar et al., 2015]. Network dynamics may also be important for language function in an aging population [Chai et al., 2016; Shafto and Tyler, 2014]. Measures of dynamic functional connectivity have been recently applied to understand how the human brain is affected by diseases such as Parkinson’s disease, Schizophrenia, Alzheimer’s disease, and major depression [Damaraju et al., 2014; Kaiser et al., 2015; Madhyastha et al., 2014; Sakoglu et al., 2010; Wee et al., 2013].

6.1.2 Studies looking at both stationary and dynamic aspects of functional connectivity

Although investigating graph theoretical metrics and dynamic connectivity have become increasingly important in clinical and neuroscience (please refer to section 4.1.2, 4.1.3, and 5.1.3 for review), not many studies evaluate both aspects simultaneously. A few studies have performed graph theoretical analysis on the windowed matrices derived from the sliding window approach to investigate how brain topological features change across time and the variation of global network characteristics [Chen et al., 2016a; Chiang et al., 2016; Kim et al., 2017; Zalesky et al., 2014]. This approach has been referred to as dynamic graph analysis and the most commonly used metrics are efficiency and modularity [Prete et al., 2017], which offers a promising way to study the balance between integration and segregation.

Compared to other resting-state networks (RSNs) such as sensory-motor, auditory, visual networks, the nodes in the salience network (SN), subcortical regions, and the frontoparietal network (FPN) showed higher flexibility and diversity (i.e. spatially varied), suggesting that the SN, FPN, and subcortical regions are more dynamic and interact with the nodes outside of the community determined by graphical analysis. Moreover, the spatiotemporal brain organization of the SN predicted processing speed, attention, executive functioning, and cognitive flexibility, suggesting that the SN is a hub to facilitate cognitive function by interacting flexibly with other networks. Furthermore, the dynamics of topological characteristics have been profiled. The hub and inter-modular connections have shown to be more dynamic, which are mainly located in the FPN and the default mode network (DMN) and included in long anatomical connections; while non-hub regions such as the cerebellum, vermis, and some nodes in temporal areas connectivity appeared to fluctuate less [Zalesky et al., 2014]. Of note, the FPN, DMN, and long anatomical

connections are highly related to cognitive function (detailed review can be found in section 1.1 and 1.4). Such brain dynamics possibly react to the balance between different principles of brain organization (i.e. efficiency of information transfer, process, and energy cost) as well as cognitive processes.

This approach for studying dynamic brain organization has been applied to a few clinical studies. In patients with epilepsy, the network characteristics represent local segregation was more dynamic; while the measures represent global integration was more stationary [Chiang et al., 2016]. In Parkinson's disease (PD), global efficiency showed higher variation across time windows, suggesting that the parallel information transfer was less efficient compared to that in healthy subjects [Kim et al., 2017]. Taken together, dynamic brain organization provides insights into how diseases affect brain connectivity spatially and temporally, which potentially helps predict disease severity. However, none of the clinical research has related dynamic brain organization to cognitive performance.

6.1.3 Study aims

In this study, the overarching purpose was to study how dynamic and static functional connectivity related to cognitive performance in MS and PD. We applied a sliding window approach and graph theory analysis to assess dynamic functional connectivity and stationary network characteristics in both neurological conditions, aiming to investigate the utility of these measures. In addition, a machine learning method, multiset canonical correlation analysis (MCCA), was applied to explore the associations between dynamic and stationary functional connectivity features, and behavioural data in order to explore models that may be beneficial for treatment development. Since previous neuroimaging studies have shown that both dynamic functional connectivity and graphical

measures are beneficial to strengthen understanding of complex cognitive processes, we hypothesize that subjects with neurological disorders demonstrating cognitive dysfunction would also demonstrate abnormal dynamic and stationary functional connectivity. Furthermore, given that human cognition is complex and operates as a network phenomenon [Petersen and Sporns, 2015], we also hypothesize that cognitive functions in neurological disorders will be jointly affected by dynamic and stationary connectivity networks as well as disease severity.

6.2 Materials and methods

6.2.1 Subjects

PD data are from GFM2 project and MS data were from COGMS project. Both cohorts are the same as chapter 5.

Ethics approval was issued by the University of British Columbia's Clinical Research Ethics Board and all subjects provided written, informed consent.

Forty-six Relapsing-Remitting Multiple Sclerosis (RRMS) patients were included in the study and all the subjects underwent both cognitive testing and Magnetic Resonance imaging (MRI). Demographics are shown in Table 2.2. All patients fulfilled the McDonald 2005 criteria [Polman et al., 2005] for diagnosis of MS and were recruited from the MS clinic at the University of British Columbia Hospital. Exclusion criteria included the following: 1) subjects with significant depression and/or other psychiatric illness, 2) history of drug or alcohol abuse, or 3) use of steroids in the last 3 months.

The same twenty-four PD patients as the last chapter were included in the study. Clinical evaluations and demographics are shown in Table 5.1. All PD patients were in on-medication state and severe depressed subjects were excluded in the study.

6.2.2 Neuropsychological and clinical assessments

All MS patients underwent a test battery which included Digit Span, Arithmetic, Letter-Number Sequencing, Symbol Search, and Symbol Coding subtests from the Wechsler Adult Intelligence Scale IV (WAIS-IV), the Verbal Letter Fluency Test (FAS), Wisconsin Card Sorting Test (WCST), and Trail Making Test A and B (TMT A and B). The Working Memory Index (WMI) is a composite score of Digit Span, Arithmetic, and Letter-Number Sequencing; while the Processing Speed Index (PSI) is another composite score of Symbol Search and Symbol Coding. These two composite scores were included in the analysis rather than the individual scores in WAIS-IV. Clinical questionnaires were administered, which included Multiscore Depression Inventory (MDI), State-Trait Anxiety Inventory (STAI), and Fatigue Severity Scale (FSS). The neuropsychological battery aimed to evaluate executive skills including mental flexibility, concept formation, attentional switching, spontaneous generation of verbal information, and working memory as well as processing speed abilities including attention and visual scanning. The subject's disability severity was rated by the Kurtzke Expanded Disability Status Scale (EDSS)[Kurtzke, 1983] as scored by a neurologist at the time of recruitment.

All PD patients were assessed with motor and non-motor symptoms with Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS UPDRS). Moreover, depression, apathy, and fatigue symptoms were evaluated with questionnaires. Cognitive abilities were assessed with Montreal Cognitive Assessment (MoCA). Details have been listed in section 5.2.1.

6.2.3 Imaging acquisition and processing

All subjects underwent imaging studies at the University of British Columbia (UBC) MRI Research Centre with a Philips Achieva 3.0 Tesla MRI scanner. Resting-state functional MRI (rsfMRI) data were acquired using an 8 channel head coil and an echo-planar imaging sequence with the following parameters: $3 \times 3 \times 3 \text{ mm}^3$ resolution, 36 slices, 2000 ms TR, 30 ms TE, 90 degree flip angle, and 240 volumes/dynamics. 3 Dimensional (3D) T1 weighted images were acquired with $1 \times 1 \times 1 \text{ mm}^3$ resolution, 60 slices, 28 ms TR, 4 ms TE and 27 degree flip angle.

The preprocessing was the same as chapter 5.

In MS, image preprocessing steps were performed in each subject's native space with the functions of slice timing and motion correction from Statistical Parametric Mapping 8 (SPM8, University College London, London) for correcting temporal and spatial differences. For registration, the FMRIB's Linear Image Registration Tool (FLIRT) from the FMRIB Software Library 6.0 (FSL, FMRIB, Oxford) was used and a brain mask was applied to remove non-brain areas before registration. Cortical parcellation was done on the T1-weighted images in Freesurfer version 4.5.0 (Massachusetts General Hospital, Boston) and 36 cognition-associated regions-of-interest (ROIs) were selected (Table 5.2). These ROIs have been commonly reported in the neuropsychological literature and frequently used to investigate the relations between cognition and resting-state functional connectivity (rsFC). Finally, the average fMRI time courses among voxels within individual ROIs were extracted using self-programmed scripts in Matlab (The MathWorks, Inc.) and the data were detrended before connectivity analyses.

In PD, similar processing steps have been applied but with AFNI (NIMH, Bethesda), including despiking, slice timing correction, 3D isotropic correction (3x3x3 mm³ resolution), and motion correction. Whole brain parcellation was done in FreeSurfer 6.0 on the T1-weighted images and the structural images were then registered to the fMRI images using rigid registration. All analyses were done in the native fMRI space rather than transforming all fMRI data to a common template. Moreover, several sources of variance such as head-motion parameters, white-matter, and CSF signals were removed using linear regression. The fMRI signals of the same 36 cognition-associated ROIs were extracted and detrended to remove any linear or quadratic trends and smoothed with 6 FWHM Gaussian kernels. Finally, bandpass filtering was performed to retain the signal between the recommended frequencies of interest for resting state activity (0.01 Hz to 0.08Hz).

6.2.4 Connectivity analysis

Dynamic functional connectivity (dFC) was evaluated in a sliding window approach with inverse covariance matrices and several dynamic features were calculated. Analysis details can be found in section 5.2.4. In total, 6 features were generated including network variation (NV), flexibility of interhemispheric connections (FOCcs), flexibility of cross-hemispheric connections (FOCcsns), flexibility of intrahemispheric connections (FOCw), density (Den), and network power (NP). Although these network features were all calculated based on learned dynamic connectivity matrices, we considered DEN and NP as stationary network features as they did not calculate the *differences* between two matrices. Rather, they represented the average values across the scanning time.

For stationary functional connectivity (sFC), graphical measures were estimated with the Brain Connectivity Toolbox. Analysis details can be found in section 4.2.4. In total, global efficiency, transitivity, modularity, assortativity, characteristic path length, and rich club coefficient were computed. Note that in order to avoid having too many features and overfitting the data in PD, rich club coefficient was not included as the highest level was only 7 in our PD data.

6.2.5 Brain-behaviour associations

We utilized MCCA to explore the associations between modalities/data sets. MCCA determines the linear combinations of data sets that maximize the correlations between data sets. MCCA is a popular method for blind source separation and has been used to explore the associations between neuroimaging and clinical/behavioural data [Chen et al., 2016b; Perry et al., 2017; Sui et al., 2013].

In this study, we included five data sets to investigate the relations between dynamic rsFC, stationary rsFC, demographics, cognitive scores, and affective variables in RRMS. Dynamic rsFC included NV, FOCcs, FOCcns, and FOCw. Stationary rsFC included DEN, NP, global efficiency, assortativity, characteristic path length, modularity, rich club coefficient, and transitivity. The demographical set included education, EDSS, and disease duration. Cognitive scores included WMI, PSI, FAS, WCST number of categories completes, TMT A and B, in which WMI, PSI, and FAS were standardized/adjusted scores. Affective variables contained MDI, trait anxiety (STAIT), state anxiety (STAIS), and FSS, in which MDI (total score), STAIT, and STAIS were transformed/standardized scores. Subjects who showed more than 1 variable that was bigger/smaller than 2 standard deviations of the mean were considered outliers. In the end, nine subjects/outliers were excluded in the MCCA analysis, resulting in 37 MS subjects in total. Age effects were regressed out in a linear regression model and all the data were whitened before

performing MCCA. A permutation test with 1000 permutations was performed to assess the significance level of each MCCA component. In order to ensure the robustness of results, we used a leave-one-out cross-validation. Finally, the MCCA loadings (i.e. correlation between transformed canonical data and input scores) and standard errors of each variable were reported.

