Investigating Simulated Driving Behaviour and Brain Activation in Mild Cognitive Impairment

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science

Institute of Medical Science University of Toronto

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Abstract

There are no guidelines or tools to help physicians assess the driving safety of patients with MCI. This study combined fMRI and driving simulation to compare the driving performance, and corresponding brain activation patterns, of patients with MCI and healthy controls. Patients with MCI committed significantly more driving errors compared to controls. Patients with amnestic multiple-domain MCI patients were at a greater risk of difficulty relative to those with amnestic single-domain MCI. Patients with MCI exhibited increased recruitment of frontal brain regions compared to controls, particularly during left turns with traffic. Patients with sd-MCI exhibited increased recruitment of frontal and medial regions across turning conditions, whereas patients with md-MCI exhibited decreased recruitment of frontal and medial regions. The results suggest that patients with MCI can demonstrate driving difficulties and deviations in brain activation compared to controls and that the areas and degree of difficulty vary across the subtypes of MCI.

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Contributions

Dr. Tom Schweizer (1) provided the funding for the current study, (2) oversaw the development of the study protocol, patient and control recruitment, participant testing, data analysis, and data interpretation of the current study, and (3) provided feedback and revisions of the thesis.

Dr. Gary Naglie and Dr. Simon Graham assisted with the development of the study protocol, provided advice on project issues that arose, and provided important and detailed revisions of the thesis.

Kristin Vesely was thoroughly involved in most aspects of the current project. She assisted with the development of the driving scenarios and participant testing. She also helped develop a data analysis plan for the behavioural driving results of the study.

Dr. Nathan Churchill trained me on how to use the PRONTO software that was used to analyze the fMRI data. He also over saw me as I analyzed the data, helped with any issues that arose with the analysis, and assisted with the interpretation of the results.

Dr. Corinne Fischer referred all of the patients with MCI included in the current study from the Memory Disorders Clinic at St. Michael's Hospital.

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List of Abbreviations

- AAL Automated Anatomical Labelling
- AD Alzheimer's Disease
- ADLs Activities of Daily Living
- AFNI Analysis of Functional NeuroImaging
- a-MCI Amnestic Mild Cognitive Impairment
- ANOVA Analysis of Variance
- AUC Area Under the Receiver Operating Characteristic Curve
- BOLD Blood Oxygenation Level Dependent
- BNA Behavioural Neurology Assessment
- CDR Clinical Dementia Rating
- CDT Clock Drawing Test
- CRF Case Report Form
- CRUNCH Compensation-Related Utilization of Neural Circuits Hypothesis
- CT Computerized Tomography
- DHQ Driving Habits Questionnaire
- DICOM Digital Imaging and Communications in Medicine
- HADS Hospital Anxiety and Depression Scale
- EEG Electroencephalography
- EPI Echo-Planar Images
- GLM General Linear Model
- FDG Fluoro-D-Glucose
- FDR False Discovery Rate
- fMRI Functional Magnetic Resonance Imaging
- fNIRS Functional Near Infrared Spectroscopy
- FOV Field of View
- FSL FMRIB Software Library
- FTD Frontotemporal Dementia
- IADLs Instrumental Activities of Daily Living

L – Left

- LBD Lewy Body Dementia
- MCI Mild Cognitive Impairment
- md-MCI Multiple Domain Mild Cognitive Impairment
- MEG Magnetoencephalography
- MNI Montreal Neurological Institute and Hospital
- MoCA Montreal Cognitive Assessment
- MR Magnetic Resonance
- MRI Magnetic Resonance Imaging
- na-MCI Non-Amnestic Mild Cognitive Impairment
- NIfTI Neuroimaging Informatics Technology Initiative
- NINCDS-ADRDA National Institute of Neurological and Communicative Disorders and
- Stroke and the Alzheimer's Disease and Related Disorders Association
- PET Positron Emission Tomography
- PRONTO Preprocessing OptimizatioN Toolkit
- R Right
- REB Research Ethics Board
- ROCF Rey- Osterrieth Complex Figure
- SD Semantic Dementia
- sd-MCI Single Domain Mild Cognitive Impairment
- SPECT Single Photon Emission Tomography
- SPSS Statistical Analysis Using Statistical Package for the Social Sciences Software
- T Tesla
- TE Echo Timing
- TMT-A Trail Making Test Part A
- TMT-B Trail Making Test Part B
- UFOV Useful Field of View
- VaD Vascular Dementia
- VCI Vascular Cognitive Impairment

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Chapter 1 Introduction

1.1 Background

Cognitive impairment can manifest across a wide spectrum, ranging from typical age-related cognitive changes, to the mild deficits associated with mild cognitive impairment (MCI), to the more moderate to severe deficits that are characteristic of Alzheimer's disease (AD). Approximately 47.5 million individuals worldwide are living with AD or a related dementia, and this number is expected to triple to 135.5 million individuals affected globally by 2050 (World Health Organization, 2015).

MCI is often conceptualized as a clinical intermediate, or transition zone, between normal healthy aging and dementia. The distinction between normal aging and MCI is often very subtle and can be difficult to differentiate (Petersen, 2004). Furthermore, the progression of MCI to very early AD (or a different form of dementia) can be difficult to identify (Petersen, 2004). Prevalence rates of MCI vary depending on a variety of factors, including the diagnostic criteria utilized as well as assessment procedures, the source of participants, and the normal reference standards (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003; Petersen, 2004; Petersen et al., 2001; Pusswald et al., 2013; Ward, Arrighi, Michels, & Cedarbaum, 2012). A systematic review conducted by Ward and colleagues (2012) supported this variability at a global level (35 studies on prevalence, 13 on incidence), suggesting that prevalence rates of MCI range from 3-42 percent and that overall incidence rates ranged from 21.5-71.3 percent per 1,000 people/year. The variability in prevalence rates is largely the result of different definitions of MCI being utilized across studies (Ward et al., 2012).

The cognitive presentation and disease progression of patients with MCI can be highly heterogeneous. Specifically, patients with MCI can maintain their clinical status, improve and revert to normal healthy aging, or progress to AD or a related dementia over time. A metaanalysis conducted by Mitchell and Shiri-Feshki (2009) investigated the conversion rates of MCI to dementia, AD, and vascular dementia (VaD) among studies that utilized Mayo Clinic diagnostic criteria (i.e. criteria developed by Petersen and colleagues (1999; 2001); see section 1.1.1 for detailed criteria) and non-Mayo Clinic criteria (i.e. criteria that deviated from the criteria developed by Petersen and colleagues). The results suggested an overall annual conversion rate of 6.7% (95% CI = 4.6-9.1%) for progression to dementia, 6.5% (95% CI = 4.8-9.1%) 8.5%) for AD, and 1.6% (95% CI = 0.8-2.7%) for VaD. Furthermore, multiple studies have reported that patients with MCI consistently demonstrate an increased risk of progression to AD or related dementia compared to individuals who never develop MCI (Mitchell & Shiri-Feshki, 2009; Petersen, 2004; Petersen et al., 2001; Roberts & Knopman, 2013). Compared to healthy elderly individuals, the relative risk of progression was 15.9 (Mayo Clinic MCI criteria) and 6.2 (non-Mayo Clinic MCI criteria) for dementia and 9.5 (Mayo Clinic MCI criteria) and 4.7 for AD (non-Mayo Clinic MCI criteria) (Mitchell & Shiri-Feshki, 2009). Furthermore, although previous research suggests that approximately 20 percent of patients with MCI improve over time (Roberts & Knopman, 2013), it has been suggested that these patients are at an increased risk of reverting back to MCI or subsequently developing AD compared to individuals who never develop MCI (Koepsell & Monsell, 2012; Lopez et al., 2012; Roberts & Knopman, 2013).

Driving is an important daily behaviour for drivers both with and without cognitive impairment. Furthermore, driving is a highly complex activity that requires the coordination of numerous cognitive functions, including memory, executive function, attention, and visuospatial ability. Although some patients with MCI and AD are not capable of driving safely, some individuals are able to maintain the ability to drive. Thus, diagnosis of MCI or AD does not definitively imply driving impairment. Given that driving is an important source of independence, and involuntary driving cessation is associated with numerous negative consequences, it is important to maximize patient autonomy while ensuring patient as well as public safety. Consequently, assessing the driving ability of individuals with cognitive impairment, including patients with MCI and AD, is an important clinical issue.

1.1.1 Diagnosis of MCI

One major factor contributing to the variability in prevalence and incidence rates of MCI is the lack of consensus on a single set of diagnostic criteria for MCI (Petersen, 2004; Stephan et al., 2013; Ward et al., 2012). Cognitive assessments and functional measures are highly useful in the diagnosis process; however, the final classification and diagnosis of patients relies on the judgement of the clinician (Petersen, 2004). Although there is no universal criteria utilized to diagnosis MCI, the criteria proposed by the National Institute on Aging-Alzheimer's Association (Albert et al., 2011), which are based on the criteria proposed by Petersen and colleagues (2004; 1999) as well as the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) ((McKhann et al., 2011), are the most widely accepted and implemented. The recommendations presented by the National Institute on Aging-Alzheimer's Association propose Core Clinical Criteria and Clinical Research Criteria for the diagnosis of MCI (Albert et al., 2011). The Core Clinical Criteria were developed for widespread application in all clinical settings without requiring highly specialized procedures, whereas the Clinical Research Criteria utilize biomarkers in the diagnostic criteria and are implemented only in research settings (i.e. clinical trials) (Albert et al., 2011).

The National Institute on Aging-Alzheimer's Association proposed four core clinical criteria for diagnosing MCI. The Core Clinical Criteria are utilized in conjunction with clinician judgement to diagnose MCI and differentiate MCI from normal cognition as well as dementia (Albert et al., 2011).

i) Concern regarding a change in cognition

There is evidence of a change in cognition (i.e. a deterioration) from the patient's previous ability level (Albert et al., 2011; Petersen, 2004). This concern is based on information obtained from a self-report from the patient, a reliable informant, or observation from a skilled clinician (Albert et al., 2011).

ii) Impairment in one or more cognitive domains

There is evidence of impairment in one or more cognitive domains (Albert et al., 2011; Petersen, 2004). This is demonstrated by the patient performing/scoring lower on cognitive assessments than would be expected for someone of that patient's age and level of education (Albert et al., 2011). Thus, objective evidence of cognitive decline is essential. Traditionally, patients with MCI score 1 to 1.5 standard deviations below the mean scores (on validated cognitive measures) of healthy individuals of their approximate age and education level using appropriate normative data (Albert et al., 2011; Peters, Villeneuve, & Belleville, 2014; Petersen, 2004; Petersen et al., 1999; Stephan et al., 2013). However, the ranges provided by normative data are guidelines rather than definitive cut-off scores (Albert et al., 2011). Impairment can be observed in various cognitive domains, including memory, attention, language, visuospatial ability, and executive function. If the clinician has performed multiple cognitive assessments over time, then a decline in performance should be observed (Albert et al., 2011).

iii) Preservation of independence in functional abilities

The patient maintains his/her functional ability to perform daily behaviours independently, with minimal aids or assistance (Albert et al., 2011; Petersen, 2004). Patients with MCI may exhibit minor difficulties in performing complex tasks, such as paying bills, preparing meals, shopping, or driving. This manifests as requiring more time, demonstrating less efficiency, or committing more errors while completing these functional tasks than was previously observed (Albert et al., 2011). Successful assessment of this criterion requires accurate knowledge of the patient's past (i.e. a reliable and accurate history of the patient is essential) as well as the patient's current level of function.

iv) Not demented

Based on the assessment of the clinician, there is evidence that the patient does not meet diagnostic criteria for dementia (Albert et al., 2011; Petersen, 2004). Thus, the patient's cognitive changes are mild and, consequently, there is no evidence of extensive impairment in social or occupational functioning (Albert et al., 2011).

Despite the widespread implementation of the criteria outlined by the National Institute on Aging- Alzheimer's Association, there is currently no standardized procedure on how to operationalize and implement these criteria. As a result, there is a great deal of heterogeneity in the procedures used to diagnose MCI across studies that utilize the same criteria to guide the diagnostic process (Stephan et al., 2013). Exacerbating this issue is the fact that it remains unclear whether there is in fact a distinction between a diagnosis of MCI and a diagnosis of very mild AD (Morris et al., 2001). The results of Morris and colleagues (Morris et al., 2001; Morris & Price, 2001) support the notion that MCI represents very mild AD, as the majority of patients with MCI demonstrated impairment in multiple cognitive domains. Furthermore, results suggested that progression of dementia severity was dependent on the degree of initial impairment. Specifically, 60.5% (50.2-70.8%) of patients classified as "CDR 0.5/AD" (CDR = Clinical Dementia Rating; i.e. defined as a patients with impairment in memory (0.5 or greater) and 3 or more cognitive domains), 35.7% (21.0-50.3%) of patients classified as "CDR 0.5/incipient AD" (i.e. defined as patients with impairment in memory and 2 or fewer other cognitive domains), and 19.9% (8.0-31.8%) of patients classified as "CDR 0.5/uncertain dementia" (i.e. defined as patients with impairment in only memory (0.5 level only) or those with questionable impairment) progressed to CDR 1 or greater within 5 years. Given the high rate of disease progression, tendency for patients classified with MCI to demonstrate some degree of impairment in activities of daily living (ADLs, as reported by an informant), and the tendency for patients with MCI to exhibit neuropathological characteristics of AD (Morris et al., 2001), Morris and Price (2001) concluded that MCI often represents an early form of AD.