In PD, 4 data sets were included. First, dynamic rsFC included NV, FOCcs, FOCcns, and FOCw. Stationary rsFC set included DEN, NP, global efficiency, assortativity, characteristic path length, modularity, and transitivity. In the clinical set, scores of UPDRS III, Beck Depression Inventory (BECK), and Apathy Scale (SAS) were incorporated. Finally, scores of MoCA sub-tests and the final full scores were involved in the cognitive set. Due to that naming test did not show impairments in any patients (everyone got full score), this sub-score was not included in the cognitive set. As the sample size of PD was relatively small, we only included the most important variables that we were interested in to avoid overfitting the data. Some demographical and clinical variables were not contained in the analysis such as gender, disease duration, MDS UPDRS part I, II, and IV, etc. No outliers have been detected in PD; therefore, 24 PD patients were counted in the MCCA analysis. MCCA was performed using the same parameters and approach as previously described.

6.3 Results

6.3.1 MCCA in MS

MCCA identified one significant component that showed moderate to strong correlations between the linear combination of almost all data sets ($p=0.01$ in a permutation test, Figure 6.1). This component represented a linear combination of features in all sets that maximally correlate with

each other. Dynamic features showed strong and moderate correlation to stationary features ($r=0.80$) and cognitive scores ($r=0.34$) as well as demographics ($r=0.22$). Stationary features also demonstrated associations to cognitive scores ($r=0.24$) but showed limited relations to other behavioural measures (i.e. demographics and affect). Demographics were strongly associated with affective variables ($r=0.60$) as well as cognition ($r=0.46$) and dynamic features ($r=0.22$). Affective (mood) variables were not strongly linked to resting-state functional connectivity (rsFC) features. However, affect was associated with cognitive performance tests and demographic features. Overall, cognition was more correlated to demographics and dynamic rsFC than static rsFC and affect. Affective variables mainly had strong relations to demographics, but they also showed mild associations to cognition.

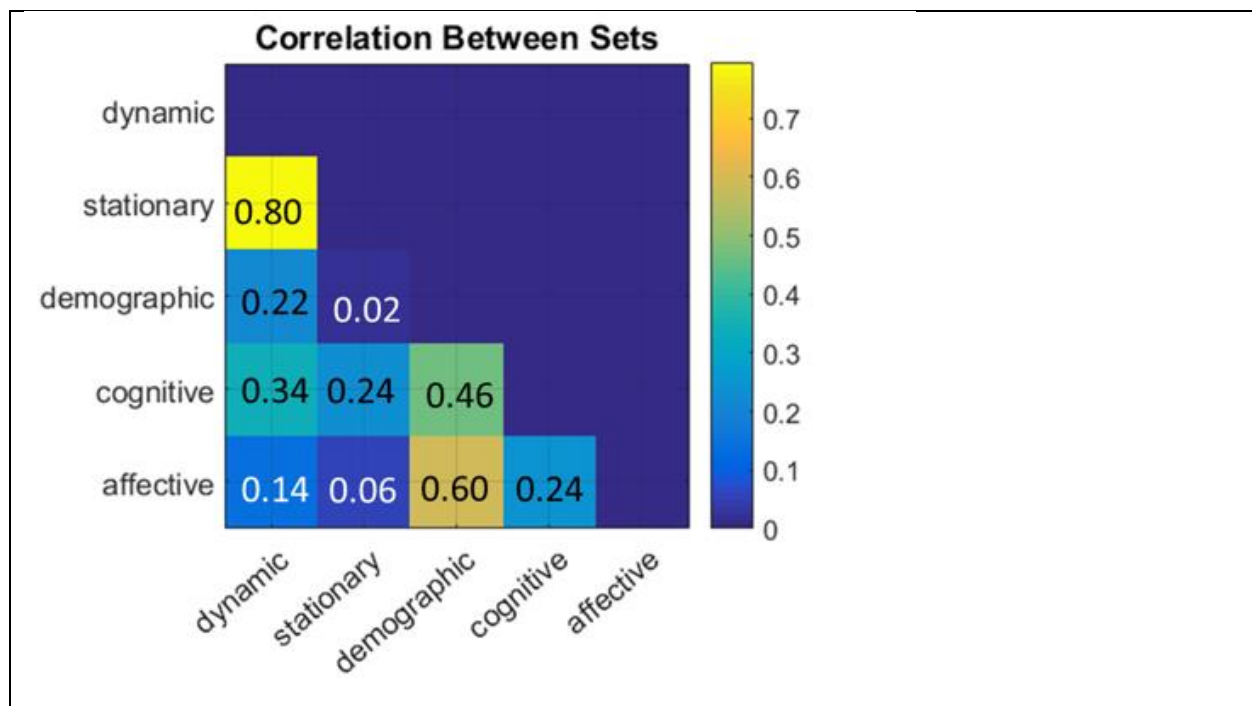
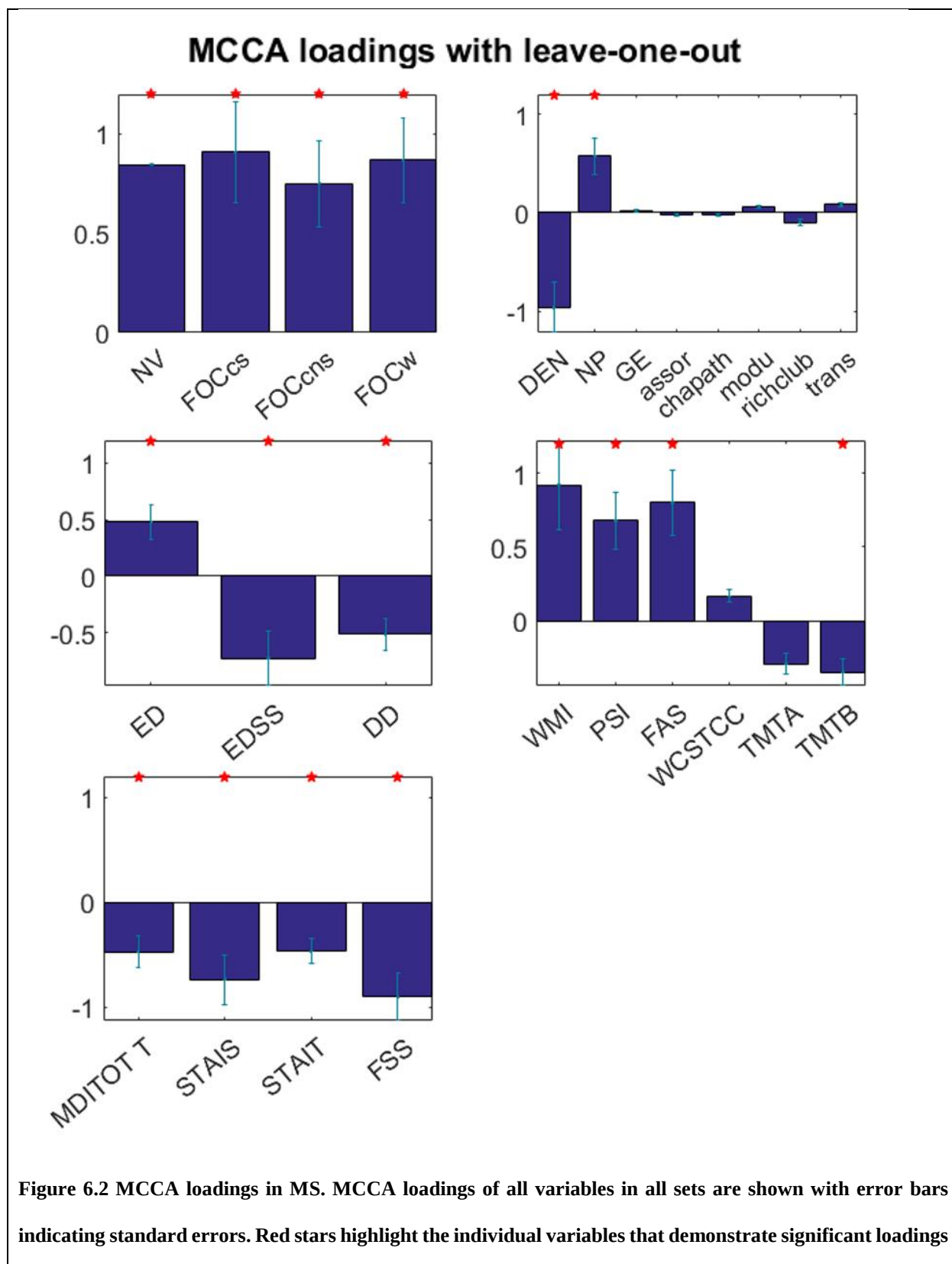


Figure 6.1 Correlation between MCCA sets in MS. The lower triangle shows the correlation coefficients between all data sets in the significant MCCA component ($p = 0.01$ in a permutation test). Each column/row represents the linear combination of the MCCA loadings from all variables within each set. The exact correlation coefficient between two sets is illustrated in each corresponding element.

Figure 6.2 demonstrates the MCCA loadings of all variables in the significant component ($p=0.01$ in a permutation test). Within each set, red stars indicated the variables that showed significant loadings and the results were mainly interpreted based on these variables. All the variables which showed positive loadings were positively correlated with each other; likewise, all the variables that demonstrated negative loadings were positively associated with each other. In short, higher dynamics, stronger static connectivity strength, longer education, and better cognitive performances were correlated with each other. On the other hand, denser static connectivity, higher EDSS and longer disease duration, worse TMTB performance, and depression/anxiety/fatigue were positively associated with each other.

Better executive functions on cognitive testing were related to higher dynamics, stronger stationary connectivity, and higher education; while worse mental flexibility measured by TMT B test are expressed with the associations of denser static connectivity, higher disease severity, and disease comorbidity (i.e. depression, anxiety, and fatigue).

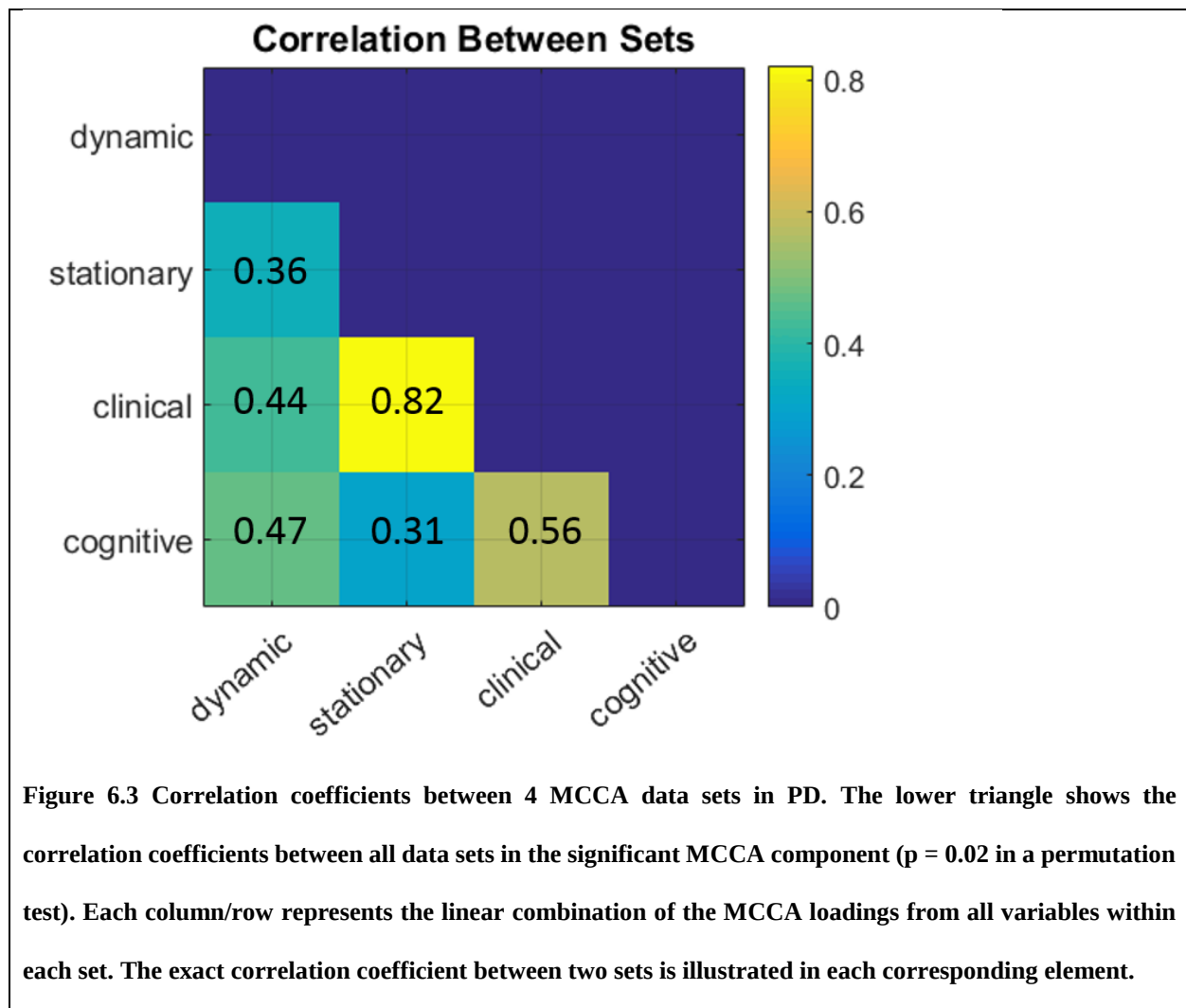


($p < 0.05$). All the variables that show positive loadings are positively associated with each other. All the variables that present negative loadings are positively correlated with each other.

[NV: network variation, FOCcs: flexibility of interhemispheric connections, FOCcns: flexibility of cross-hemispheric connections, FOCw: flexibility of intrahemispheric connections, DEN: density, NP: network power, GE: global efficiency, assor: assortativity, chapath: characteristic path length, modu: modularity, richclub: rich club coefficient, trans: transitivity, ED: education, EDSS: Expanded Disability Status Scale, DD: disease duration, WMI: Working Memory Index, PSI: Processing Speed Index, FAS: Verbal Fluency Test, WCSTCC: Wisconsin Card Sorting Test number of categories completes, TMTA: Trail Making Test A, TMTB: Trail Making Test B, MDITOTT: Multiscore Depression Inventory Total T Score, STAIS: Anxiety Inventory-State, STAIT: Anxiety Inventory-Transit, FSS: Fatigue Severity Scale]

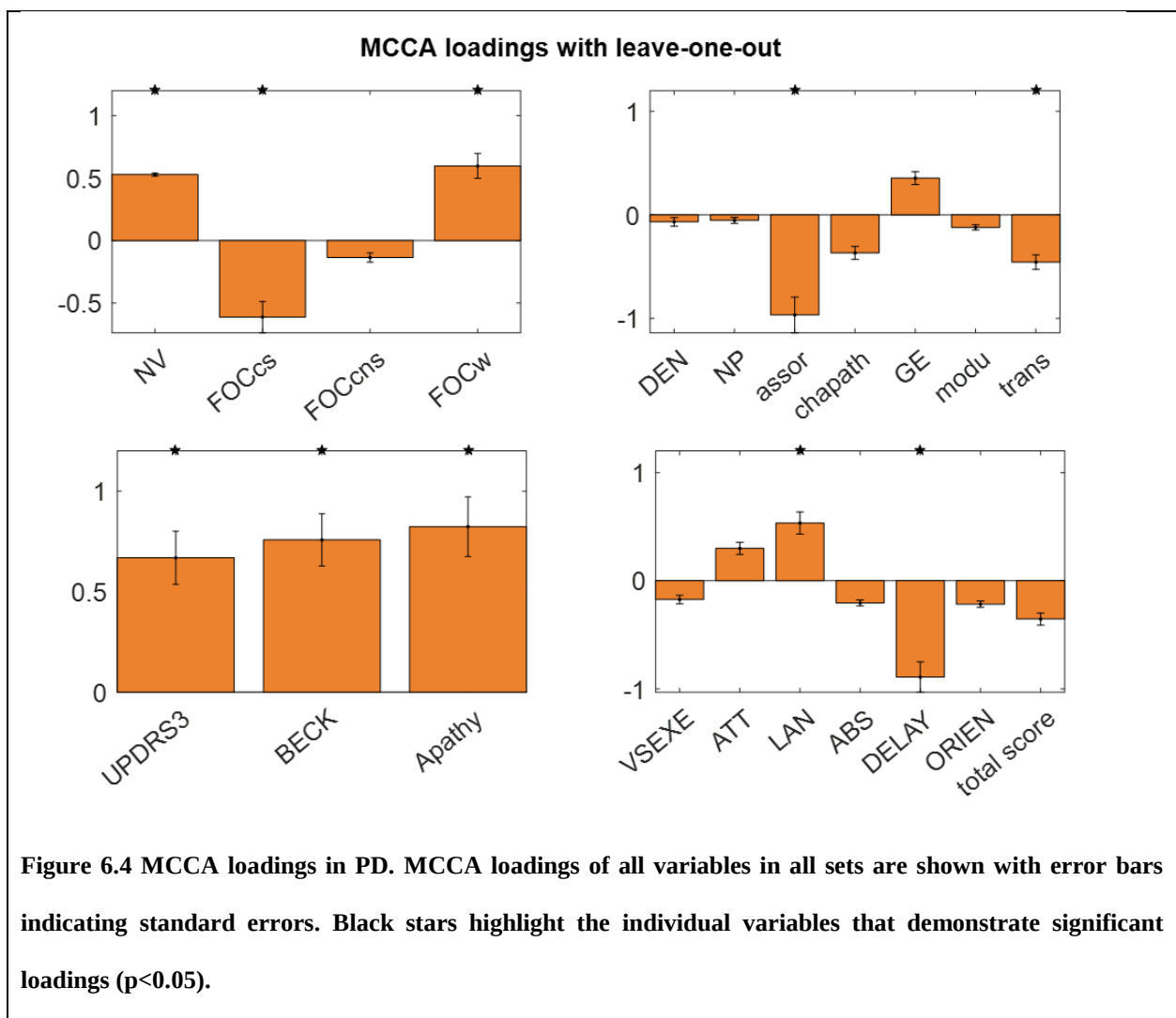
6.3.2 MCCA in PD

MCCA also revealed one significant component that showed moderate to strong correlations between the linear combination of all data sets in PD ($p = 0.02$ in a permutation test, Figure 6.3). Stationary FC and clinical data sets demonstrated the strongest correlation with $r = 0.82$. The rest sets all showed moderate correlations: $r = 0.58$ for clinical set vs cognitive set, $r = 0.47$ for dynamic FC vs cognitive set, $r = 0.44$ for dynamic FC vs clinical set, $r = 0.36$ for dynamic vs stationary FC, and $r = 0.31$ for stationary FC vs cognitive set. In short, the linear combination of stationary features was strongly correlated with clinical data. On the other hand, dynamic features were more correlated with cognitive function than other sets. Clinical data and cognitive function also showed strong correlation.



The MCCA loadings of the significant component are shown in Figure 6.4 ($p=0.02$ in a permutation test). Within each set, black stars indicated the variables that showed significant loadings and the error bars showed standard errors across subjects. In the dynamic FC set, NV and FOCw showed significant positive loadings, while FOCs demonstrated negative loadings. Assortativity and transitivity in the stationary set both exhibited significant negative loadings. All variables in the clinical data showed significant positive loadings. In the cognitive set (i.e. MoCA

scores), LAN was loaded positively and DELAY was loaded negatively. All the variables which showed positively loadings were correlated with each other and variables with negative loadings were positively related to each other, which resulted in a “positive-negative pattern”. In other words, higher dynamics in global and intrahemispheric FC, higher disease severity, more severe depression and apathy symptoms were correlated with better language ability. Higher interhemispheric dFC, assortativity, and transitivity were related to better memory function measured by the delayed recall test in MoCA.



[NV: network variation, FOCcs: flexibility of interhemispheric connections, FOCcns: flexibility of cross-hemispheric connections, FOCw: flexibility of intrahemispheric connections, DEN: density, NP: network power, assor: assortativity, chapath: characteristic path length, GE: global efficiency, modu: modularity, trans: transitivity, UPDRS3: Unified Parkinson's disease rating scale part III, BECK: Beck Depression Inventory, Apathy: apathy scale, VSEXE: visuospatial/executive function, ATT: attention, LAN: language, ABS: abstraction, DELAY: memory test delayed recall, ORIEN: orientation, total score: MoCA full score]

6.4 Discussion

6.4.1 Relations between dynamic, stationary functional connectivity, education, and cognition in MS

We found two major patterns of the associations between rsFC and behavioural data with the MCCA approach in MS. Better working memory, processing speed, and verbal fluency abilities were associated with higher education, stronger stationary rsFC as well as higher network variability. The other pattern demonstrated that poor switching ability was associated with higher depression, state and trait anxiety, fatigue, higher disease severity, longer disease duration, and denser but perhaps more rigid rsFC (as density was anti-correlated with all dynamic features).