Future longitudinal research is required to determine (1) whether there is in fact a distinction between AD and MCI, or whether MCI represents the earliest stage of AD or related dementia, and (2) the optimal operationalization and implementation of the diagnostic criteria of MCI outlined by the National Institute on Aging- Alzheimer's Association.

1.1.2 Presentation of Subtypes of MCI

Traditionally, MCI was thought of as a single entity marked by memory impairment; however, current research suggests that MCI is a highly heterogeneous disorder, which can be characterized by impairment in various cognitive domains (Busse et al., 2003; Busse, Hensel, Gühne, Angermeyer, & Riedel-Heller, 2006; Petersen, 2004; Petersen et al., 2001). Patients with MCI can be classified into two broad categories—amnestic MCI (a-MCI) and non-amnestic MCI (na-MCI). Patients with a-MCI demonstrate a significant memory impairment, whereas no memory impairment is present in patients with na-MCI (Petersen et al., 2004). Within each of these categories, patients can be further classified as having multiple domain MCI (md-MCI), which is characterized by the presence of impairment in multiple cognitive domains, or single domain (sd-MCI), which manifests as impairment in a single cognitive domain (Petersen, 2004).

i) Amnestic single domain MCI

Patients with amnestic sd-MCI present with memory impairment, and memory is the only domain that is impaired (Petersen, 2004; Petersen et al., 2001). Cognitive function remains preserved in all other domains (e.g. language, executive function, attention, visuospatial function).

ii) Amnestic multiple domain MCI

Patients with amnestic md-MCI present with impairment in multiple cognitive domains (i.e. deficits are apparent in ≥ 2 cognitive domains), of which one of the impaired domains is memory (Petersen, 2004; Petersen et al., 2001).

iii) Non-amnestic single domain MCI

Patients presenting with impairment in a single domain and intact memory function are classified with non-amnestic sd-MCI (Petersen, 2004; Petersen et al., 2001). Thus, the domain that is impaired in patients with non-amnestic sd-MCI is any domain other than memory (e.g. language, executive function, attention, visuospatial function).

iv) Non-amnestic multiple domain MCI

Patients with non-amnestic md-MCI present with impairment in multiple cognitive domains (i.e. \geq deficits are apparent in \geq 2 cognitive domains); however, memory function remains intact (Petersen, 2004; Petersen et al., 2001).

A longitudinal study of 980 participants (\geq 75 years old) conducted by Busse and colleagues (2006) investigated the prevalence rates of MCI subtypes using Petersen criteria (Petersen, 2004) as well as a modified version of the criteria (i.e. a subjective memory complaint was not required). Statistical analyses revealed that prevalence rates were lowest for non-amnestic md-MCI and highest for non-amnestic sd-MCI (Busse et al., 2006). Specifically, using Petersen criteria, 3.0% (1.5 SD cut-off; 95% CI = 1.9-4.1%) to 4.5% (1 SD cut-off; 95% CI = 3.2-5.8%) of patients met criteria for amnestic sd-MCI, 0.9% (1.5 SD cut-off; 95% CI = 0.3- 1.5%) to 5.5% (1 SD cut-off; 95% CI = 4.1-6.9%) of patients met criteria for amnestic md-MCI, 0.4% (1.5 SD cut-off; 95% CI = 0.0-0.8%) to 2.1% (1 SD cut-off; 95% CI = 1.2-3.0%) of patients met criteria for non-amnestic met criteria for non-amnestic met criteria for non-amnestic met criteria for non-amnestic sd-MCI, 0.5% CI = 3.6-6.4%) to 7.1% (1 SD cut-off; 95% CI = 5.5-8.7%) of patients met criteria for non-amnestic sd-MCI (Busse et al., 2006).

Differentiating between the various subtypes of MCI (i.e. amnestic single domain, amnestic multiple domain, non-amnestic single domain, non-amnestic multiple domain) has important clinical implications, as specific subtypes of MCI may be at a differential risk of progression to AD and other related dementias (e.g. VaD, frontal temporal dementia (FTD), Lewy body dementia (LBD)) as well as functional decline (i.e. basic activities and instrumental activities of daily living (IADLs)). Specifically, results suggest that patients with amnestic MCI may be at a greater risk for dementia conversion than patients with non-amnestic MCI (11.7% versus 4.1%, $X^2 = 35.1$, p = 0.0001; Busse et al., 2006; Mitchell & Shiri-Feshki, 2009). In addition, patients with md-MCI may have a higher risk of conversion to dementia (23.4% versus 5.3%) and a lower rate of reversion to normal cognitive functioning (10.9% versus 43.4%) than patients with sd-MCI (Han et al., 2012).

1.1.3 Performance on IADLs in MCI and Subtypes of MCI

The original diagnostic criteria outlined by Petersen and colleagues (1999) stated that individuals with MCI demonstrate "normal" performance on activities of daily living, including IADLs such as driving. However, this criterion has been revised (Burton, Strauss, Bunce, Hunter, & Hultsch, 2009), stating that patients with MCI maintain functional independence, but may exhibit minor difficulties or impairments in more complex daily behaviours (Albert et al., 2011; Petersen, 2004; Winblad et al., 2004). This modification is supported by the results of numerous studies, which demonstrate that patients with MCI often exhibit some degree of impairment in complex activities of daily living, primarily while performing IADLs, such as driving/transportation, managing finances, navigating through an unfamiliar place, keeping appointments, multi-tasking, performing a task while under pressure, global IADL indices, etc. (Aretouloi & Brandt, 2010; Artero, Touchon, & Ritchie, 2001; Burton et al., 2009; Gold, 2012; K. R. Kim et al., 2009; Reppermund et al., 2013; Tabert et al., 2002). This minor impairment in IADLs has been consistently demonstrated across self-report measures (Burton et al., 2009; Tabert et al., 2002), informant reports (Burton et al., 2009; Reppermund et al., 2013), and functional tasks (Artero et al., 2001; Burton et al., 2009; Gold, 2012). Given that performance on a variety of IADLs has been shown to involve numerous cognitive processes (e.g. executive function, memory, verbal learning, reasoning, visuospatial function, etc.) (Aretouloi & Brandt, 2010; Artero et al., 2001; Farias et al., 2010), it follows that patients with MCI may perform worse than cognitively healthy older adults on IADLs that require these cognitive resources.

A few studies have compared the degree of functional decline among various subtypes of MCI, and results suggest that certain subtypes of MCI may be at an increased risk of impairment while performing complex daily behaviours (Aretouloi & Brandt, 2010; Burton et al., 2009; Gold, 2012; K. R. Kim et al., 2009; Reppermund et al., 2013; C. Tam, Lam, Chiu, & Lui, 2007). In particular, patients with md-MCI may exhibit some degree of functional impairment compared to individuals with sd-MCI (Aretouloi & Brandt, 2010; Burton et al., 2009; C. Tam et al., 2007). However, results remain inconsistent as to whether patients with amnestic MCI perform comparably better (Aretouloi & Brandt, 2010) or worse (Reppermund et al., 2013) to patients with non-amnestic MCI on complex daily tasks. Furthermore, the results of Tam and colleagues

(2007) suggested that patients with amnestic MCI were able to maintain performance on IADLs to a similar degree as cognitively normal participants.

Thus, results suggest that on a group level, patients with MCI demonstrate some degree of functional impairment compared to cognitively intact individuals (Aretouloi & Brandt, 2010; Artero et al., 2001; Burton et al., 2009; Gold, 2012; K. R. Kim et al., 2009; Reppermund et al., 2013; Tabert et al., 2002) and that patients with md-MCI, particularly patients with amnestic md-MCI (K. R. Kim et al., 2009), may be at the greatest risk for functional decline (Aretouloi & Brandt, 2010; Burton et al., 2009; K. R. Kim et al., 2009; C. Tam et al., 2007).

1.2 The Complex and Multi-Faceted Nature of Driving

Driving is an important daily behaviour and has been identified as an important clinical issue in numerous neurological conditions, including AD (Barrash et al., 2010; Bieliauskas, Roper, Trobe, Green, & Lacy, 1998; Brown, Ott, et al., 2005; Brown, Stern, et al., 2005; D. J. Cox, Quillian, Thorndike, Kovatchev, & Hanna, 1998; Davis et al., 2012; Dawson, Anderson, Uc, Dastrup, & Rizzo, 2009; Duchek et al., 2003; Duchek, Hunt, Ball, Buckles, & Morris, 1998; Fitten et al., 1995; Frittelli et al., 2009; Grace et al., 2005; Hunt et al., 1997; Hunt, Morris, Edwards, & Wilson, 1993; Lafont et al., 2010; Logsdon, Teri, & Larson, 1992; Ott et al., 2000, 2003; Ott, Papandonatos, Davis, & Barco, 2012; Ott, Festa, et al., 2008; Ott, Heindel, et al., 2008; Rizzo, McGehee, Dawson, & Anderson, 2001; Rizzo, Reinach, McGehee, & Dawson, 1997; Stein & Dubinsky, 2011; Tomioka et al., 2009; Trobe, Waller, Cook -Flannagan, Teshima, & Bieliauskas, 1996; Uc, Rizzo, Anderson, Shi, & Dawson, 2004, 2005, 2006), MCI (Devlin, McGillivray, Charlton, Lowndes, & Etienne, 2012; Frittelli et al., 2009; Kawano, Iwamoto, Iidaka, & Ozaki, 2012; Wadley et al., 2009), multiple sclerosis (Akinwuntan et al., 2012, 2013; Dehning, Kim, Nguyen, Shivapour, & Denburg, 2014; Devos, Brijs, Alders, Wets, & Feys, 2013), and stroke (Akinwuntan et al., 2006; Eby & Molnar, 2010; George & Crotty, 2010; Hird

et al., 2015). This is due to the fact that driving is a highly complex daily behaviour that requires the coordination of perceptual (Coeckelbergh, Brouwer, Cornelissen, van Wolffelaar, & Kooijman, 2002; Higgins & Wood, 2005; Walter et al., 2001), motor (Calhoun et al., 2002; Graydon et al., 2004; Walter et al., 2001), and multiple cognitive functions (Adrian, Postal, Moessinger, Rascle, & Charles, 2011; Calhoun et al., 2002; Graydon et al., 2004; Hargrave, Nupp, & Erickson, 2012; Motta, Lee, & Falkmer, 2014; Schweizer et al., 2013; Walter et al., 2001).

Given that driving requires the integration of multiple cognitive functions, including executive function (Adrian et al., 2011; Hargrave et al., 2012; Motta et al., 2014; Walter et al., 2001), attention (Calhoun et al., 2002; Graydon et al., 2004; Schweizer et al., 2013; Walter et al., 2001), visuospatial ability (Calhoun et al., 2002; Graydon et al., 2004; Schweizer et al., 2013), and memory (Walter et al., 2001), it follows that patients with MCI and AD may be at an increased risk of driving impairment compared to cognitively intact individuals. However, a diagnosis of MCI or AD does not definitively imply that the patient is unfit to drive, as many patients retain the ability to drive safely. Furthermore, driving is an important source of independence for many older adults, both with and without cognitive impairment. Involuntary driving cessation can lead to many negative consequences, including an increased risk of depression (Marottoli et al., 1997; Ragland, Satariano, & MacLeod, 2005; Windsor, Anstey, Butterworth, Luszcz, & Andrews, 2007), feelings of embarrassment (Chacko, Wright, Worrall, Adamson, & Cheung, 2015), loneliness and social isolation (Chacko et al., 2015; Johnson, 1999; Liddle et al., 2013; Marottoli et al., 2000; Windsor & Anstey, 2006), stress with loved ones (Chacko et al., 2015; Liddle et al., 2013, 2015), and institutionalization (Freeman, Gange, Munoz, & West, 2006). Thus, when assessing the driving fitness of a patient with MCI or AD, it is important for clinicians to achieve a balance between patient autonomy and the safety of the patient as well as the general public.

1.2.1 Guidelines for Driving with MCI and AD

There are no published guidelines as to when patients with mild AD (or related dementia) or MCI should be referred for a formal driving assessment or reported to the driving authorities.

However, those with moderate to severe AD should be reported to the driving authorities (American Medical Association, 2010; Canadian Medical Association, 2012; Driver and Vehicle Licensing Agency, 2014). As a general rule, any physician who suspects that a patient's cognitive impairment may impact their ability to drive safely is expected to refer that patient for a functional driving test (Canadian Medical Association, 2012).