Previous research has proposed that more variability in functional connectivity is related to better cognitive performance [Kucyi et al., 2016; Mattar et al., 2015; McIntosh et al., 2008]. In our results, we also observed positive correlations between variable network features and cognitive performance. These cognitive performances not only required attention but also a variety of executive skills such as working memory (to temporary hold and manipulate information to formulate an answer), processing speed abilities (to perform focused attention, visual scanning,

and discriminating visual details under timed conditions), and fluency (to spontaneously generate information according to rules and retrieve information from memory) [Kreutzer et al., 2011], which were all higher-order cognitive functions and required more neuronal resources [Miller and Wallis, 2009].

We found higher education and stronger static connectivity strength were also associated with better higher-order cognitive functions, in keeping with prior results [Alosaimi et al., 2017] and “cognitive reserve theory” which suggests that education may provide neuroprotection effects and enhance plasticity and flexibility in a variety of neural circuits imparting protection in neurodegenerative disease [Stern, 2002; Vance et al., 2010]. Prior studies relating functional connectivity with cognition have been variable; stronger [Smith, 2015], or weaker but more efficient connections [Santarnecchi et al., 2014] have both been proposed for supporting cognitive functions. We suggest, that, the balance between dynamic and stationary connectivity and coordination of information flow might be the key factor to facilitate cognition.

6.4.2 Disease effects on cognition and comorbidity in MS

The MCCA model also suggested a relation between disease severity, comorbidity, and worsening executive functions. Depression and anxiety are frequent comorbidities in MS and are often associated with more severe physical disability and disease progression, and poorer quality of life [Marrie, 2016]. Although comorbidities in MS have been extensively studied in the clinical literature (e.g., [Alosaimi et al., 2017; Marrie, 2017; Rahn et al., 2012]), the relations between disease severity, comorbidity, cognition, and rsFC have not been previously investigated. We found affective variables were highly correlated with demographics as shown in Figure 6.1. Within this association, higher disease severity, reflected by higher EDSS and longer disease duration,

was related to higher depression, state and transit anxiety, and fatigue. Worse TMTB performance (higher scores) was correlated with above-mentioned associations and higher network density, which might be more rigid as DEN was anti-correlated with all dynamic features. TMTB performance required a great deal of executive components especially task switching abilities and mental speed; therefore, this MCCA pattern indicated a co-existence of disease severity, comorbidity, reduced shifting abilities, mental speed, and denser but rigid static rsFC in MS.

Recent studies have investigated the relations between cognitive decline and psychiatric comorbidity in neurological diseases and three theories have been proposed, 1) comorbidity is *independent* of cognitive decline, 2) cognitive dysfunction is *qualitatively* influenced by comorbidity, and 3) comorbidity manifests the existing cognitive impairments in neurological diseases (i.e. cognition is *quantitatively* affected) [Barone and Santangelo, 2010; Karadayi et al., 2014; Mavandadi et al., 2009]. We found that disease severity exhibited the strongest association with depression, anxiety, and fatigue; while it demonstrated the second strongest correlation to cognitive scores. In addition, the correlation between affect and cognition was relatively mild. Affective status might have relatively weaker interactions with rsFC but indirectly impact higher-order cognitive functions in early-stage MS. Therefore, our results are most supportive of the theory that psychiatric comorbidity does not directly impact cognition, but rather, it exacerbates existing cognitive problems in MS.

6.4.3 Better memory function in PD is related to dynamic interhemispheric connectivity and stationary network segregation

Delayed recall test in MoCA reflects memory retrieval and encoding function [Julayanont and Nasreddine, 2017]. In PD, whether memory deficits are caused by impairments in retrieval or

consolidation (i.e. whether patients are unable to re-access information or acquire new information) is still under debate [Chiaravalloti et al., 2014; Costa et al., 2014]. However, the striatum has been proposed to primarily support memory retrieval and the deficits might be related to executive dysfunction [Costa et al., 2014; Scimeca and Badre, 2012]. In this study, although we were unable to pinpoint which kinds of memory deficits were represented in our data with only sub-tests in MoCA, we demonstrated inter-correlations between better memory function, network segregation, and dynamic coordination between two hemispheres.

In our results, better performance of memory test was associated with 1) higher transitivity and assortativity as well as 2) higher dFC in interhemispheric connections. As transitivity is a measure of functional segregation, higher value represents that the brain networks are more segregated than integrated. Assortativity is a correlation coefficient of node degrees of connected pairs, representing the tendency that similar nodes (with similar degree) are linked to each other. Therefore, higher value represents higher resilience. Of note, the values of assortativity in all subjects were small, which means that resilience may not be very obvious, but the subtle changes might still be related to cognition in PD. Higher FOCs represents higher variation in the homologous connections across time, that is, higher dFC in interhemispheric connections. Taken together, better memory function in PD was correlated with the segregated and resilience in the stationary FC and also related to more dynamic coordination of two hemispheres, supporting that 1) higher cognitive function is related to functional segregation proposed in Chapter 4 and 2) the important role of information transfer through interhemispheric connectivity toward cognition stated in Chapter 3.

6.4.4 Disease severity and comorbidities are related to compensated dynamics in PD

The other pattern in our results demonstrated that higher disease severity and comorbidities (depression and apathy) were associated with higher global dynamics and connectivity variation in intra-hemispheric connections as well as better language functions measured with sentence repetition and verbal fluency, which possibly indicated that increased dFC compensated for functional disruptions elsewhere. These increased dynamics may therefore facilitate language processes, causing paradoxical associations between higher disease severity and better relative language functions.

Although the exact mechanisms of altered language function in PD remains unclear [McNamara and Durso, 2018], novel analysis investigating dFC has revealed that flexible and dynamic networks facilitate language function [Chai et al., 2016], which explained the inter-correlations between language performance and increased dynamic features especially dFC in intra-hemispheric connections in our results. In addition, the language sub-test in MoCA actually reflects both language ability and executive function because verbal fluency is one of the tasks. As previously discussed, dFC has been associated with executive function in several studies [Mattar et al., 2015; Nomi et al., 2017], the findings further strengthened the conclusion that better language/executive function in PD is associated with increased dFC features rather than disease severity and comorbidities directly.

Interestingly, among the 4 data sets in the MCCA, clinical and stationary FC sets expressed the strongest correlation compared to other sets ($r=0.8$). UPDRS scores, depression and apathy symptoms were strongly anti-correlated with functional segregation measured with transitivity. The loadings of these two sets supported the conclusion in the previous chapters that disease

severity and comorbidity are related to functional segregation, and FC in PD has shifted toward a segregation-orientated brain organization (please see Chapter 4).

6.4.5 Limitations and future work

There are several limitations to our study. All MS subjects were relapsing remitting in the study. Therefore, the results might not be representative enough to the whole MS population, but the connectivity profile related to cognition in the RRMS disease stage was suggested. Several MS subjects were considered outliers and removed from the analysis, which reduced the sample size. In PD, as the sample size was relatively small for machine-learning approaches, we only included the variables that we were mostly interested in in order to avoid overfitting the data. Therefore, some effects of demographic and clinical features were not assessed. A previous chapter discussed heavily on gender effects to cognition in PD and MS, but we were unable to evaluate such an effect in this study. During the analysis, if gender was included in the demographics data set, none of the components were significant and the correlation coefficients between data sets were small ($r=0.01\sim0.4$). Perhaps, compared to gender, cognitive function was more associated with other variables such as education, disease severity, and fMRI measures in a multivariate relation.

As the original study design focused on the cognitive impairments commonly seen in the clinic, the selected ROIs covered the areas that have been identified in the traditional neuropsychological literature. However, with a greater recognition that complex cognition is a network phenomenon, complete whole brain coverage should be included in the future research. The issue of window length and the ways to report connectivity changes might be confounding factors while investigating dynamic functional connectivity. In this study, we used suggested window length parameters and selected six network features to summarize connectivity differences, which might

not capture all the potential connectivity changes. Recently other approaches have been proposed to study network dynamics in an unbiased manner, such as the Sticky Weighted Regression Model [Liu et al., 2015] and Dynamic Conditional Correlations [Lindquist et al., 2014]. Furthermore, other methods have been applied to report meaningful connectivity patterns other than selecting certain features [Leonardi et al., 2013]. These methods should also be tested with clinical data in the future. We included graphical measures as stationary features, but other network representations such as whole-brain connectivity matrices are also alternatives. In addition, nine MS subjects were considered outliers, implying inter-subject variability may still be an issue for robustness. Finally, changes in functional connectivity might be a result of compensation and adaptation for structural damages in MS. We did include brain volume and lesion load to test whether structural damages had impact on the results, but the MCCA model was not significant (data are not shown). Although structural damage is not commonly considered in PD, recent studies have discovered white matter microstructural changes with novel analyses [Zeighami et al., 2017]. Combining structural MRI data and functional connectivity in a sophisticated way is beyond the scope of this thesis, but it will be implemented to further investigate the disease effects structurally and functionally.

6.5 Conclusion

In this study, we performed a sliding window approach and a graph theoretical analysis on rsfMRI data to investigate dynamic functional connectivity and stationary network characteristics. MCCA was applied to explore the associations between dynamic, static network measures and behavioural data which included demographics, clinical data, cognitive performances, and affective status in subjects with RRMS and PD.

With an MCCA approach that controlled for age effects, we discovered that better executive functioning in MS was supported by higher education, stronger rsFC, and dynamic functional connectivity; whilst disease severity was highly related to poor executive functioning and affective variables, reinforcing the strong relationship between pathology and comorbidities. In PD, the inter-correlations in MCCA revealed that better memory function was related to segregated brain networks and dynamics of interhemispheric connections, reinforcing the role of interhemispheric connectivity to cognition; while disease severity and comorbidity were associated with increased dFC in global and intra-hemispheric connections, suggesting a compensatory effect and perhaps causing the paradoxical association between disease severity and language performance.

The brain-behaviour relations revealed in this study may provide influential information for the development of customized cognitive treatment and rehabilitation in neurological conditions (e.g. rehab in specific domains based on disease severity), but further research is necessary to better understand the disease effects as a whole such as combining structural, functional, and behavioural data.

Chapter 7: Conclusion

The research presented in this dissertation utilized novel approaches to study resting-state functional connectivity (rsFC) and the associations to cognitive deficits in two distinct neurological conditions: Parkinson's Disease (PD) and Multiple Sclerosis (MS). The goals were to investigate whether advanced network measures have potential to serve as biomarkers, explore relations between altered rsFC and cognitive performance, and predict cognitive function and disease severity based on rsFC. The knowledge provides important insights to the understanding of disease effects and treatment development.

7.1 Summary of the research

The included data in each chapter are summarized in Table 7.1.

Chapter	Subjects	Age	Cognitive tests	Project
Ch2	31 PD 46 MS	PD: 59.9±10.8(f), 61.5±9.4(m) MS: 41.1±10.3(f), 45.8±11.6(m)	Comprehensive battery	PD: PPMI MS: COGMS
Ch3	12 PD & 10 NC 25 MS & 41 NC	PD: 60.0±9.9, NC: 59.4±6.1 MS: 37.2±9.5, NC: 34.9±10.1	PD: limited MS: PASAT/SDMT	PD: BCT MS: OPERA
Ch4	23 PD & 19 NC (8 showed artifacts) 18 MS & 15 NC 46 MS for BBA	PD: 60.95±9.7, NC: 56.13±16.9 MS: 32.00±4.9, NC: 28.93±5.0 46 MS: 42.89±10.9	Comprehensive battery as ch2	PD: PPMI MS: COGMS
Ch5	24 PD & 15 NC 18 MS & 15 NC 46 MS for BBA	PD: 68.38±4.7, NC: 69±4.8 MS: same as ch4	PD: MoCA sub-scores MS: as ch2	PD: GFM2 MS: COGMS
Ch6	24 PD 37 MS (9 outliers)	same as ch5	PD: as ch5 MS: as ch2,4,5	PD: GFM2 MS: COGMS

Table 7.1 The summary of data used in each chapter.

7.1.1 Cognitive impairments and functional connectivity

Chapter 1 presented a literature review on cognitive deficits in PD and MS – two distinct neurological diseases that both demonstrate similar cognitive deficits especially executive dysfunction – as well as a summary of the clinical research which investigates rsFC and cognitive impairments with both traditional (i.e. seed-based connectivity and independent component analysis-derived resting networks) and novel/advanced approaches (i.e. graph theory analysis and time-varying approaches). This chapter concluded that there are common causes and unique features for executive impairments in PD and MS. Impaired long-range connections potentially impact the “input component” of executive function, which is a common feature in both diseases. Decreased efficiency of global neuronal transfer has been commonly reported in MS, which might be a result of hub failure. In PD, the frontal-striatal loops affected by dopamine depletion affects the “output component” of the executive function and hub reorganization (i.e. non hubs become more important and hubs lose the central role in the networks) altered brain organization. In addition, as cognitive inflexibility has been commonly seen in PD clinically, the chapter also hypothesizes that connectivity flexibility might be impaired (i.e. dynamic functional connectivity which facilitates higher-order cognition) as well and connectivity flexibility shall share certain degrees of association with cognitive flexibility.

7.1.2 Cognitive profiles and the associations to demographical features

In Chapter 2, Canonical Correlation Analysis (CCA), a multivariate approach, revealed complex inter-correlated patterns between cognitive performance and demographical characteristics to compare PD and MS in terms of cognitive deficits reported in the literature. In MS, female gender

was associated with better executive functions such as set-shifting ability; while male gender and disease severity were related to poor performance in card sorting tests. In PD, female gender and education were associated with better performance in almost all the cognitive domains that are commonly impaired such as verbal learning and memory, executive function, attention, and processing speed. On the other hand, age and depression were anti-correlated with better cognitive abilities.

Taken together, the chapter reveals an inter-correlated pattern between cognitive performance, clinical evaluation, and demographical characteristics in PD and MS. Moreover, this study concluded that gender is an influential factor in preserving cognitive function regardless of pathology, possibly due to the purported neuroprotective effects of estrogen.

7.1.3 Long-range connections, interhemispheric connectivity, and cognitive function

As Chapter 1 hypothesized that long-range connections might be the common cause to cognitive deficits, Chapter 3 utilized whole brain connectivity analysis to investigate long-range connection as well as interhemispheric functional connectivity. Several machine learning methods were carried out to explore the relations between rsFC and cognitive performance.

In MS, interhemispheric connectivity appeared to be enhanced and homogenized, possibly indicating a compensatory effect. With robust and LASSO regression, we reported that adequate cognitive performance requires distributed homologous brain regions, and that interhemispheric connectivity can accurately predict performance of attention, processing speed, and working memory functions. With an exploratory approach, frontal-parietal/occipital connections were significantly different between controls and MS and such pattern was correlated with cognitive

performance that required attention and memory, supporting the important role of long-range connections in cognitive processes.

In PD, enhanced interhemispheric connectivity was observed in the medial prefrontal cortex, possibly as a compensatory mechanism. Only dopaminergic medication dose could be mildly predicted by the altered interhemispheric connectivity. In addition to interhemispheric connectivity, several connections within frontal-striatal loops showed differences in PD. Although they were part of the “output component” of executive function, no significant associations with behavioural scores were found, possibly due to the fact that the patients were very mild and none showed significant cognitive impairment.

Overall, long-range connections and interhemispheric connectivity could predict cognitive performance in MS, which supported the hypothesis in Chapter 1. However, the brain-behaviour associations in PD were not very promising. Perhaps, other aspects of rsFC should be taken into account such as dynamic functional connectivity.

7.1.4 Topological brain organization and executive function

In Chapter 4, graph theoretical approaches were applied to capture rsFC network characteristics. As functional integration and segregation are important principles of brain organization, we mainly calculated the measures representing these two characteristics. In addition, as hubs have been associated with higher-order cognitive function, measures of hub structures were included as well. In order to explore the brain-behaviour relations reflecting how brain organization is associated with cognitive function, we utilized several methods such as correlation, regression, and machine learning approaches.

In PD, although global measures did not show any differences, several local measures demonstrated alterations across cortices, indicating 1) a segregation-oriented brain organization and 2) hub vulnerability. Moreover, increased functional segregation was correlated with better cognitive performance which requires executive skills as well as verbal learning and memory abilities. The observed brain-behaviour relations further supported that FC has become more segregated in order to support cognitive function in PD.

In MS, there were no alterations in brain organization, which might due to the mild disease course in our cohort. However, interestingly, brain-behaviour analyses revealed promising results. First, modularity, a measure of functional segregation, was related to the performance of verbal fluency test, indicating that executive skills were associated with functional segregation in MS. In addition, in several linear regression models, disease severity, psychiatric comorbidities, and cognitive performance in executive and processing speed domains could be significantly predicted by local measures located across cortices and the cerebellum. Moreover, with a machine learning approach, such predictability was enhanced between local efficiency and disease duration. Taken together, the brain-behaviour associations illustrated that the disease was affected/predicted by distributed regions and executive skills were significantly associated with the coordination between not only frontal, temporal, and parietal regions but also cerebellum, supporting the “cognitive role” of cerebellum in neurological diseases.

In short, brain organization reflected information transfer in a topological fashion, which allowed us to investigate how diseases altered communication between brain regions. In PD, we demonstrated hub vulnerability, which is consistent with previous studies not only in PD but other

neurological and psychiatric disorders. In MS, we revealed robust brain-behaviour relations and highlighted the influence of distributed brain regions to both disease course and cognitive function.

7.1.5 Dynamic functional connectivity and executive function

In Chapter 5, a sliding window approach with inverse covariance matrix estimation was used to estimate dynamic functional connectivity with features representing dynamics in global and specific connections. Correlation was carried out to explore the associations between dynamics features and behavioural data (demographics, clinical measures, and cognitive scores). Linear regression was applied to study the relations between principal components of dynamic features and behavioural data.

In MS, global dynamics and connectivity strength/density were decreased, but interhemispheric connections increased their dynamics, suggesting a compensatory mechanism whereby interhemispheric connections become more variable to compensate for global functional disruption. Longer disease duration was related to decreased dFC in several specific connections and could be predicted by principal components of dynamic features. Although components representing main effects of interhemispheric dynamics could predict set-shifting ability in a regression model, this relation was not representative of the whole data set.

In PD, none of the dynamics features were different between healthy subjects and patients, which could be explained by the fact that all PD subjects were very mildly affected. However, subtle changes of dFC were related to cognitive performance. Higher dynamics in interhemispheric connections were related to better performance in a memory test, emphasizing the importance of dynamic coordination between two hemispheres in cognitive processes. Two regression models

showed significant brain-behaviour associations. A principal component that represented overall dynamics could predict disease severity; while age and a component which contrasted effects from interhemispheric vs non-interhemispheric dFC could predict memory function. The regression results supported the interpretation of the correlation patterns but with stronger robustness.

To conclude, with dynamic features derived from the analysis, we observed compensatory effects in MS, whereby increased dynamics in interhemispheric connections compensated for reduced dynamics in global networks. Furthermore, dynamic connectivity patterns could predict disease duration. In PD, although no network changes were observed, subtle dFC alterations were related to cognitive performance, highlighting the role of dFC to cognition and supporting the idea that dFC may be a key role in PD, as proposed in Chapter 1.

7.1.6 Combining dynamic, stationary functional connectivity and behavioural data reveals complementary information

As mentioned in Chapter 1, more sophisticated statistical approaches are needed to explore brain-behaviour associations. In chapter 6, Multiset Canonical Correlation Analysis (MCCA), a multivariate and machine learning approach, was applied to investigate the relations between different aspects of FC (i.e. stationary and dynamic), demographics, clinical data, and cognitive scores jointly. The dynamic FC set contained dynamic features derived from a sliding window approach as described in Chapter 5. For the stationary set, graph theory measures were calculated to represent functional integration, segregation, and hub structures as mentioned in Chapter 4. This multivariate approach allowed us to combine different modalities to come up with complementary information to understand disease effects clinically, functionally, and cognitively.

In MS, five data sets were included in the MCCA: dynamic and stationary rsFC, demographics, cognitive scores, and affective variables. Better cognitive performance in several tests were correlated with higher dynamics, stronger static connectivity strength, and longer education; whilst worse set-shifting abilities were related to denser static connectivity, higher disease severity, longer disease duration, and comorbidities such as depression, anxiety, and fatigue. Based on these inter-correlated patterns, we suggest that the balance between dynamic and stationary connectivity and coordination of information flow might be the key factor to facilitate cognition. In addition, this MCCA pattern also indicated a co-existence of disease severity, psychiatric comorbidity, reduced shifting abilities, mental speed, and denser but rigid static rsFC in MS.

In PD, the MCCA model utilized four data sets: dynamic and stationary rsFC, clinical data, and cognitive performance measured in MoCA sub-tests. Better memory function was associated with higher dynamics in interhemispheric, graphical measures assortativity and transitivity, supporting the conclusion in the previous chapters that 1) dynamic coordination between two hemispheres was important for cognitive function, and 2) rsFC in PD shifts toward a more segregation-oriented brain organization. On the other hand, better language performance was related to higher dynamics in global and intrahemispheric FC, higher disease severity, more severe depression and apathy symptoms. In this brain-behaviour pattern, perhaps higher dynamics represented compensatory effects and therefore facilitated language function. As disease severity, depression, and apathy jointly are less likely to improve cognitive function, we propose that better language performance might be due to compensated higher dynamics.

Using MCCA with different modalities to examine the brain-behaviour relations provided complementary information for the development of customized cognitive treatment and

rehabilitation in neurological conditions. Although choosing the data sets included in MCCA could be challenging, this approach offers another opportunity to assess brain-behaviour relations more comprehensively and supports the benefits of using advanced methods mentioned in Chapter 1.