The Third Canadian Consensus on Dementia (Hogan et al., 2007) provided recommendations regarding the fitness to drive of patients with AD or related dementia and MCI:

- i) Diagnosis is not sufficient to withdraw driving privileges (Hogan et al., 2007).
- ii) Moderate to severe dementia is a contraindication of safe driving (Hogan et al., 2007).
- iii) Driving is contraindicated, when for cognitive reasons, individuals are not capable of performing multiple IADLs or any basic ADLs (Hogan et al., 2007).
- iv) Individuals with mild AD or related dementia should undergo comprehensive off- and on-road testing (Hogan et al., 2007).
- v) No test has acceptable sensitivity or specificity to be used as the only determinate of driving fitness; however, abnormalities on cognitive assessments suggest that the patient should potentially undergo comprehensive assessments (Hogan et al., 2007).

Given the lack of concrete guidelines and valid screening tools, physicians often feel burdened with the task of determining whether a patient's licence should be reported or not reported. Results of current studies suggest that 57-76% of physicians (Jang et al., 2007; Leinberger, Janz, Musch, Niziol, & Gillespie, 2013; Marshall, Demmings, Woolnough, Salim, & Man-Son-Hing, 2012; Marshall & Gilbert, 1999) worry about the negative consequences that reporting can have on patient independence and quality of life (Hum, Cohen, Persaud, & Lee, 2014), the families of patients (Marshall et al., 2012), and the patient-physician relationship (Hum et al., 2014; Jang et al., 2007; Leinberger et al., 2013; Marshall et al., 2012; Marshall & Gilbert, 1999). Thus, although most clinicians acknowledge that determining the driving fitness of their patients is an important issue, many do not feel confident in their ability to assess fitness to drive (Jang et al., 2007; Marshall et al., 2012). This is largely due to the ambiguous and limited guidelines available at the national and regional levels, the variable empirical data investigating the driving

performance of patients with AD and MCI, as well as the absence of accurate and wellestablished screening tools.

1.2.2 The Primary Methods of Driving Assessment

The three most commonly used and cited methods of driving assessment are cognitive measures, on-road evaluations, and simulator-based assessments.

i) Cognitive measures

Cognitive assessment is a cost-effective and potentially clinically useful screening tool for isolating which patients require a more in-depth driving assessment (Dobbs, 2013; Lincoln, Taylor, Vella, Bouman, & Radford, 2010). Administration typically involves paper and pencil or computer-based assessments. Given that driving requires the integration of multiple cognitive functions and that these functions can all be impaired in patients with AD and MCI, it follows that identifying impairment in these cognitive domains may offer utility in predicting driving performance.

Multiple studies have investigated the ability of cognitive tests to predict driving performance (e.g., on-road classification, on-road and driving simulator scores, on-road and driving simulator errors, driving status, caregiver ratings of driving ability) The results of a recent meta-analysis (Hird, Egeto, Fischer, Naglie, & Schweizer, 2016) suggested that measures of executive function, attention, visuospatial function, and global cognition offer some utility in predicting driving performance (effect sizes ≥ 0.5) in patients with AD and MCI. In addition, multiple individual cognitive tests have been shown to be predictive of driving ability in patients with AD and MCI, such as the Trail Making Test Part A (TMT-A; Grace et al., 2005; Ott, Festa, et al., 2008) and Part B (TMT-B; Grace et al., 2005; Ott et al., 2003; Rizzo et al., 2001, 1997; Uc et al., 2005, 2006), maze tasks (Ott et al., 2003; Ott, Festa, et al., 2008), the Useful Field of View (UFOV; Rizzo et al., 1997; Uc et al., 2005; Grace et al., 2005; Rizzo et al., 2001, 1997; Uc et al., Rey-Osterrieth Complex Figure (ROCF; Grace et al., 2005; Rizzo et al., 2001, 1997; Uc et al., 2005; Rizzo et al., 2001, 1

2005, 2006). However, the results of other studies suggest that these same measures are not correlated with driving outcomes (Grace et al., 2005; Ott, Festa, et al., 2008; Rizzo et al., 2001; Uc et al., 2006).

Variability in the results of cognitive predictors is likely the result of numerous factors, including variable driving outcomes utilized across studies, and differing degrees as well as areas of cognitive impairment across and within study samples. Furthermore, few studies report evidence-based cut-off scores (Molnar, Patel, Marshall, Man-Son-Hing, & Wilson, 2006) that consistently classify safe and unsafe drivers. Given that no single cognitive measure has been thoroughly investigated, as well as the absence of validated cut-off scores, it is impossible to translate cognitive results into clinical practice at an individual patient level. Consequently, there are no valid cognitive measures with sufficient specificity or sensitivity to help healthcare professionals determine the driving fitness of individual patients with MCI or AD.

ii) On-road evaluations

The on-road test is traditionally presumed to be the gold standard method of driving assessment ("Driving and Parkinson's disease," 1990). The two main subdivisions of on-road assessment are: (1) closed-course driving tests and (2) open-road driving tests. In a closed-course driving evaluation, the driver is required to execute manoeuvres on a highly controlled stretch of road (i.e. the surface of the road, the lighting condition, route to follow, and length of run are controlled) that is closed to other traffic (Wood, Lacherez, & Tyrrell, 2014; Wood, Tyrrell, & Carberry, 2005). An open-road driving test is more commonly used in driving research, including within the MCI and AD populations (Brown, Ott, et al., 2005; Davis et al., 2012; Duchek et al., 2003; Grace et al., 2005; Hunt et al., 1997, 1993; Lafont et al., 2010; Ott, Festa, et al., 2008; Ott, Heindel, et al., 2008). Such a test involves completing various manoeuvres onroad, with real-world traffic, following a specific and pre-determined route. Based on performance on an on-road test, patients receive an overall rating of driving performance with three possible classifications: pass/safe, marginal/borderline, or fail/unsafe. Other outcomes widely reported for on-road evaluations include: score (i.e. total score and score on different manoeuvres), rating scales for various manoeuvres (e.g. Likert scale of 1-5), and the number and type of errors committed.

Similar to cognitive tests and driving simulators, on-road evaluations have both strengths and limitations. On-road tests have been demonstrated to have high face validity (Akinwuntan et al., 2005; Galski, Bruno, & Ehle, 1992) and high reliability (Akinwuntan et al., 2003, 2005). However, on-road assessments lack a standardized method of administration (e.g. route being followed, variables assessed) (Mazer, Korner-Bitensky, & Sofer, 1998) and scoring (Akinwuntan et al., 2002; Mazer et al., 1998). Furthermore, on-road assessments are expensive (Klavora, Heslegrave, & Young, 2000; Marshall et al., 2007). Finally, few studies have assessed their validity, particularly within the population of MCI and AD (Davis et al., 2012; Ott et al., 2012; Shechtman, Awadzi, Classen, Lanford, & Joo, 2010). It has been suggested that the on-road test is unidimensional, only capturing awareness of road signs and traffic behaviour (Ott et al., 2012). In contrast, during naturalistic driving, maintenance of proper lane position emerged as a factor critical to safe driving (Ott et al., 2012). Furthermore, it is not possible to use on-road assessments to assess performance during complex and potentially dangerous situations, such as collision avoidance, high traffic conditions, and distracted driving, due to the safety concerns inherent in these situations. Future research is required to identify the differences between onroad and naturalistic driving assessments (Davis et al., 2012) and further validate the on-road evaluation.

iii) Simulator-based assessments

The use of simulator technology to assess driving ability has become increasingly prevalent in multiple neurological populations, including MCI (Devlin et al., 2012; Frittelli et al., 2009; Kawano et al., 2012), AD (Barrash et al., 2010; D. J. Cox et al., 1998; Frittelli et al., 2009; Rizzo et al., 2001, 1997; Shua-Haim & Gross, 1996; Stein & Dubinsky, 2011; Tomioka et al., 2009; Uc et al., 2006), multiple sclerosis (Devos et al., 2013; Kotterba, Orth, Eren, Fangerau, & Sindern, 2003), brain tumor (Yuen et al., 2007), cerebellar damage (Y. Hung et al., 2014), and stroke (Hird et al., 2015; Kotterba, Widdig, Brylak, & Orth, 2005; Lundqvist, Gerdle, & Ronnberg, 2000; McKay, Rapport, Coleman Bryer, & Casey, 2011). Driving simulators typically come equipped with a fully functioning steering wheel, pedal system (i.e. including accelerator and brake pedals), software for image generation and data collection, and visual projection (i.e. one or more monitors).

There are a few limitations in using driving simulator technology, such as the risk of simulator sickness (Classen & Brooks, 2014; Domeyer, Cassavaugh, & Backs, 2013; Lee, Cameron, & Lee, 2003; Mullen, Weaver, Riendeau, Morrison, & Bedard, 2010). Simulator sickness is a type of motion sickness and evokes symptoms such as nausea, oculomotor disturbance (e.g. fatigue, headache, eyestrain, blurred vision), and disorientation (e.g. dizziness, vertigo) (Mullen et al., 2010). Reported prevalence rates of simulator sickness vary greatly, with some studies reporting rates of 10% (Lee et al., 2003; Mullen et al., 2010) and others reporting rates as high as 50% and above in fully immersive simulator set-ups (Mullen et al., 2010; Ramkhalawansingh, Keshavarz, Haycock, Shahab, & Campos, 2016; Stanney, Kingdon, & Kennedy, 2002). In addition, some patients find the system more difficult to operate than a motor vehicle (Lew et al., 2005). Finally, simulators may be less realistic compared to real-world driving (E. Chung & Dumont, 2009; de Winter et al., 2009; Hallvig et al., 2013). In particular, some studies have questioned whether driving simulation is a valid representation of on-road driving performance and have suggested that the validity of a simulator is dependent on a variety of factors, including fidelity (Riener, 2010) as well as the quality of the learning and the data produced (de Winter et al., 2009).

Despite these potential limitations, other studies have supported the validity of driving simulation (Bedard, Parkkari, Weaver, Riendeau, & Dahlquist, 2010; Frittelli et al., 2009; Lee et al., 2003; Lew et al., 2005; Mayhew et al., 2011; Reimer, D'Ambrosio, Coughlin, Kafrissen, & Biederman, 2006; Shechtman, Classen, Awadzi, & Mann, 2009; Y. Wang et al., 2010; Yan, Abdel-Aty, Radwan, Wang, & Chilakapati, 2008) in terms of being related to real-world, or naturalistic, driving (Lew et al., 2005) as well as on-road driving performance (Bedard et al., 2010; Helland et al., 2013; Lundqvist et al., 2000; Mayhew et al., 2011; Shechtman et al., 2009). This includes the use of both three-screen and one-screen simulators (Bedard et al., 2010; Gibbons, Mullen, Weaver, Reguly, & Bédard, 2014). Studies have also shown that simulation is reliable and reproducible (Bedard et al., 2010; Classen & Brooks, 2014; Frittelli et al., 2009) as well as highly standardized (Lundqvist et al., 2000).

The use of simulator technology has emerged as a useful and valid tool in many professional assessment and training settings, including pilot training, the training of healthcare professionals (e.g. surgical skills training), as well as driving assessment and rehabilitation procedures. There

are many critical advantages to utilizing driving simulation over on-road assessments. Driving simulation offers a safe environment to evaluate driving fitness (Bedard et al., 2010; Classen & Brooks, 2014). This safety benefit is particularly advantageous when assessing the driving performance of at-risk populations, such as patients with MCI and AD. Secondly, driving simulator technology has the ability to expose patients to complex and potentially dangerous situations without the risk of real-world collisions (Lengenfelder, Schultheis, Al-Shihabi, Mourant, & DeLuca, 2002; Lew et al., 2005). Furthermore, driving simulation offers a highly controlled and standardized environment (i.e. a set degree of traffic, weather and road conditions, data collection, etc.). Driving simulation may be best suited for isolating the subtle impairments that are related to mild deficits in cognitive function and that may go otherwise undetected using on-road assessments. Nevertheless, both on-road assessments and driving simulation have advantages, and both methods of assessment should be explored further within the populations of MCI and AD.

1.2.3 Driving in the Context of MCI

There is a limited amount of research that has investigated the driving performance of patients with MCI (Devlin et al., 2012; Frittelli et al., 2009; Kawano et al., 2012; Wadley et al., 2009). Consequently, the areas and degree of driving impairment among patients with MCI remains unclear.

On-road test outcomes in MCI

Only one study has used an on-road evaluation to investigate the driving performance of individuals with MCI (n = 46) compared to healthy age-matched control drivers (n = 59) (Wadley et al., 2009). The results suggested that overall, patients with MCI demonstrated less than optimal performance, assessed via a Likert scale (1 = evaluator took control of the car, 2 = unsafe, 3 = unsatisfactory, 4 = not optimal, 5 = optimal) rather than definitive driving impairments. Specifically, after adjusting effect sizes for age and sex, patients with MCI were 4.23 times (95% CI = 1.47, 12.15) more likely to receive a less than optimal rating on global performance (p<0.05) and 3.69 (95% CI = 1.30, 10.46) times more likely to receive a less than

optimal rating on lane control (p<0.05) than cognitively normal drivers (Wadley et al., 2009). Although patients with MCI tended to perform less optimally than healthy drivers during left turns (OR = 1.93; 95% CI = 0.82, 4.54), results were no longer significant after controlling for age and sex (Wadley et al., 2009).