7.2 Strengths and limitations

7.2.1 Strengths: functional connectivity analysis

Unlike the traditional clinical research in PD and MS, this thesis research carried out whole brain connectivity analysis with a focus on brain organization and dynamic functional connectivity as opposed to targeting front-striatal loops in PD and independent component analysis (ICA) derived resting-state networks in MS. With graphical analysis, we have a border view on how brain organization is altered and how connections between regions are changed as a whole. Moreover, with whole brain analyses, there is a better chance to investigate compensatory mechanisms as it is unclear whether and where these effects appear. Additionally, with a time- varying approach, we were able to study how connectivity changes temporally and whether such temporal transitions were related to specific aspects of the disease. Traditional analysis methods assume that connectivity remains relatively constant, neglecting the variable and fluctuating nature of the brain. Although how to report connectivity variation remains an issue with the sliding window approach, the current method in the thesis research shed light on dynamic nature of information transfer in the brain. Taken together, the approaches utilized in this thesis research were able to study the *system-level neurophysical events* in the brain.

7.2.2 Strengths: tested domains

Several tests were used throughout the studies to evaluate patients' cognitive function and the tested domains were the commonly affected domains in PD and MS. Although these tested domains were not exactly the same between two populations, executive function was a common theme in both PD and MS. Throughout the thesis research, several domains have been associated with demographics and fMRI measures. In chapter 2, all the tested domains (visuospatial, executive function, verbal learning and memory, processing speed, working memory) were related to demographics in PD; while executive function was most significantly affected domain in MS. In chapter 3, due to the original study design, no tested domains were significant in PD; while processing speed and working memory were associated with fMRI measures in MS. In chapter 4, processing speed was associated with fMRI graphical measures in PD; while executive function is the only significant variable in MS. In chapter 5, due to study design (i.e. only MoCA sub-scores were used to assess cognition), only memory was strongly related to dynamic fMRI measures (relevant discussion in section 5.4.4); while no cognitive domains were significantly related to dynamic features in MS. In chapter 6, memory, language, and executive function were correlated with FC in PD; while working memory, processing speed, and executive function were associated with FC in MS. Overall, executive function has been associated with demographics and fMRI measures in three of the chapters. In the remaining two chapters where overall executive function was not reported, working memory, processing speed, and memory retrieval function were specifically assessed. These cognitive functions all required certain degree of executive skills to achieve the oriented behaviour and are routinely considered to subserve higher-order cognitive function [Miller and Wallis, 2009]. Therefore, the results still reflected how brain networks and

connections facilitated executive skills in PD and MS. To conclude, with whole brain connectivity analysis and the tested domains reported in the thesis, the goal to probe the systems-level neurobiological bases for executive function in patient populations has been achieved.

7.2.3 Strengths: brain-behaviour analysis

Many studies use cognitive scores to evaluate the cognitive states of patients rather than looking into how task performance is related to functional connectivity. A few studies have implemented statistical approaches such as correlation analysis to explore the associations between connectivity and cognitive function; however, as we have proposed, univariate methods may not be able to reveal complex interactions and results are either unpromising or hard to interpret. In this dissertation, several chapters reported brain-behaviour associations with both univariate (e.g. correlation, regression) and multivariate approaches (e.g. PCA, MCCA, CCA). The multivariate approaches take into account the complex inter-correlated nature of human brain and behaviour, which is especially important for diseased populations due to disease heterogeneity. Therefore, the use of multivariate/machine learning methods in this thesis research is significant.

7.2.4 Limitations: study design

There are several limitations to the studies. First, multivariate and machine learning approaches usually require a big sample size. However, with neuroimaging data, it is more costly and time consuming to acquire a huge sample compared to other types of data. Therefore, very often one may over-fit the data. Although some common strategies potentially solve this problem (such as perform the analysis in a leave-one-out fashion, reduce data dimension first, etc.), overfitting data is still a big problem given the sample size in our cohort. In any future study, a power analysis

would be beneficial to estimate the required sample size, now that the current studies could provide an approximation for effective size. Sample size of training data is one of the key factors in generating efficient predictors/classifiers, especially for some of the machine learning approaches utilized here [Varoquaux and Thirion, 2014]. In our preprocessing steps, we used standard approaches and did not perform extra steps to remove physiological noise caused by heart beat and respiratory rhythm, which may or may not affect connectivity analysis. Therefore, in the connectivity analysis, partial correlation or regularized partial correlation were preferred as they tend to be more robust to noise compared to pairwise correlation. Furthermore, as highlighted in the thesis title, one of the main focuses is executive function even though executive function and cognitive function are both used throughout the chapters. In fact, it is difficult to clearly separate executive function from other cognitive abilities. Many cognitive processes require more or less executive skills and the neuropsychological tests in the research may not reflect pure executive functioning. Yet the main focus still lay on higher-order cognitive processes which require intensive thinking and planning in opposed to lower-order functions such as vision, long-term memory, and motor as discussed in section 7.2.2.

7.2.5 Limitations: gender issues

In chapter 2, we found that gender appears to be a strong influential factor for cognition in both disease populations; however, this factor was less prominent in the rest of the chapters. Gender was mostly included in multivariate analyses such as CCA in chapter 2 and MCCA in chapter 6. As previously mentioned in section 6.4.5, including gender in MCCA did not provide significant or robust results. Based on results in chapter 2 and 6, gender is indeed an influential factor in cognition *when no imaging modalities are included*; however, when fMRI measures are included,

gender effects are overwhelmed by FC measures. Taken together, we conclude that cognition is likely affected by gender, but functional connectivity, which underlines neural activity in a macroscale, is a more powerful factor to cognition compared to gender. This may be because functional connectivity itself is strongly affected by gender [Gong et al., 2011].

7.2.6 Limitations: compensatory effects

In disease populations, increased FC or expanded activation map is frequently interpreted as compensation. However, whether the observed alterations represent *successful* compensation or (mal)adaptation remains debated [Scheller et al., 2014]. Simply demonstrating changes of fMRI measures without supporting by concomitant behavioural changes may not necessarily represent successful compensation. Instead, this could be a process of maladaptation (i.e. disinhibition) [Schoonheim et al., 2015]. Throughout the research chapters, we also discovered connectivity changes that were correlated with better performance, indicating that these changes likely served as compensatory mechanisms. For example, in chapter 3, increased interhemispheric connectivity was related to better performance of tasks probing processing speed and working memory in MS. In chapter 4, increased functional segregation was also associated with better performance of processing speed in PD; while subtle changes of segregation was related to executive function in MS. Hub reorganization in PD may indicate compensation, whereby hub regions lost their central role in the network and non-hub regions, which may still receive dopamine from the ventral tegmental area, became more important. In chapter 5, interhemispheric connections became more dynamic to possibly compensate for decreased global measures in MS. Although the brain-behaviour association did not explain the majority of the variance in the data, such increased interhemispheric dynamics was related to better executive function in MS (Appendix D). Overall,

our observations of altered connectivity were supported by brain-behaviour relations, allowing us to conclude that these connectivity changes were related to compensation. Since the included cohorts in the studies were all mildly affected and most of the subjects did not demonstrate severe cognitive impairments, the compensatory effects in the thesis only represent adaptation at early stage before network collapse [Schoonheim et al., 2015]. In order to comprehensively study compensation, more imaging data, bigger sample size, and subjects at different disease stage would be required.

7.3 Future research directions

One of the biggest goals in the research is to define the connections, networks, and/or brain regions that are important to cognitive dysfunction in neurological disorders. With the knowledge, it would be beneficial to develop efficient treatment for cognitive deficits. For example, as Chapter 3 and 4 revealed, long-range connections, interhemispheric connections, and hub regions have potential to predict cognitive functions. A cognitive rehabilitation strategy that specifically targets these regions and networks might provide a more efficient treatment. As the current pharmaceutical approaches to treat cognitive dysfunction in PD and MS produce only modest improvements, cognitive training as a rehabilitation strategy could be an alternative. In fact, such strategy has been applied to MS subjects. Although there are some promising results, the overall literature is about such interventions [Mitolo et al., 2015]. However, implementing the knowledge of network effects to cognition may provide insights to design more effective interventions.

For future research, there are several possible directions. First, different models of connectivity analysis are desirable. The current research utilized the most common ones in neuroscience field, but models with different technical and mathematical assumptions might be able to reveal hidden

patterns in connectivity. Moreover, in this thesis research, we used resting-state data and tried to link rsFC with cognitive performance outside of the scanner as patients are more able to cope with resting-state scans than tasks. Although it has been shown that rsFC reflects neuronal activity of cognitive tasks [Smith et al., 2009], task-driven fMRI may be more suitable to investigate brain-behaviour associations of executive function. Furthermore, there has been a tremendous interest in linking functional and structural connectivity. In MS, for example, it would be interesting to know whether functional connectivity is related to lesions and/or other structural changes. In PD, it would be challenging but exciting to explore whether microstructural changes affect dynamic functional connectivity. With both functional and structural information, together with clinical data and cognitive scores, scientists will be able to understand diseases structurally, functionally, clinically, and cognitively.

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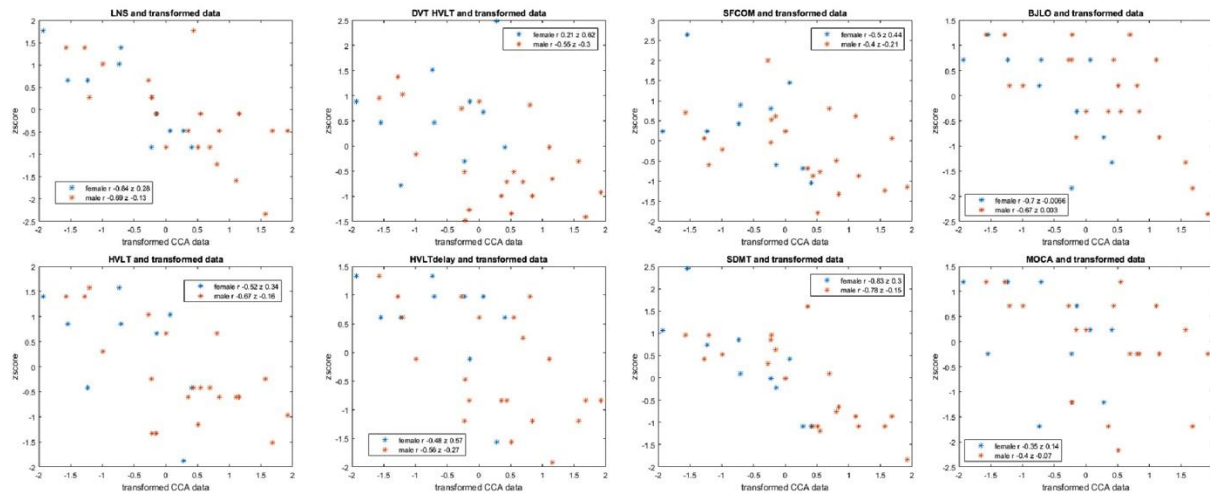
interhemispheric synchrony in Parkinson's disease with depression. *Sci Rep* 6:1–9.