Driving simulator results in MCI

A few studies have used driving simulator technology to investigate the driving performance of patients with MCI (Devlin et al., 2012; Frittelli et al., 2009; Kawano et al., 2012). Mirroring the results of on-road evaluations (Wadley et al., 2009), the results of driving simulator studies suggest that individuals with MCI tend to exhibit more minor or subtle difficulties with driving rather than definitive and overt driving impairments (Devlin et al., 2012; Frittelli et al., 2009; Kawano et al., 2012). Studies have investigated a variety of driving behaviours, including performance at intersections (i.e. braking response, foot hesitations, stopping at stop signs and traffic lights) (Devlin et al., 2012; Frittelli et al., 2009), car following ability (Kawano et al., 2012), and overall driving (e.g. length of run, total number of infractions, mean time to collision, number of road edge excursions) in an urban setting (Frittelli et al., 2009). Specifically, results suggest that patients with MCI showed no or minimal impairment (i.e. results did not reach statistical significance, p>0.05) compared to cognitively normal drivers at braking (Devlin et al., 2012; Kawano et al., 2012), stopping at stop signs and stop lights (Devlin et al., 2012; Frittelli et al., 2009), and road tracking (Kawano et al., 2012). Furthermore, patients with MCI committed a similar number of infarctions and road edge excursions (i.e. when the vehicle travels off the road, crossing onto the shoulder) as healthy control drivers (Frittelli et al., 2009). However, patients with MCI performed worse on a car following task (Kawano et al., 2012) and had a shorter mean time to collision (i.e. the time to make contact with an oncoming or same-lane vehicle if the driver kept moving at a constant velocity) compared to healthy control drivers.

Thus, current research suggests that patients with MCI tend to demonstrate no or minor impairment across most driving outcomes, and may demonstrate more significant impairments in other aspects of driving, such as car following (Kawano et al., 2012) and mean time to collision (Frittelli et al., 2009). Given the tendency for patients with MCI to exhibit less than optimal global driving performance as well as the risk for patients with MCI to transition to dementia, it

is important for physicians and other healthcare professionals to be aware and alert to subtle changes in driving performance that may be (or may become) a safety concern (Wadley et al., 2009). However, despite this general trend for patients with MCI to demonstrate minor impairment in most driving situations, current results are based on a very small number of studies, and consequently, a relatively small sample of patients with MCI (n <100). Furthermore, with the exception of Kawano, Iwamoto, Iidaka, and colleagues (2012), who exclusively evaluated patients with aMCI, current studies do not differentiate between different subtypes of MCI (i.e. amnestic, non-amnestic, single-domain, multiple-domain). Future research is required to validate the tendency for patients with MCI to demonstrate minor driving impairments, identify areas of driving in which patients may be at risk for more significant impairment, and to differentiate patterns of driving impairment across different subtypes of MCI.

1.2.4 Driving in the Context of AD

The AD and driving literature is more extensive and substantial than the MCI and driving literature. Various studies have investigated the driving performance of patients with AD using an on-road evaluation (Barrash et al., 2010; Bieliauskas et al., 1998; Brown, Ott, et al., 2005; Brown, Stern, et al., 2005; Davis et al., 2012; Dawson et al., 2009; Duchek et al., 2003, 1998; Fitten et al., 1995; Grace et al., 2005; Hunt et al., 1997, 1993; Lafont et al., 2010; Ott, Festa, et al., 2008; Ott, Heindel, et al., 2008; Ott et al., 2012; Uc et al., 2004, 2005) as well as driving simulation (D. J. Cox et al., 1998; Frittelli et al., 2009; Rizzo et al., 2001, 1997; Stein & Dubinsky, 2011; Tomioka et al., 2009; Uc et al., 2006). The majority of research has investigated the driving performance of patients with AD by differentiating between individuals with very mild AD (CDR = 0.5) (Brown, Ott, et al., 2005; Brown, Stern, et al., 2005; Davis et al., 2012; Duchek et al., 2003, 1998; Grace et al., 2005; Hunt et al., 1997, 1993; Ott et al., 2012; Ott, Festa, et al., 2008; Ott, Heindel, et al., 2008; Ott et al., 2000, 2003; Stein & Dubinsky, 2011) and mild AD (CDR = 1) (Brown, Ott, et al., 2005; Davis et al., 2012; Duchek et al., 2003, 1998; Fitten et al., 1995; Frittelli et al., 2009; Grace et al., 2005; Hunt et al., 1997, 1993, Ott et al., 2003, 2012; Ott, Festa, et al., 2008; Ott, Heindel, et al., 2008; Ott et al., 2000; Stein & Dubinsky, 2011; Uc et al., 2004, 2005, 2006). Although all drivers with AD across the studies, including those diagnosed with very mild AD, met NINCDS-ADRDA (McKhann et al., 2011) or similar criteria

for AD, it is important to note that a CDR score (Morris, 1993) of 0.5 is used to classify patients with very mild AD as well as MCI. Furthermore, as previous research suggests (Morris et al., 2001), it may be very difficult, if not impossible, for clinicians to differentiate between patients with MCI and early AD. Thus, there is potential that some patients classified with MCI may in fact meet diagnostic criteria for very mild AD and vice versa.

On-road test outcomes in AD

The results of on-road driving assessments in patients with AD are highly variable, with some studies reporting a fail rate of over 25% of AD patients (Duchek et al., 2003; Hunt et al., 1997; Lafont et al., 2010), whereas others report a patient failure rate of 10% or less (Davis et al., 2012; Grace et al., 2005). A recent meta-analysis (Hird et al., 2016) reported that of 460 patients with AD who were assessed using an on-road evaluation, 214 (46.5%) received a pass classification, 87 (18.9%) received a fail classification, and 159 (34.6%) received a marginal classification. In contrast, of 364 cognitively normal drivers assessed, 289 (79.4%) received a pass classification, 6 (1.6%) received a fail classification, and 69 (19%) received a marginal classification. Thus, although patients with AD most typically receive a pass classification, patients with AD are over ten times more likely to receive a fail classification (18.9% vs. 1.6%) than cognitively normal drivers.

Hird and colleagues (2016) performed a chi-square analysis of on-road performance in patients with AD (very mild and mild AD) and healthy control drivers. A significant relationship was revealed between on-road outcome (i.e. pass/safe, marginal/borderline, and fail/unsafe) and CDR score (0, 0.5, 1) ($X^2 = 116.634$, p<0.001). Compared to healthy older drivers (CDR = 0, n = 364), drivers with very mild AD (CDR = 0.5, n = 154) were significantly more likely to receive a marginal (19.0% vs. 29.9%, p<0.05) or fail rating (1.6% vs. 13.6%, p<0.05), and significantly less likely to receive a pass rating (79.4% vs. 56.5%, p<0.05; Hird et al., 2016). Drivers with mild AD (CDR = 1, n = 120) were more likely to receive a fail rating than both healthy drivers (33.3% vs. 1.6%, p<0.05) and drivers with very mild AD (33.3% vs. 13.6%, p<0.05). Furthermore, drivers with mild AD were less likely to receive a pass rating than both healthy drivers (41.7% vs. 79.4%, p<0.05) and drivers with very mild AD (41.7% vs. 56.5%, p<0.05) (Hird et al., 2016).

Despite the variability in results observed across studies investigating on-road outcomes, results suggest that safety to drive appears to be associated with the degree of cognitive impairment (Hird et al., 2016). Specifically, fail ratings significantly increase with increasing severity of cognitive impairment (i.e. from cognitively normal drivers to drivers with very mild AD to drivers with mild AD).

Driving simulator results in AD

Similar to the results of on-road assessments, the findings from driving simulator studies demonstrate that some drivers with AD are able to retain their ability to drive safely (Rizzo et al., 2001, 1997; Uc et al., 2006), driving impairment increases with the severity of AD (Stein & Dubinsky, 2011), and results are highly variable, and often contradictory. This literature is summarized in more detail immediately below.

Although few studies have used driving simulator technology to investigate the driving performance of patients with AD, results confirm that driving deficits become more severe with increasing cognitive impairment (Frittelli et al., 2009; Stein & Dubinsky, 2011). The results of Stein and Dubinsky (2011) revealed that patients with mild AD (CDR = 1.0) performed significantly worse than healthy controls on 75% (6/8) of the variables of interest, whereas patients with very mild AD (CDR = 0.5) performed significantly worse than healthy controls on 50% (4/8) of the variables of interest. Furthermore, drivers with mild AD were involved in more collisions with pedestrians than drivers with very mild AD (Stein & Dubinsky, 2011). A similar pattern of results were obtained by Frittelli and colleagues (2009). Results showed that patients with mild AD (CDR = 1) and patients with MCI (CDR = 0.5) had a shorter mean time to collision than healthy controls. However, drivers with mild AD committed significantly more road edge excursions (2.9 \pm 0.8) than both healthy control drivers (0.8 \pm 0.2) as well as drivers with MCI (1.2 \pm 0.4) (Frittelli et al., 2009).

Number of errors, and in particular, collision involvement (Rizzo et al., 2001, 1997; Stein & Dubinsky, 2011; Uc et al., 2006; Yamin et al., 2015) is an outcome variable depicting lack of safety that is often reported in driving simulator research. Results of driving simulator studies that assessed collision rates in patients with AD are highly variable, with some studies reporting

that drivers with AD are involved in significantly more collisions than cognitively normal drivers (D. J. Cox et al., 1998; Rizzo et al., 1997; Stein & Dubinsky, 2011; Yamin et al., 2015), whereas other studies report no significant difference in collision rates (Rizzo et al., 2001; Uc et al., 2006). Across studies, collision rates for persons with AD range from 5 to 62 percent (D. J. Cox et al., 1998; Rizzo et al., 2001, 1997; Uc et al., 2006). This variability in collision involvement among patients with AD compliments the results of studies of on-road evaluations, which report fail classification rates ranging from 1.7 to 30 percent (Davis et al., 2012; Duchek et al., 2003; Lafont et al., 2010).

Contradictory results extend beyond collision involvement (D. J. Cox et al., 1998; Rizzo et al., 2001, 1997; Stein & Dubinsky, 2011; Uc et al., 2006) across studies investigating other driving variables in patients with AD. In particular, variables involved in vehicle control are often subdivided into two classes: (1) steering control (e.g. number of centre line crossings, number of road edge excursions, standard deviation of lane position, standard deviation in steering, etc.) and (2) speed control (e.g. time/distance over the speed limit, standard deviation in velocity, average speed etc.). In terms of steering control, some studies reported that patients with AD commit significantly more road edge excursions or centre line crossing (i.e. shoulder crossings, off-road events) (D. J. Cox et al., 1998; Frittelli et al., 2009; Yamin et al., 2015) and demonstrate significantly greater standard deviation or variability in steering (Uc et al., 2006) as well as lane position (Stein & Dubinsky, 2011 for CDR = 1; Yamin et al., 2015) than healthy controls. In contrast, other studies reported that drivers with AD perform similarly to cognitively normal drivers, or demonstrate only minor impairments, on the same variables, including number of road edge excursions (Rizzo et al., 2001; Yamin et al., 2015), number of centreline crossings (D. J. Cox et al., 1998; Rizzo et al., 2001), lateral and longitudinal vehicle control (Rizzo et al., 2001), and standard deviation/variability in lane position (Stein & Dubinsky, 2011 for CDR = 0.5) as well as steering (D. J. Cox et al., 1998). Similarly, some studies report that patients with AD are impaired on a number of variables related to speed control, including average speed (i.e. an increased tendency to drive slower than healthy controls) (D. J. Cox et al., 1998; Frittelli et al., 2009), standard deviation or variability in speed (Stein & Dubinsky, 2011 for CDR = 1; Uc et al., 2006), and increased number of speed exceedances (Yamin et al., 2015); however, other studies

report that drivers with AD are not impaired on these same variables (Cox et al., 1998; Rizzo et al., 2001; Stein & Dubinsky, 2011 for CDR = 0.5).

Specific driving impairments have been identified in individuals with AD, including driving slower (D. J. Cox et al., 1998; Frittelli et al., 2009; Stein & Dubinsky, 2011) applying less brake force when attempting to stop (D. J. Cox et al., 1998) and during collision avoidance (Tomioka et al., 2009), taking longer to complete left-hand turns (D. J. Cox et al., 1998), making judgement errors at traffic lights (Stein & Dubinsky, 2011), unsafe outcomes in rear-end collision avoidance (Uc et al., 2006), shorter mean time to collision (Frittelli et al., 2009), greater risk of collisions (Rizzo et al., 1997; Stein & Dubinsky, 2011), and driving more poorly in general (D. J. Cox et al., 1998; Frittelli et al., 2009). However, other studies report a no significant difference between drivers with AD and healthy controls in terms of vehicle control (Rizzo et al., 2001), centreline crossings (D. J. Cox et al., 1998; Rizzo et al., 2001), and collision involvement (Rizzo et al., 2006).

1.2.5 The Current AD & MCI and Driving Literature: Summary and Limitations

Across both on-road and driving simulator studies, results consistently suggest that an increased severity of cognitive impairment (i.e. MCI vs. AD; very mild AD vs. mild AD) is associated with greater driving impairment (Brown, Ott, et al., 2005; Duchek et al., 2003; Frittelli et al., 2009; Hird et al., 2016; Hunt et al., 1997; Ott, Heindel, et al., 2008; Stein & Dubinsky, 2011). This pattern has been observed across numerous variables, including road test fail rates (Brown, Ott, et al., 2005; Duchek et al., 2003; Frittelli et al., 2008; Stein & Lubinsky, 2011). This pattern has been observed across numerous variables, including road test fail rates (Brown, Ott, et al., 2005; Duchek et al., 2003; Hird et al., 2016; Hunt et al., 1997; Ott, Festa, et al., 2008) as well as simulator collision risk and involvement (Frittelli et al., 2009; Stein & Dubinsky, 2011). Despite this trend, results remain highly variable in terms of the areas and degree of driving impairment that are characteristic of patients with MCI and AD. Numerous factors likely contribute to these variable and often contradictory results, including procedural inconsistencies across studies (e.g. road test routes and simulator scenarios, the driving situation/task of interest,

road test scoring, test/scenario level of difficulty, level of traffic, operationalization of variables, etc.), the lack of standardization of MCI and AD diagnosis across studies, as well as the heterogeneous cognitive presentation of AD and MCI. As a result of these inconsistent findings, there are no tools or concrete guidelines to assist physicians in assessing the driving fitness of patients (Hird et al., 2016).

Given the variability in results in the current literature, there is limited knowledge about the areas and degree of driving impairment that are characteristic of cognitively normal drivers as well as cognitively impaired drivers (i.e. both individuals with AD and MCI, including subtypes of MCI). Structural and functional brain changes have been well-established in patients with MCI and AD (Bakker, Albert, Krauss, Speck, & Gallagher, 2015; Lam, Masellis, Freedman, Stuss, & Black, 2013; Peters et al., 2014; Sperling et al., 2010). These brain changes ultimately give rise to the cognitive deficits that are characteristic of these populations. Given this, coupled with the fact that driving is a highly complex and cognitively demanding task that requires the integration of multiple brain regions (Schweizer et al., 2013), it follows that the driving impairments of patients with MCI may be linked to the underlying brain changes associated with the disease. Thus, understanding the brain regions associated with different aspects of driving in patients with MCI, compared with healthy controls, would provide important information regarding the cognitive processes involved in various aspects of driving.

1.3 Neuroimaging Methods

Neuroimaging involves a variety of techniques that are used to image the structure and function of the nervous system. Structural neuroimaging is used to visualize physical changes in the brain, including atrophy, microangiopathic changes and small vessel disease, ventricular enlargement, and diffusivity (Joko et al., 2016; Kilimann et al., 2016; Krumm et al., 2015; Wirth et al., 2016). In contrast, functional neuroimaging methods measure parameters or aspects of brain function,

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including cerebral perfusion and glucose metabolism (Cai et al., 2016; Foster et al., 2016; Hays, Zlatar, & Wierenga, 2016; Y. Li et al., 2016; Wirth et al., 2016; L. Xu et al., 2016). Functional neuroimaging can also be used to capture brain function at rest or in response to various stimuli to investigate the relationship between brain activity and cognitive function.

Structural and functional techniques have been widely used for both clinical and research purposes in patients with MCI, AD, and related dementias (Cai et al., 2016; Foster et al., 2016; Hays et al., 2016; Joko et al., 2016; Kilimann et al., 2016; Krumm et al., 2015; Y. Li et al., 2016; Wirth et al., 2016; L. Xu et al., 2016). Structural imaging techniques, including computerized tomography (CT) and magnetic resonance imaging (MRI), are used to investigate several biomarkers commonly associated with MCI and AD. When possible, MRI is preferred over CT due to its ability to image a variety of brain tissue properties, increased precision, and absence of radiation. There are multiple structural biomarkers of interest in the MCI and AD populations, including hippocampal atrophy, cortical thickness, cerebral atrophy, and microangiopathic changes (i.e. white matter hyperintensitives). Functional biomarkers have also been identified using positron emission tomography (PET) and single photon emission tomography (SPECT), including decreased perfusion in the temporal, parietal, and frontal regions (Frings et al., 2015; Herholz, 2011; Moretti, 2015). Furthermore, PET techniques can be used to measure beta amyloid and tau protein levels in patients with AD, patients with MCI, and cognitively normal individuals (Barthel, Seibyl, & Sabri, 2015; Bauckneht, Picco, Nobili, & Morbelli, 2015; Landau et al., 2014; Nordberg, 2004; Tateno et al., 2015).

Both structural and functional techniques are used clinically to confirm diagnoses and to identify the severity of disease progression. Structural and functional imaging techniques are also used for research purposes to identify the clinical and cognitive (i.e. including task-based) correlates of imaging findings, identify how imaging findings change with disease progression, and to identify novel biomarkers in patients with MCI, AD, and those at risk for developing cognitive impairment.
1.3.1 fMRI and Blood Oxygen Level Dependency (BOLD) Signal

Functional MRI (fMRI) is a common functional neuroimaging technique that identifies alterations in neural metabolism through the imaging of certain signal changes in brain tissue (Chen & Glover, 2015). These changes in neural metabolism can occur at rest, without any mental operation (i.e. resting state fMRI), or in response to performance of a task that requires certain cognitive or mental operations (i.e. task-based fMRI) (Chen & Glover, 2015). Both resting state (Bai et al., 2008; Jin, Pelak, & Cordes, 2012; Z. Wang et al., 2011; Zhou, Yu, & Duong, 2015) and task-based fMRI (Bakker et al., 2015; H.-J. Li et al., 2015) have been increasingly utilized in research investigating cognitive changes in patients with MCI and AD.

Functional MRI uses blood oxygenation level dependent (BOLD) changes in brain tissue. When performing a task or at rest, changes in metabolic activity (i.e. both up and down regulation) in specific brain regions cause fluctuations in oxygen consumption in those same brain regions. The BOLD signal measures these fluctuations in oxygen consumption (Chen & Glover, 2015; Ogawa et al., 1992 as cited in Chen & Glover, 2015). Specifically, when there is an increase in neural activity, there is a corresponding increase in the delivery of oxygenated hemoglobin to these regions (Chen & Glover, 2015). At this point, the supply of oxygen is greater than the demand for oxygen, causing an increase in the regional oxygenation for several seconds (Chen & Glover, 2015). Physiologically, the precise BOLD signal level is the result of simultaneous and complex changes in oxygenation, blood flow, as well as blood volume (Chen & Glover, 2015; Crosson et al., 2010). Given that oxygenated hemoglobin is diamagnetic, whereas deoxygenated hemoglobin is paramagnetic, the BOLD signal utilizes differences in these magnetic properties to detect changes in neuronal activity.

Typically, fMRI is performed on clinical systems that are available either at the magnetic field strength of 1.5 Tesla (T) or 3.0 T MRI. Acquisition of fMRI data is preferable at 3.0 T (i.e. as used in the present study) as the higher magnetic field produces greater BOLD signal and enables higher spatial resolution.

1.3.2 Strengths and Limitations of fMRI versus Other Functional Neuroimaging Modalities

Several neuroimaging modalities have been used to identify the brain regions associated with various cognitive tasks and processes, such as fMRI, electroencephalography (EEG), magnetoencephalography (MEG), and functional near infrared spectroscopy (fNIRS) (Gherri & Forster, 2015; Hiroyasu & Fukushima, 2012; Karimpoor et al., 2015; Monden et al., 2015; Morrison et al., 2016; Tschentscher & Hauk, 2016; Vlahou, Thurm, Kolassa, & Schlee, 2014). Multiple factors are considered when evaluating the utility of functional neuroimaging modalities, including spatial resolution, temporal resolution, susceptibility to motion and noise, expense, harmfulness to patients or participants (e.g. presence of radiation), feasibility of conducting a given experiment. Each modality has strengths as well as limitations.

Functional MRI has several advantages and strengths over other functional neuroimaging modalities. One major advantage of fMRI over some techniques that requires the injection of a radioactive agent, such as PET and SPECT, is that it is a non-invasive procedure (Crosson et al., 2010). Another important advantage of fMRI over all other techniques, is its superior spatial resolution for localizing brain activity in space (Crosson et al., 2010; Lev & Grant, 2000). Spatial resolution refers to the accuracy in which brain activity can be localized in space (Crosson et al., 2010). In fMRI, spatial resolution is based on the voxel size of image acquisition. Spatial resolution to superior spatial resolution, fMRI has an advantage in that an MRI system can be used to acquire both structural and functional images. As a result, functional images can be overlaid onto structural images (Crosson et al., 2010). Thus, fMRI is capable of acquiring precise anatomical localization (Crosson et al., 2010).

Furthermore, fMRI is superior to other techniques, such as fNIRS, EEG, and MEG, in its imaging depth. In these other imaging techniques, only surface-level cortical structures (e.g. frontal lobes, parietal lobes, etc.) can be imaged and activity in deeper regions, including subcortical regions, such as the hippocampus, the thalamus, and the amygdala as well as the

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cerebellum cannot be easily measured. Many of these deep brain structures are important for various cognitive functions, including memory, movement and coordination, and emotional processing as required in functional tasks, such as driving (section 1.3.3). In contrast to these other techniques, fMRI is able to image deep brain structures in addition to surface-level cortical brain regions.

There are a few disadvantages and potential limitations associated with fMRI. Although fMRI has a greater temporal resolution over PET (i.e. resolution of tens of seconds versus seconds), other techniques such as EEG and MEG have a superior temporal resolution (i.e. resolution of milliseconds) to that of fMRI. This decreased temporal resolution comes at the expense of the far superior spatial resolution of fMRI. Although images can be acquired using smaller voxels than 2 mm, temporal resolution decreases with increased spatial resolution (i.e. smaller voxels). Thus, when using fMRI, it is important to achieve a balance between spatial and temporal resolution (Crosson et al., 2010).

Another limitation of fMRI is its expense (especially relative to EEG and fNIRS). Furthermore, a group of limitations associated with fMRI is related to participant comfort. The fMRI acquisition requires individuals to lie still, in a confined space, as MRI is very susceptible to motion. This can be particularly difficult when investigating the brain activation patterns of cognitively impaired and elderly populations, such as those with MCI. Furthermore, the noise produced by BOLD acquisition is quite loud, which can increase discomfort in participants and make it difficult for participants to hear auditory stimuli and instructions.

Although fMRI has a few notable disadvantages, as a functional neuroimaging technique it has important advantages over other methods (Crosson et al., 2010). The temporal resolution of fMRI is inferior to some techniques (EEG, MEG); however, its temporal resolution is overall moderate (i.e. it is greater than other techniques, such as PET), and its spatial resolution, imaging depth, and anatomical localization remains superior to other techniques (Crosson et al., 2010). Furthermore, although fMRI is susceptible to motion and other artifacts, multiple robust preprocessing techniques have been developed to correct for these noise sources and thus to increase the BOLD signal contract to noise ratio.

1.3.3 Functional Neuroimaging and Driving

Driving is a highly complex daily behaviour that requires the integration of multiple cognitive functions, including attention, executive function, visual spatial ability, psychomotor skills, and memory. All of these cognitive functions can be affected by MCI and AD. However, the frequency, areas, and degree of driving impairment within these populations remain unclear. Fundamental knowledge of the underlying brain regions associated with various aspects of driving in both cognitive impaired (i.e. MCI, AD, and related dementia) and cognitively normal populations is important for understanding the driving impairment characteristic of these patient populations and for the ultimate development of accurate tools to help physicians assess the driving fitness of patients (Schweizer et al., 2013). Several studies have combined driving assessments (e.g. driving simulation, on-road driving, caregiver reports, etc.) with various functional neuroimaging modalities, including fMRI (Calhoun et al., 2002; Callan, Osu, Yamagishi, Callan, & Inoue, 2009; S. C. Chung et al., 2014; Graydon et al., 2004; Hirth, Davis, Fridriksson, Rorden, & Bonilha, 2007; Just, Keller, & Cynkar, 2008; H. S. Kim et al., 2014; Mader et al., 2009; Schweizer et al., 2013; Spiers & Maguire, 2007; Uchiyama, Ebe, Kozato, Okada, & Sadato, 2003; Walter et al., 2001), EEG (Dahal et al., 2014; Haufe et al., 2014; Huang, Pal, Chuang, & Lin, 2015; Jancke & Brunner, 2008; I.-H. Kim, Kim, Haufe, & Lee, 2015; C. T. Lin et al., 2014; C.-T. Lin, Chen, Chiu, Lin, & Ko, 2011; Papadelis et al., 2006; Sonnleitner, Simon, Kincses, Buchner, & Schrauf, 2012), fNIRS (Harada, Nashihara, Morozumi, Ota, & Hatakeyama, 2007; Liu, 2014; Liu, Pelowski, Pang, Zhou, & Cai, 2015; Liu, Saito, & Oi, 2012; Tomioka et al., 2009), MEG (Fort et al., 2010; Sakihara et al., 2014; Yokosawa et al., 2013), SPECT (Ott et al., 2000) and PET (Jeong et al., 2006; Luzzi et al., 2015), to identify the neural networks associated with driving in cognitively normal (Calhoun et al., 2002; Just et al., 2008; Schweizer et al., 2013; Spiers & Maguire, 2007; Walter et al., 2001) and cognitively impaired (Luzzi et al., 2015; Ott et al., 2000; Tomioka et al., 2009) drivers. This literature is briefly reviewed below.