Appendices

Appendix A

Appendix A lists supporting materials of Chapter 2.

A.1 Canonical loadings of individual PD subjects.

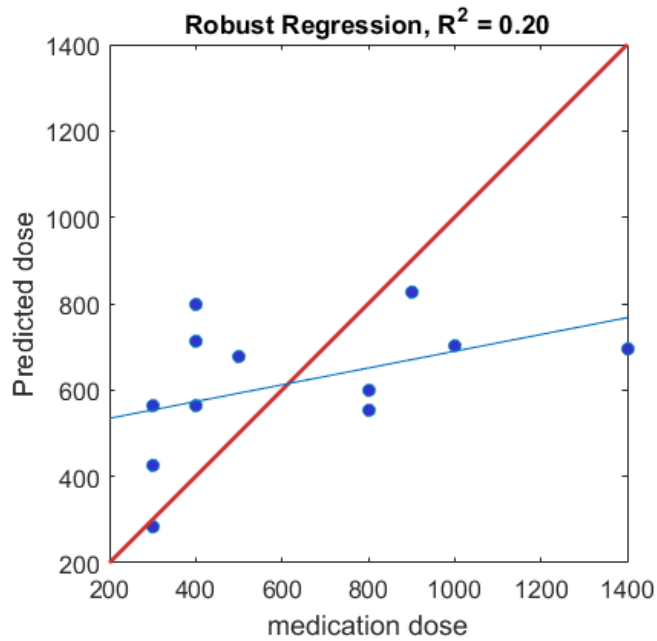


The figure illustrates canonical loadings (correlation between transformed CCA data and raw scores of CCA input) of the cognitive variables which show significant impacts in the CCA model. In each score, blue dots represent female data and red dots are male data. Average canonical loadings (indicated as r in the legend) are calculated as well as average cognitive z-scores in both groups. Except BJLO (the upper right corner), female subjects show higher average cognitive scores, indicating better performances.

Appendix B

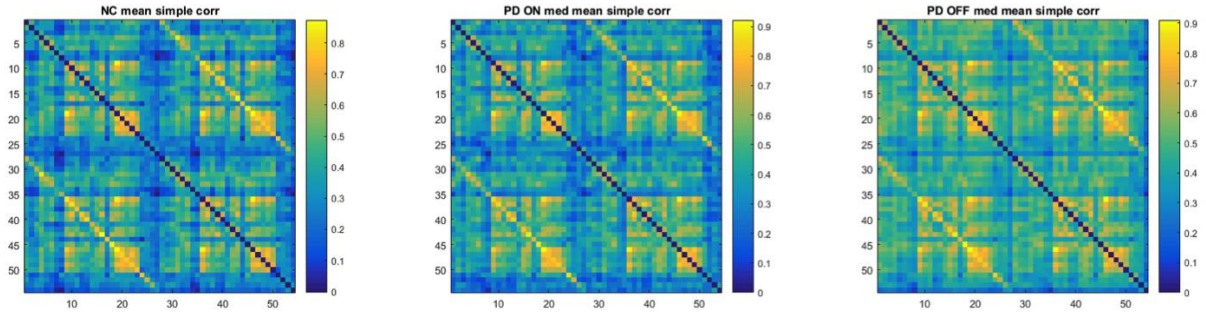
Appendix B lists the supporting materials of Chapter 3.

B.1 Robust regression in PD on-medication



Only medication dose could be predicted with the interhemispheric connectivity of the ventral medial prefrontal cortex in PD on-medication. The rest scores cannot be well-predicted (R -square < 0.2) by this interhemispheric connectivity pair. The red line indicates perfect prediction. The blue line indicates current prediction.

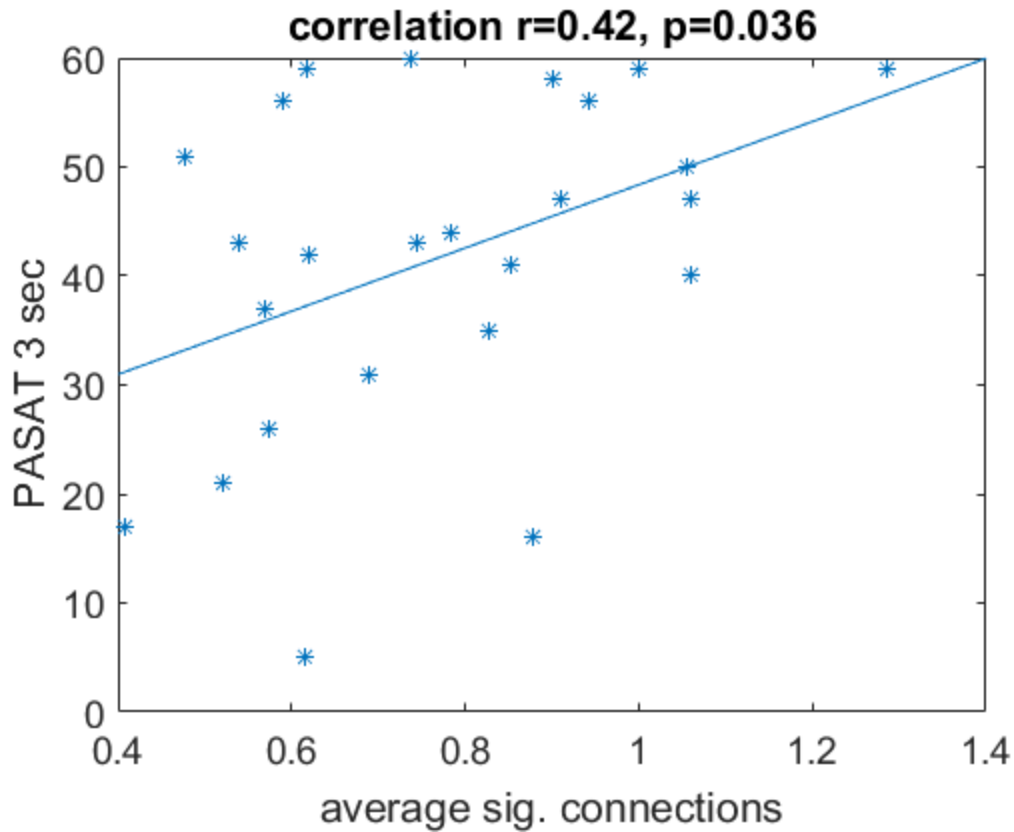
B.2 Whole brain connectivity matrix of HC and PD



Simple correlation (Pearson's r) was conducted among 54 ROIs in normal control (NC), PD on-medication, and PD off-medication subjects. The figure shows the average connectivity matrix of three populations. Overall, PD off-medication (the right panel) showed higher global connectivity. Compared to NC, PD off-medication and PD on-medication did not show significant connectivity difference after corrected for FDR. However, on-medication and off-medication demonstrated significant different connections. The results were reported in section 3.3.

B.3 Correlation between long-range connections and cognitive performance

In order to study whether the long-range connections observed in MS were related to cognitive functions, we performed a simple *post hoc* analysis. Connections significantly different between HC and MS in figure 3.6 were averaged and pairwise correlation was conducted on the mean long-range connectivity against cognitive scores in MS.



SDMT scores did not show correlation to the mean connectivity values; however, PASAT performance showed moderate correlation with the mean long-range connection ($r=0.42$, $p=0.036$) as shown in this figure.

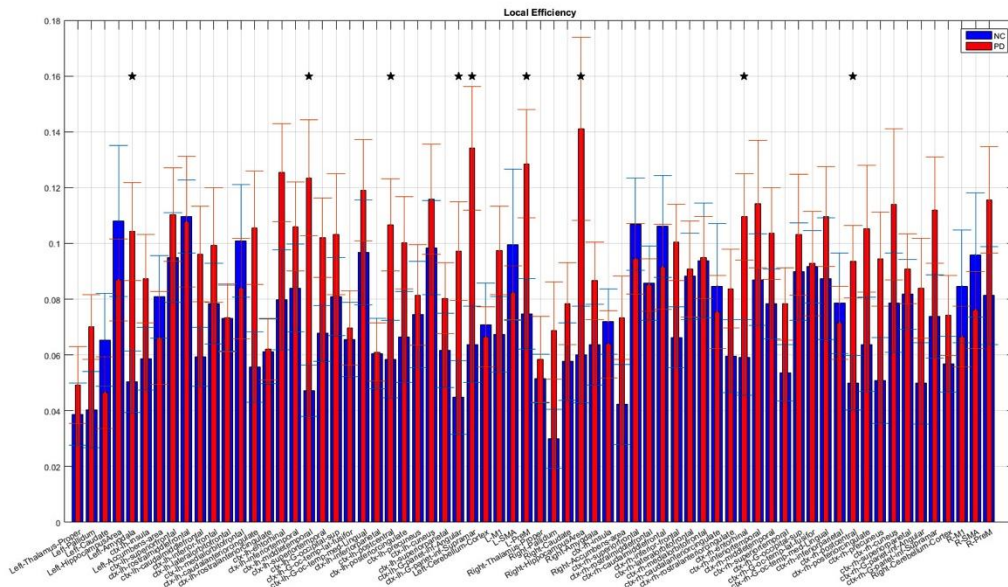
The results further support that SDMT performance requires more interhemispheric connectivity, while PASAT performance engages more long-range connections linking frontal and parietal areas.

In PD, connections which were significantly different between PD on-medication and off-medication did not show any correlations to the clinical scores.

Appendix C

Appendix C lists the supporting materials of Chapter 4.

C.1 Significantly different local measures between PD and HS



Nine ROIs show higher local efficiency in PD indicated with black stars ($p < 0.05$, uncorrected). These ROIs are the left amygdala, left middle temporal gyrus, left postcentral gyrus, left angular gyrus, left supramarginal gyrus, left pre-motor area, right hippocampus, right entorhinal cortex, and right postcentral gyrus.

almost insignificant in t-tests ($p=0.0415$). For global measures, logistic LASSO was not able to differentiate PD and HS.

The logistic LASSO model demonstrated that these altered local measures were clearly able to distinguish the PD from the HS group. This implies that while individual ROIs may only be mildly discriminative, collectively they provide a robust way to distinguish between groups. Although not all ROIs selected by the logistic LASSO model were hubs, the results indicated an altered network phenomenon may be initiated at hub regions.