Other Functional Neuroimaging Techniques and Driving

Numerous studies have used EEG to investigate brain activation patterns during driving simulation (Bueno, Fabrigoule, Deleurence, Ndiaye, & Fort, 2012; Dahal et al., 2014; Jancke &

Brunner, 2008; I.-H. Kim et al., 2015; C. T. Lin et al., 2014; C.-T. Lin et al., 2011; Sonnleitner et al., 2012) and closed-course on-road assessments (Haufe et al., 2014). The results of these studies suggest that multiple brain regions are involved in driving, including frontal (Dahal et al., 2014; C.-T. Lin et al., 2011; Sonnleitner et al., 2012), temporal (Dahal et al., 2014; Sonnleitner et al., 2012), motor (C.-T. Lin et al., 2011), parietal (Sonnleitner et al., 2012), and occipital regions (Sonnleitner et al., 2012). For example, Jancke and Brunner (2008) investigated alpha-band activity during fast driving. Results suggested that driving fast is associated with greater alpha-band activity in the left anterior lateral prefrontal cortex (Jancke & Brunner, 2008). Given that an increase in alpha-band activity is associated with less hemodynamic responses, which corresponds to less neurophysiological activation, this increase in alpha-related activity suggests less neural activation in the left anterior lateral prefrontal cortex is associated with risk taking (Jancke & Brunner, 2008).

Jeong and colleagues (2006) used PET and [ISF]2-deoxy-2-fluoro-D-glucose (FDG) to investigate brain activity of healthy drivers during active (i.e. actively driving) and passive (i.e. passively observing in the passenger seat) actual-car driving. Participants were injected with FDG, performed the task, and then underwent PET scans immediately following the passive or active session. Results suggested that several brain regions are recruited during active car driving, including visual cortices, primary sensorimotor areas, premotor areas, parietal regions, the cingulate gyrus, the parahippocampal gyrus, the thalamus, and the cerebellum. Similar brain regions have been shown to be recruited during driving when using MEG, including visual (Fort et al., 2010), parietal (Fort et al., 2010; Sakihara et al., 2014), temporal (Sakihara et al., 2014), sensory (Sakihara et al., 2014) and frontal regions (Fort et al., 2010; Sakihara et al., 2014).

Functional NIRS is increasingly being used as a tool to investigate prefrontal and parietal lobe activation (i.e. changes in the concentration of oxyhemoglobin and deoxyhemoglobin) during driving simulation and on-road assessments (Harada et al., 2007; Liu et al., 2015, 2012; Shimizu et al., 2009 retrieved from Liu et al., 2015; Tsunashima & Yanagisawa, 2009 retrieved from Liu et al., 2015; Yoshino, Oka, Yamamoto, Takahashi, & Kato, 2013 retrieved from Liu et al., 2015). The results of these studies show that activation in the prefrontal cortex increases during a car

following task (Liu et al., 2015; Shimizu et al., 2009 retrieved from Liu et al., 2015; Tsunashima & Yanagisawa, 2009 retrieved from Liu et al., 2015), faster deceleration (Yoshino, Oka, Yamamoto, Takahashi, & Kato, 2013 retrieved from Liu et al., 2015), as well as collision avoidance (Tomioka et al., 2009). Harada and colleagues (2007) compared prefrontal activation in elderly and young drivers and found that elderly drivers showed less variation in activation compared to young drivers.

A few studies have used functional neuroimaging to investigate the brain activation patterns associated with driving in patients with dementia (Luzzi et al., 2015; Ott et al., 2000; Tomioka et al., 2009). Ott and colleagues (2000) correlated degree of driving impairment (i.e. based on caregiver ratings) of patients with very mild, mild, and moderate AD (i.e. CDR scores 0.5, 1, and 2) with SPECT perfusion. Increased driving impairment was associated with reduced right hemisphere perfusion, particularly in temporal-occipital regions. Similarly, Luzzi and colleagues (2015) used PET to correlate cerebral hypometabolism with road sign knowledge and route learning in patients with AD and semantic dementia (SD). In patients with SD, FDG uptake in left temporal regions was correlated with road sign naming and road sign comprehension. Furthermore, FDG uptake in the orbitofrontal cortex was correlated with road sign comprehension. In patients with AD, FDG uptake in the posterior parahippocampal gyrus was correlated with road sign naming and FDG uptake in the superior frontal gyrus/anterior cingulate was correlated with performance on route learning. These results suggest that individuals with dementia show deviations in brain activation compared to healthy drivers during tasks related to driving (e.g. road sign test and route learning) and that different subtypes of dementia (e.g. AD versus SD) demonstrate different patterns of activation related to driving (Luzzi et al., 2015).

Only one study has combined functional neuroimaging and a realistic driving simulator to investigate the neural correlates of driving in patients with cognitive impairment, including MCI, AD, and related dementia. Specifically, Tomioka and colleagues (2009) investigated the prefrontal activation of patients with AD during a collision avoidance task. Results revealed a correlation between a delay in braking and prefrontal activation, which was positive in healthy controls and negative in patients with AD (Tomioka et al., 2009).

Functional MRI and Driving

Functional MRI has been combined with various technologies, including joystick or controller technology (Calhoun et al., 2002; Just et al., 2008; Spiers & Maguire, 2007; Uchiyama et al., 2003; Walter et al., 2001), passively viewing driving scenes (Callan et al., 2009; Graydon et al., 2004; Hirth et al., 2007; H. S. Kim et al., 2014; Mader et al., 2009), as well as fully functioning driving simulation with a wheel and pedal system (S. C. Chung et al., 2014; Schweizer et al., 2013). Mirroring the results of EEG, PET, MEG, and fNIRS studies, the results of fMRI studies suggest that an extensive brain network is required to drive safely (Calhoun et al., 2002; Just et al., 2008; H. S. Kim et al., 2014; Y.-O. Li, Eichele, Calhoun, & Adali, 2012; Schweizer et al., 2013; Spiers & Maguire, 2007; Uchiyama et al., 2003). Specifically, the parietal (Calhoun et al., 2002; S. C. Chung et al., 2014; Graydon et al., 2004; Just et al., 2008; H. S. Kim et al., 2014; Y.-O. Li et al., 2012; Schweizer et al., 2013; Spiers & Maguire, 2007; Uchiyama et al., 2003; Walter et al., 2001), occipital (Calhoun et al., 2002; S. C. Chung et al., 2014; Hirth et al., 2007; Just et al., 2008; H. S. Kim et al., 2014; Y.-O. Li et al., 2012; Mader et al., 2009; Schweizer et al., 2013; Spiers & Maguire, 2007; Walter et al., 2001), motor (Calhoun et al., 2002; S. C. Chung et al., 2014; Just et al., 2008; Y.-O. Li et al., 2012; Schweizer et al., 2013; Spiers & Maguire, 2007; Uchiyama et al., 2003), premotor (Schweizer et al., 2013; Spiers & Maguire, 2007; Uchiyama et al., 2003), cerebellar (Calhoun et al., 2002; S. C. Chung et al., 2014; Graydon et al., 2004; Just et al., 2008; Y.-O. Li et al., 2012; Mader et al., 2009; Schweizer et al., 2013; Spiers & Maguire, 2007; Uchiyama et al., 2003; Walter et al., 2001), and frontal (Calhoun et al., 2002; S. C. Chung et al., 2014; Graydon et al., 2004; Hirth et al., 2007; H. S. Kim et al., 2014; Y.-O. Li et al., 2012; Mader et al., 2009; Schweizer et al., 2013; Spiers & Maguire, 2007; Uchiyama et al., 2003) regions have been repeatedly identified as important regions involved in safe driving.

Furthermore, different brain regions may be recruited during different aspects of driving. (Calhoun et al., 2002; Callan et al., 2009; Mader et al., 2009; Schweizer et al., 2013; Spiers & Maguire, 2007). Specifically, increased driving speed has been shown to be associated with decreased activity in the anterior cingulate cortex (Calhoun et al., 2002). Additionally, the anterior cingulate as well as other areas, including the cerebellum, basil ganglia, thalamus, and pre-motor regions, were recruited during a car-following task (Uchiyama et al., 2003). Task performance was negatively correlated with activation in the anterior cingulate, suggesting that

the task required error detection and response selection (Uchiyama et al., 2003). Spiers and Maguire (2007) investigated the brain regions involved in various driving conditions and situations, including prepared actions (e.g. turning, reversing, stopping, and starting), planning and monitoring traffic, collision avoidance, and processing road traffic rules. Prepared actions were associated with activation in premotor, parietal, and cerebellar regions (Spiers & Maguire, 2007). Planning and monitoring correlated with activation in superior parietal, lateral occipital, and cerebellar regions (Spiers & Maguire, 2007). Lateral occipital and parietal areas, the insular, and the posterior region of the medial premotor cortex were implicated during collision avoidance (Spiers & Maguire, 2007). Finally, processing road traffic rules was associated with activation in the lateral prefrontal cortex (Spiers & Maguire, 2007).

A few studies (Callan et al., 2009; Schweizer et al., 2013; Spiers & Maguire, 2007) have investigated the brain regions associated with turning at intersections. Schweizer and colleagues (2013) used a fully immersive, ecologically valid, MR-compatible driving simulator (Kan, Schweizer, Tam, & Graham, 2013) with a fully functioning steering wheel and pedal system (i.e. accelerator and brake pedal) to expose participants to turning conditions that increased in complexity, including right turns, left turns, and left turns without oncoming traffic. Executing right turns resulted in minimal activation compared to the straight driving condition (Schweizer et al., 2013). Left turns without traffic were associated with greater activation in posterior brain regions, such as occipital, parietal, motor, and cerebellar regions (Schweizer et al., 2013). Furthermore, left turns with oncoming traffic were associated with greater activation in posterior brain regions as well as increased activation in the cingulate cortex and superior frontal gyrus. Given the cognitively complex nature of left turns at a busy intersection, it follows that this turning condition was associated with increased activation in brain regions implicated in alertness, response-selection, and complex visual processing compared to more routine aspects of driving (Schweizer et al., 2013). Similar results were obtained by Callan and colleagues (2009), who showed that resolving uncertainty in decision making at high traffic intersections was associated with activation in the anterior cingulate as well as the amygdala.

1.4 Knowledge Gaps

Currently, guidelines provided by the Canadian Medical Association are highly limited, with no specific recommendations on how to effectively assess the driving performance of patients with MCI or mild AD. Furthermore, there are no cognitive tools with adequate sensitivity or specificity to assess driving safety in a clinical setting. Consequently, physicians and other healthcare professions do not feel confident or comfortable in assessing the driving fitness of patients with MCI and related dementias. One major factor contributing to this is the limited and variable results of driving simulator and on-road studies investigating the performance of drivers with MCI. A fundamental understanding of the driving impairments, and corresponding brain activation patterns, of patients of MCI as well as the various subtypes of MCI (e.g. amnestic single domain and amnestic multiple-domain subtypes) represents an important first step in addressing these issues.

Chapter 2 Specific Research Questions and Hypotheses

2.1 Summary and Rationale

The prevalence of MCI is widespread, with approximately 10-20% of individuals aged 65 years or older meeting diagnostic criteria (Alzheimer's Association, 2016). With the aging of the population, this prevalence rate is projected to increase substantially. Patients with MCI exhibit objective and subjective cognitive deficits in one or more cognitive domains (i.e. single domain versus multiple domain MCI; amnestic versus non-amnestic MCI). Although MCI is characterized by minor deficits in cognitive functioning, current research suggests that patients with MCI can exhibit subtle deficits in a variety of IADLs, including managing finances, keeping appointments, and driving (Albert et al., 2011; Aretouloi & Brandt, 2010; Artero et al., 2001; Burton et al., 2009; Gold, 2012; K. R. Kim et al., 2009; Petersen, 2004; Reppermund et al., 2013; Tabert et al., 2002; Winblad et al., 2004). Furthermore, patients presenting with certain subtypes of MCI may be at a greater risk of impairment when performing complex daily behaviours compared to other subtypes (Aretouloi & Brandt, 2010; Burton et al., 2009; Gold, 2012; K. R. Kim et al., 2009; Reppermund et al., 2013; C. Tam et al., 2007). This is a result of the fact that the various subtypes of MCI have different areas and degrees of cognitive impairment, likely translating into different degrees of functional impairment. Given that effective performance on complex tasks, such as driving, involve the integration of multiple cognitive functions, it follows that those with impairment in multiple cognitive domains beyond memory dysfunction, including impairments in attention, executive function, and visuospatial ability, may exhibit a greater degree of impairment when performing these complex daily activities, including certain aspects of driving. This has been supported by studies, which demonstrate that patients with md-MCI, who exhibit deficits in more than one cognitive domain, may exhibit greater impairment in performing daily tasks compared to individuals with sd-MCI, who demonstrate impairment in only one cognitive domain (Aretouloi & Brandt, 2010; Burton et al., 2009; C. Tam et al., 2007).

Driving is an important and complex daily behaviour. The ability to drive safely requires the integration of multiple motor, perceptual, and cognitive functions (e.g. attention, visual spatial functioning, memory, and executive functioning) as well as recruitment of the brain regions associated with these abilities. The results of fMRI studies investigating the brain activation patterns associated with driving in healthy, young drivers consistently report activation in the occipital, parietal, frontal, and cerebellar regions during a variety of driving tasks. Furthermore, given the multi-faceted nature of driving, different aspects of driving, including more routine compared to more cognitive demanding tasks, may result in different activation patterns. Schweizer and colleagues (2013) demonstrated that in healthy young adults, executing right and left turns without traffic were associated with activation in posterior brain regions (e.g. occipital, parietal, motor, cerebellar areas). Cognitively demanding left turns with oncoming traffic were associated with greater activation in these posterior brain regions as well as increased activation in the cingulate cortex and the superior frontal gyrus (Schweizer et al., 2013).

Given that the above brain regions recruited during driving are associated with numerous cognitive functions, it follows that patients with MCI may exhibit some degree of driving impairment, and deviation in brain activation, compared to cognitively healthy individuals. Current research suggests that patients with MCI tend to demonstrate no or minor impairment across most driving outcomes, rather than definitive driving impairments (Devlin et al., 2012; Frittelli et al., 2009; Kawano et al., 2012; Wadley et al., 2009). Despite this general trend, current results are based on a small number of studies (Devlin et al., 2012; Frittelli et al., 2009; Kawano et al., 2012; Wadley et al., 2012; Frittelli et al., 2009; Kawano et al., 2012; Wadley et al., 2012; Frittelli et al., 2009; Kawano et al., 2012; Wadley et al., 2012; Frittelli et al., 2009; Kawano et al., 2012; Wadley et al., 2012; Frittelli et al., 2009; Kawano et al., 2012; Wadley et al., 2009) and no study has differentiated between the subtypes of MCI (i.e. amnestic, non-amnestic, single-domain, multiple-domain) in terms of driving performance. Although it is important for healthcare professionals to be alert to the more subtle driving impairments among patients with MCI, there are currently no tools or guidelines to aid in the assessment of fitness to drive. Thus, research is urgently needed to improve the understanding of the specific areas and degree of driving impairment, and corresponding brain activation patterns, characteristic of patients with MCI.

Furthermore, different subtypes of MCI are associated with varying degrees and areas of cognitive impairment. This, coupled with the fact that research has shown that different subtypes

of MCI, may be at an increased risk of functional impairment (Aretouloi & Brandt, 2010; Burton et al., 2009; Gold, 2012; K. R. Kim et al., 2009; Reppermund et al., 2013; C. Tam et al., 2007), and that driving is a highly complex and multi-faceted task (Schweizer et al., 2013), it follows that different areas and degrees of driving impairment may be characteristic of different subtypes of MCI. Specifically, those with md-MCI have been shown to demonstrate widespread cognitive deficits (Petersen et al., 2001), including impairment in domains repeatedly shown to be important in safe driving (e.g. attention, executive function, visual spatial ability). Thus, it is critical for research to differentiate between different subtypes of MCI when investigating driving performance. Isolating the aspects of driving that patients with MCI (i.e. MCI patients as a whole as well as different subtypes) have the most difficulty with, as well as the critical brain regions that are recruited during these driving situations, is an important first step in the ultimate development of accurate assessment tools and targeted rehabilitation strategies to help assess and retrain driving ability in patients with MCI.

2.2 Research Objectives and Hypotheses

The primary aims of this thesis are to use driving simulation to determine (1) the areas and degree of driving difficulty characteristic of patients with MCI, including two prominent subtypes of MCI; and (2) the brain activation patterns characteristic of patients with MCI across driving conditions of varying levels of complexity.

2.2.1 Investigating the Areas and Degree of Driving Impairment Characteristic of Patients with MCI and Subtypes of MCI

The first set of objectives involve using driving simulation to investigate the driving performance of patients with MCI, as well as two different subtypes of MCI (amnestic sd-MCI and amnestic

md-MCI), and to compare patient performance to cognitively healthy age-matched control participants. The following objectives and hypotheses will be addressed in Chapter 3 of the current thesis. The objectives are:

- To determine which aspects of driving patients with MCI exhibit difficulty compared to healthy control drivers
- To determine whether patients with amnestic sd-MCI and patients with amnestic md-MCI demonstrate different driving profiles (i.e. areas and degree of driving impairment) compared to healthy control drivers.

The hypotheses associated with these objectives are:

- Given that patients with MCI exhibit impairments in cognitive functioning (i.e. including attention, executive function, and visual spatial ability) and the cognitively complex nature of driving, patients with MCI will exhibit increased driving errors (e.g. collisions, centre line crossings, road edge excursions, stop signs missed) compared to healthy control participants.
- Because of the subtle nature of the cognitive deficits associated with MCI, drivers with MCI will tend to demonstrate difficulty in more cognitively demanding aspects of driving (e.g. performing left turns with oncoming traffic) compared to more routine aspects of driving (e.g. performing right and left turns without traffic)
- 3) Given the presence of more widespread cognitive deficits (e.g. attention, executive function, etc. in addition to memory), patients with md-MCI will exhibit greater driving difficulty than controls, relative to those with sd-MCI, particularly during more cognitively demanding aspects of driving (e.g. left turns with traffic)

2.2.2 Investigating the Brain Activation Patterns Characteristic of Patients with MCI during Routine and Cognitively Demanding Driving Tasks

The second set of objectives involve combining fMRI and a fully immersive fMRI-compatible driving simulator to identify the brain activation patterns characteristic of patients with MCI while they are performing driving tasks that vary in complexity (i.e. right and left turns without traffic, left turns with oncoming traffic). The following objectives and hypotheses will be addressed in Chapter 4 of the thesis.

- 1) To compare the brain activation patterns of patients with MCI to cognitively healthy ageand sex-matched controls during various turning conditions
- To obtain preliminary data on the brain activation patterns of different subtypes of MCI (i.e. md-MCI and sd-MCI) relative to healthy age- and sex-matched controls during the same turning conditions

The hypothesis associated with these objectives are:

- Patients with MCI and cognitively healthy controls will show reliable activation in the brain regions previously identified as being activated during both routine and complex aspects of driving (e.g. occipital, parietal, motor, cerebellar, and frontal regions).
- 2) In addition, patients with MCI will show reliable deviations in brain activation compared to healthy control drivers, particularly during more cognitively demanding aspects of driving (i.e. left turns with oncoming traffic), and specifically, increased activation in frontal regions.

Given that the investigation of the activation patterns associated with subtypes of MCI (amnestic sd-MCI and amnestic md-MCI) was preliminary and exploratory in nature, no specific hypotheses were pre-defined.

Chapter 3

Driving Impairments in Patients with MCI, Including the Amnestic Single-Domain and Multiple-Domain Subtypes of MCI

Currently, there are no guidelines or objective tools with sufficient reliability and validity to assist healthcare professionals in assessing the driving fitness of patients with MCI. One major factor contributing to this issue is that the areas and degree of driving impairment among patients with MCI remain unclear. Only four studies to date have investigated the driving performance of patients with MCI (across all studies, the total number of patients is <100), with three studies using driving simulation (Devlin et al., 2012; Frittelli et al., 2009; Kawano et al., 2012) and one study using an on-road assessment (Wadley et al., 2009). In general, the results of these studies suggest that individuals with MCI exhibit minor or subtle difficulties rather than definitive and overt driving impairments (Devlin et al., 2012; Frittelli et al., 2009; Kawano et al., 2012; Wadley et al., 2009). Specifically, patients with MCI showed no or minimal impairment (i.e. results did not reach statistical significance) in braking (Devlin et al., 2012; Kawano et al., 2012), stopping at stop signs and stop lights (Devlin et al., 2012; Frittelli et al., 2009), road tracking (Kawano et al., 2012) and performing left turns (Wadley et al., 2009). However, patients with MCI performed significantly worse on a car following task (Kawano et al., 2012), had a shorter mean time to collision (Frittelli et al., 2009), and were more likely to receive a less than optimal rating on global performance as well as lane control compared to healthy control drivers (Wadley et al., 2009).

Given the limited amount of research to date, there is a need to confirm the results of previous studies that patients with MCI exhibit minor impairments in several aspects of driving and to identify better the specific areas of driving in which patients with MCI may be at risk for more severe impairment. Furthermore, given the heterogeneous nature of MCI, it is critical to investigate the driving performance of various subtypes of MCI separately (e.g. amnestic versus non-amnestic; single-domain versus multiple domain). Given the widespread cognitive deficits

associated with patients with md-MCI (Petersen, 2004; Petersen et al., 2001), including key cognitive functions that have been shown to be implicated in driving (e.g. attention, executive function, visual spatial ability), it follows that patients with amnestic md-MCI may be at a greater risk of driving impairment compared to those with amnestic sd-MCI. Understanding the areas of driving for which certain subtypes of MCI may be at an increased risk of difficulty will lay the foundation for ultimate development of accurate screening tools, informative driving guidelines, and effective rehabilitation strategies for patients.

3.1 Experimental Materials and Methods

3.1.1 Statement of Ethical Approval

Ethical approval for the current study was obtained from the Research Ethics Board (REB) at St. Michael's Hospital, Toronto Canada under REB 16-036 titled, "Investigating the driving behaviour and underlying neural networks in aging cohorts and patients with neurological conditions". All participants provided written informed consent before participating in the research study.

3.1.2 Participants

Twenty-two (22) patients with MCI (mean age = 66.8; mean years of education 15.0; Male, n = 14), including 11 patients with amnestic sd-MCI (mean age = 67.3; mean years of education 15.1; Male, n = 5) and 11 patients with amnestic md-MCI (mean age = 66.4; mean years of education 15.0; Male, n = 8) were recruited from the Memory Disorders Clinic at St. Michael's Hospital. In addition, twenty (20) age-matched cognitively healthy controls (mean age = 66.7;

mean years of education 16.7; Male, n = 14) were recruited from the community. Although patients and control participants were not sex- or education-matched, statistical analyses (i.e. chi-square analysis and Kruskal-Wallis H test, respectively) revealed patients with MCI (including the sd-MCI and md-MCI subgroups) and healthy control participants did not differ significantly in terms of sex ($X^2 = 2.325$, p > 0.05) or mean number of years of education ($X^2 = 4.758$, p > 0.05). Demographic information is listed in Table 3.1.

	Healthy	All MCI	sd-MCI	md-MCI	p-value
	Controls	Patients	Patients	Patients	
	(n = 20)	(n = 22)	(n = 11)	(n = 11)	
Age, years	66.7 ± 8.2	66.8 ± 9.6	67.3 ± 9.2	66.4 ± 10.3	0.972
	(47-79)	(50-83)	(52-83)	(50-81)	
Education, years	16.7 ± 2.0	15.0 ± 2.7	15.1 ± 2.7	15.0 ± 2.7	0.093
	(14-22)	(12-21)	(12-21)	(12-19)	
Sex, n (%) Male	14 (70.0%)	13 (59.1%)	5 (45.4%)	8 (72.7%)	0.313

Table 3.1. Demographic characteristics of patients with MCI and healthy controls

Note. Values reported in mean ± standard deviation (range) format unless otherwise indicated. p-values are reported for the one-way ANOVA/Kruskal Wallis analysis (healthy control versus sd-MCI versus md-MCI comparison). n, number of participants; % = percentage of participants; MCI = mild cognitive impairment; sd-MCI = amnestic single-domain MCI; md-MCI = amnestic multiple-domain MCI.

Inclusion Criteria

Both patients with MCI and healthy control participants: (1) held a valid driver's licence, (2) were age 45-85 years old, and (3) were fluent in English. Patients and controls with a history of clinical depression were included if depressive symptoms were controlled. All cases of uncontrolled depression were excluded.