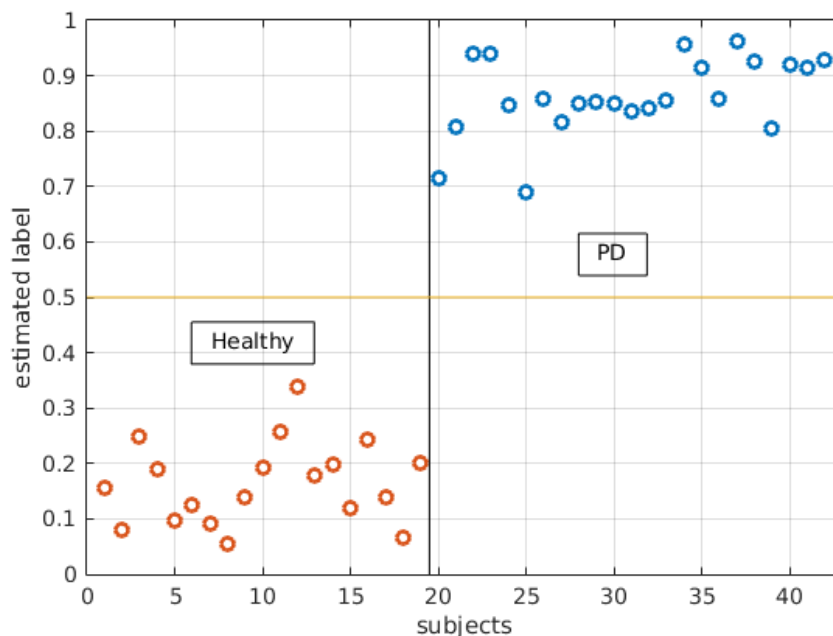


Figure C.3 Logistic LASSO distinguishes PD and healthy subjects with all the local measures. In the analysis, PD subjects were assigned 1 and healthy subjects were assigned 0 as their labels. Logistic LASSO predicts the labels based on all local measures (both local efficiency and betweenness centrality). The estimated/predicted labels are accurately categorized into two groups.

C.3 Canonical correlation analysis (CCA) between cognitive performance and global measures

We further tested whether graphical measures were correlated with cognitive performance in a multivariate manner using CCA. All global measures were concatenated to form one set and the other set included cognitive scores. Likewise, the local measures which showed differences in the t-tests were included as one set and cognitive scores were included as the other set. All variables were normalized into z-scores and then processed with CCA. The canonical loadings with leave-one-out cross validation of all variables were reported and a permutation test was carried out with 1000 iterations to evaluate the significance of the correlation in CCA.

The global graphical measures showed a significant correlation with behavioral scores in CCA ($r=0.98$, $p=0.01$, Figure C.4). The variables were considered significant if the error bars did not cross zero. In global measures, assortativity, modularity, rich club coefficient, and transitivity demonstrated significant canonical loadings; while MoCA, BJLO, HVLY delay recall, standardized HVLT total, standardized HVLT retention, LNS, and SF scores appeared influential in the model. Modularity, rich club coefficient, and transitivity were positively correlated with scores of BJLO, HVLY delay recall, standardized HVLT total, standardized HVLT retention, and SF. In the other hand, assortativity was correlated with MoCA and LSN performance.

A CCA model attempting to relate local graphical measures and cognitive scores was not significant.

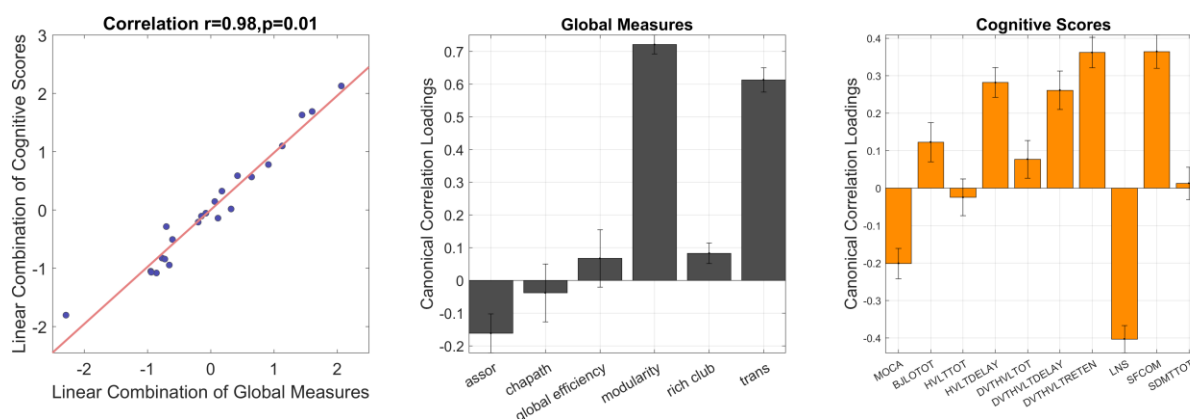


Figure C.4 CCA reveals inter-correlations between global graphical measures and cognitive scores (correlation = 0.98, $p = 0.01$, left panel). The error bars indicate 95% confidence interval in leave-one-out cross validation. If the error bars do not cross zero, the variables are recognized as significant. Among global measures (middle panel), assortativity, modularity and transitivity show significant loadings. In the combination of cognitive scores (right panel), MoCA, BJLO, HVLY delay recall, standardized HVLT total, standardized HVLT retention, LNS, and SF scores contribute significant loadings.

[assort: assortativity, chapath: characteristic path length, rich club: rich club coefficient, trans: transitivity, MOCA: Montreal Cognitive Assessment, BJLOTOT = Bento Line Orientation Total Score, HVLTTOT = Hopkins Verbal Learning Test-Revised Total Score, HVLTDelay = HVLT Delayed Recall Score, DVT-HVLTOT = standardized HVLT Total Score, DVT-HVLTDELAY = standardized HVLT Delayed Recall Score, DVT-HVLTRETENTION = standardized HVLT Recognition Trial Score, LNS = raw Letter-Number Sequencing Test Score, SFCOM = Sematic Fluency Test – combination, SDMTTOT = Symbol Digit Modalities Test total scores]

We found that segregation-oriented brain organization was related to better cognitive performance with a multivariate approach. Modularity and transitivity, which are both measures of segregation, were significantly correlated with better performances in line orientation, verbal learning, and semantic fluency tests. This pattern indicated that better visuospatial, verbal learning and memory

functions, and executive skills were correlated with segregated brain organization in PD. In addition, rich club coefficient, an indication of rich club structure which is thought to facilitate cognitive processes [van den Heuvel and Sporns, 2011], was also related to better performance of the above-mentioned tests, further emphasizing the important role of rich club structure in cognition. On the other hand, assortativity, which shows the tendency of nodes with similar connectivity to link with each other, was correlated with overall cognitive function as well as memory, attention, and mental manipulation skills. However, as assortativity was ultimately a correlation coefficient between node degrees and the measure was small in all subjects (maximum value=0.09, minimum value=-0.1), we did not think this measure itself represented very meaningful information in this cohort even though it was correlated with MoCA and LNS scores. Therefore, taken together, we interpreted that *multivariate approach also revealed similar findings as univariate analysis but with greater robustness, whereby better cognitive function was related to segregated brain networks as well as rich club characteristics in PD.*

In this study, we did not report significant relations between local measures and cognitive performance. This is somewhat surprising since the local graphical measures could be used to distinguish between subject groups, while the global measures could not. The reason could be that the overall, global brain organization is more related to cognitive performance, while smaller, more subtle changes in local network characteristics may be related to other non-cognitive differences between groups (e.g. related to motor function).

Appendix D

Appendix D lists the supporting materials of Chapter 5.

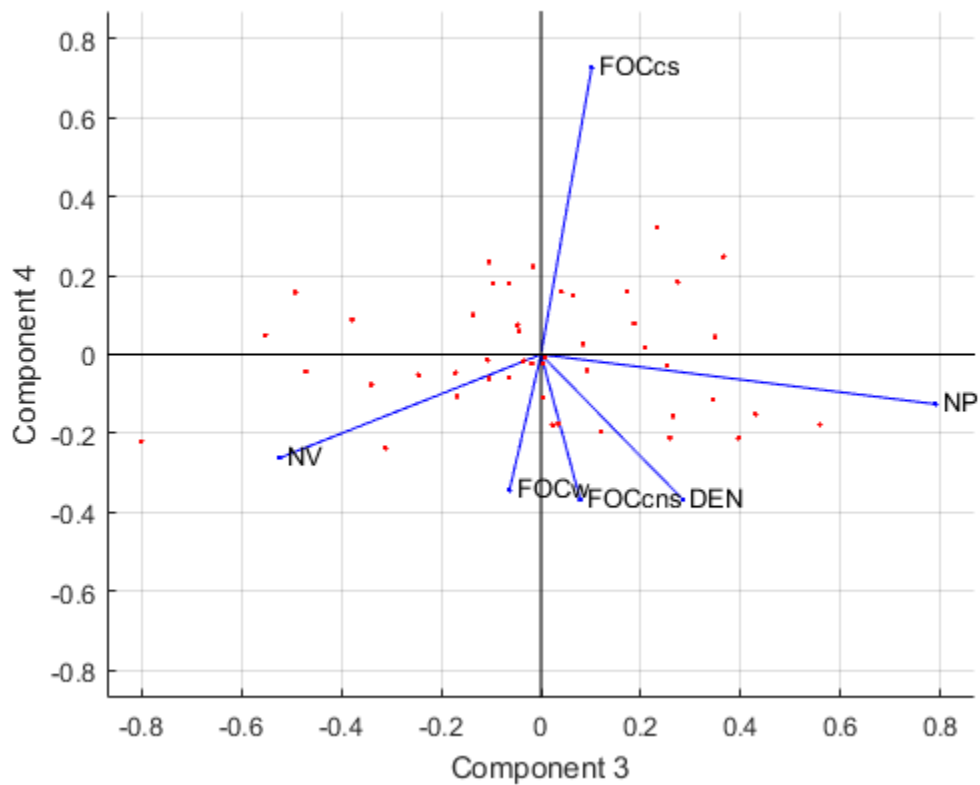
D.1 Linear regression model of dynamic features and WCSTCC

The Wisconsin Card Sorting Test Complete Categories score was modulated by one principal component analysis (PCA) component of dynamic features as shown in the following table. However, this component only explained 1.8% of the variance. In addition, this component was dominated by the effects of flexibility of interhemispheric connections (FOCs). The PCA coefficient of FOCs was 0.7 and the rest features showed coefficients ranged between -0.13 and -0.36.

For individual predictors				
behavioural	PCA components of	estimate in regression	standard	p
WCSTCC	component 1	0.01	0.1	0.94
	component 2	0.14	0.28	0.61
	component 3	0.18	0.35	0.61
	component 4	2.45	0.69	0.001
	age (covariance)	-0.32	0.02	0.15
For the whole model				
Number of observations: 46, Error degrees of freedom: 40				
Root Mean Squared Error: 1.5				
R-squared: 0.314, Adjusted R-Squared 0.229				
p-value = 0.008				

[WCSTCC: the Wisconsin Card Sorting Test Complete Categories]

D.2 The component which significantly modulated cognitive flexibility



The flexibility of interhemispheric connections (FOCcs) loaded heavily than other features in component 4. Although this component only explained limited variance of the data, it could predict the performance of Wisconsin Card Sorting Test Complete Categories.