All patients with MCI were formally diagnosed by a geriatric psychiatrist in the Memory Disorders Clinic at St. Michael's Hospital, based on a comprehensive patient history, as well as the results of clinical neuroimaging (e.g. MRI, CT, SPECT to rule out other diagnoses) and objective cognitive testing, including the Behavioural Neurological Assessment (BNA; Darvesh, Leach, Black, Kaplan, & Freedman, 2005) and the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). All patients met the National Institute on Aging-Alzheimer's Association criteria for MCI (Albert et al., 2011). Specifically, patients demonstrated: (1) a concern regarding change in cognition (i.e. self-reported, reported by a caregiver, or recognized by a clinician), (2) impairment in one or more cognitive domains, (3) preservation of independence in functional abilities, (4) no presence of dementia (see Chapter 1, section 1.1.1, pages 3-5 for a comprehensive summary of these diagnostic criteria). All patients classified with sd-MCI demonstrated subjective and objective complaints/impairments in one or more cognitive domains (e.g. executive function, attention, visuospatial ability, etc.) in addition to memory.

Exclusion Criteria

The following represent the exclusion criteria for both patient and control participants: (1) history of severe neurological diagnoses (e.g. traumatic brain injury, brain tumour, Parkinson's disease, stroke, multiple sclerosis, Alzheimer's disease, epilepsy, etc.), (2) history of severe psychiatric diagnosis (e.g. schizophrenia, uncontrolled depression or anxiety, etc.), (3) severe microangiopathic changes, (4) presence of a serious sensory or motor impairment, (5) presence of a significant visual abnormality that was not corrected with lenses, (6) history of substance abuse or dependence, and (7) diagnosed or treated learning disabilities. All controls who scored less than 26 on the MoCA were also excluded from the analysis (see Chapter 3, section 3.1.3.3, pages 49-50 for more detailed information). All inclusion and exclusion criteria were evaluated clinically for patients by a geriatric psychiatrist and by self-report for healthy controls.

3.1.3 Experimental Procedures

The experimental design aimed to use driving simulation to investigate the driving performance, and more specifically the driving impairments, of patients with MCI including individuals with amnestic single-domain (sd-MCI) and individuals with amnestic multiple-domain (md-MCI) MCI. Each participant (including MCI patients and healthy controls) completed (1) driving scenarios on a portable driving simulator, (2) cognitive tests, which have been widely utilized in the driving literature and assess a variety of cognitive domains, and (3) questionnaires assessing mood and driving habits. Each participant completed the driving scenarios, cognitive tests, and questionnaires on the same day. The driving scenarios took approximately 1-1.5 hours to complete.

3.1.3.1 Clinical Data Collection

The relevant clinical data of all consenting patients with MCI were obtained through the online medical record system at St. Michael's Hospital (Soarian Clinicals, Version 4.00 SP06). The electronic medical records, including imaging results (i.e. CT, MRI, SPECT scans), of all individuals with MCI were screened for any history or presence of any conditions that would warrant exclusion (see Chapter 3, section 3.1.2, pages 40-41 for inclusion and exclusion criteria). Electronic medical records also indicated the subtype (e.g. amnestic MCI, amnestic multiple-domain MCI) in which patients with MCI met diagnostic criteria. Subtype classification was determined by a geriatric psychiatrist in the Memory Disorders Clinic at St. Michael's Hospital, based on consistent (i.e. repeated assessments) areas of impairment identified through objective testing (BNA and/or MoCA) as well as the subjective cognitive complaints of the patients.

3.1.3.2 Driving Simulation

Although some studies have questioned the validity of driving simulation, other research studies have supported the utility driving simulators in assessing driving performance (Bedard et al., 2010; Frittelli et al., 2009; Lee et al., 2003; Lew et al., 2005; Mayhew et al., 2011; Reimer et al.,

2006; Shechtman et al., 2009; Y. Wang et al., 2010; Yan et al., 2008). More specifically, simulation has been shown to be related to real-world driving (Lew et al., 2005), which is assessed in a naturalistic driving situation, as well as on-road driving performance (Bedard et al., 2010; Helland et al., 2013; Lundqvist et al., 2000; Mayhew et al., 2011; Shechtman et al., 2009).

In the current study, driving simulator performance was assessed using a non-immersive, portable driving simulator (LogitechG25 model), equipped with a fully functioning steering wheel, accelerator pedal, brake pedal, and signalling system. Driving simulator scenarios were generated using STISIM Drive® Software (version 2.08.08). Scenarios were run on a Dell XPS1730 gaming laptop computer (17-inch display, 2.4 GHz Intel Core Duo T7700 Processor, 4.0 GB RAM, 512MB NVIDIA GeForce 8700M GT graphics card) and projected onto a 30-inch (diagonal) monitor (NEC MultiSync LCD3090WQXi), with a field of view (FOV) of 45 degrees. The STISIM Drive® Software collected and saved data on the driving variables of interest (e.g. distance, lateral lane position, vehicle heading angle, collision involvement) 30 times per second.

Before commencing the driving simulator scenarios, participants were oriented to the virtual reality environment, including the location of the speedometer, the rear-view mirror, the hood of the car, etc. (Figure 3.1). At the beginning of the driving scenarios, in addition to the instructions unique to each scenario, participants were instructed to "adhere to the posted speed limit signs, drive safely, and follow the rules of the road". Audio instructions (e.g. turn right at the stop sign, turn left at the traffic light, go straight at the next street) were embedded within the driving simulator scenarios and were presented through audio speakers. Individuals with MCI and healthy controls completed the same three standardized driving simulator scenarios, including one training scenario and two experimental scenarios, as detailed below. All scenarios provided audio feedback of engine and braking noise. All participants were offered optional break periods in between each of the driving scenarios.



Figure 3.1. Screen shots of the three driving tasks assessed in the driving scenarios: (a) right turns, (b) left turns, and (c) left turns with oncoming traffic. Similar conditions were used during the behavioural and fMRI driving scenarios; however, in the fMRI driving session, excessive visual stimuli were excluded (i.e. buildings; cars, other than left turns with traffic; pedestrians).

Training Session

All participants completed a training session (approximately 15 minutes in duration; 6130 m in length), which allowed participants to gain familiarity with the virtual-reality environment as well as the weight and feel of the steering wheel, accelerator, and brake. At the beginning of the session, participants were required to drive along a straight road along which the speed limit changed. This allowed participants to practice changing their speed in response to speed limit signs. Participants were also required to execute right turns, left turns, and left turns with traffic at intersections controlled by stop signs as well as traffic lights. The scenario involved both rural (i.e. minimal traffic, trees and sparse buildings) and urban city driving (i.e. high-level traffic, pedestrians, many buildings) components. At the end of the training session, all participants reported feeling comfortable with the equipment and were able to move to the experimental sessions.

Full Scenario 1 and Full Scenario 2

Patients with MCI and healthy controls were asked to complete two experimental driving scenarios (Full Scenario 1 and Full Scenario 2) that were similar in content, duration (i.e. approximately 12 minutes, each), and length (approximately 5700 m, each). Both scenarios

included two-way traffic, with one lane of traffic in each direction, as well as pedestrians and buildings. Scenarios exposed participants to a variety of driving conditions that ranged in complexity from straight driving, to right turns and left turns without traffic, to left turns with oncoming traffic. At intersections with oncoming traffic in which drivers were instructed to turn left, a condition that involves higher cognitive demands (Schweizer et al., 2013), participants were required to judge accurately when it was possible to execute the manoeuvre safely. The scenario involved both rural and urban city driving components. Speed limit signs ranged from 40 km/h to 90 km/h.

The variables of interest that were collected in this scenario included: number of collisions, number of centre line crossings, number of road edge excursions, number of stop signs missed, number of speed exceedances (>5 km/h over the posted speed limit sign), total number of driving errors (i.e. the sum of the above errors), number of errors during each turning condition (i.e. collisions, centre line crossings, road edge excursions), the percentage of the time spent out of the legal driving lane, the percentage of time over the posted speed limit, and standard deviation in speed. A centre line crossing occurs anytime the wheels of the driver's vehicle make contact with the other side of the centre line. A road edge excursion occurs every time the tires leave the paved portion of the road (in the driver's direction). Maintaining the vehicle over the centre line or on the paved portion of the road contributes to the variable "percentage of time out of the legal driving lane". Maintaining a speed 5 km/h over the speed limit contributes to the variable "percentage of time out of the legal driving lane". Number of errors during each turning condition was reported as the average number of errors committed per one turn (i.e. average number of errors committed per one right turn, per one left turn, and per one left turn with traffic).

Procedures to Minimize Simulator Sickness

Simulator sickness is a prominent issue in driving simulator research and assessments. An evidence-based review conducted by Classen, Bewernitz, and Shechtman (2011) investigated the factors contributing to simulator sickness. Results suggested that multiple participant factors contribute, including age (Brooks et al., 2010; Domeyer et al., 2013; Matas, Nettelbeck, & Burns, 2015), sex (Matas et al., 2015), the virtual reality environment, and the virtual reality equipment. Specifically, individuals 70 and older were significantly more likely to experience

simulator sickness than individuals under the age of 50 (Classen et al., 2011). Furthermore, women are more likely to experience simulator sickness than men. In terms of environmental factors, previous research has suggested that decreasing the visual "choppiness" of graphics, using fog, decreasing the complexity of visual stimuli or starting with less visually complex tasks and moving to more complex scenarios, starting with straight driving and progressing to curves and turns, and decreasing the field of view of the screen (i.e. a small single monitor or three-screen monitors versus a single large monitor) can all help to decrease instances of simulator sickness (Classen et al., 2011). Finally, activity demand factors, including the illusion of motion when a person remains stationary and driving at high speeds may contribute to simulator sickness (Classen et al., 2011).

Mullen, Weaver, Riendeau, Morrison, and Bedard (2010) compared the on-road driving and cognitive performance of individuals who successfully completed driving simulation (n = 12) to those who dropped out due to simulator sickness (n = 13). Importantly, results suggested that individuals who were prone to simulator sickness did not perform poorer on an on-road assessment or cognitive testing compared to individuals who were able to complete the simulated drive without experiencing simulator sickness (Mullen et al., 2010).

To help minimize the rate of simulator sickness, the current study used a single smaller monitor that did not span the entire field of view (FOV = 45 degrees). The training session began with straight driving and progressed to turns and curves, started the training procedure with less visually complex events and moved to more complex events, minimized the "choppiness" of the visual graphics, and provided participants with brakes between each of the scenarios. In the current study, simulator sickness was measured via verbal-self report of symptoms. Throughout the driving simulator session, research personnel checked with each participant to ensure he/she was not experiencing symptoms of simulator sickness.

3.1.3.3 Cognitive Tests and Questionnaires

Questionnaires that were administered included: a demographic questionnaire, the Driving Habits Questionnaire (DHQ; Owsley, Stalvey, Wells, & Sloane, 1999), and the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). Cognitive tests that were consistently administered to patient and control participants included: the MoCA, the Trail Making Test Part A (TMT-A) and Part B (TMT-B), and the Useful Field of View test (UFOV). The MoCA, TMT, as well as the UFOV were used to compare the cognitive test performance of patients with MCI and healthy controls.

Demographic Questionnaire

All MCI patients and controls were administered a brief demographic questionnaire that asked participants to report: age and date of birth, handedness, highest level of education, occupation (or previous occupation), and retirement status.

Driving Habits Questionnaire

The DHQ was adapted from a questionnaire produced by Owsley and colleagues (1999). The DHQ represents one of the highest cited and most commonly utilized driving questionnaires that is currently available (Ackerman, Vance, Wadley, & Ball, 2010; Croston, Meuser, Berg-Weger, Grant, & Carr, 2009; Edwards, Bart, O'Connor, & Cissell, 2010; O'Connor, Kapust, Lin, Hollis, & Jones, 2010; Song, Chun, & Chung, 2015). Recent research (Song et al., 2015) suggests that the DHQ is a reliable, internally consistent, measure of self-reported driving behaviour.

Key items of interest for the current study included: number of years of driving experience, total number of hours spent per week driving, number of hours per week driving on the highway, number of self-reported accidents, self-reported quality of driving (1 = poor; 2 = fair; 3 = average; 4 = good; 5 = excellent), and self-reported ratings on various difficult driving situations (0 = no difficulty; 1 = little difficulty; 2 = moderate difficulty; 3 = severe difficulty), including driving at night, driving on the highway, driving alone, and executing left turns with oncoming traffic (see Table 3.2).

	Healthy	All MCI	sd-MCI	md-MCI	p-value
	Controls	Patients	Patients	Patients	-
	(n = 20)	(n = 22)	(n = 11)	(n = 11)	
Driving experience,	44.3 ± 12.6	45.9 ± 10.7	47.6 ± 8.6	44.3 ± 12.7	0.675†
vears	(20-63)	(27-65)	(33-63)	(27-65)	0.801‡
J			()		
Driving experience.	6.8 ± 6.2	6.1 ± 4.5	6.4 ± 3.8	5.7 ± 5.3	0.641†
hours/week	(0-20)	(0-15)	(1-14)	(0-15)	0.857*
	(0 = 0)	(0 10)	()	(0 10)	01007.4
Driving experience.	2.1 + 2.4	2.5 + 2.5	3.2 + 2.1	1.9 + 2.7	0.587†
hours/week on	(0-10)	(0-8)	(0.5-8)	(0-7)	0.419†
highway	(0 10)	(0 0)	(0.0 0)		0.1224
Self-reported quality	4.1 ± 0.7	4.0 ± 0.7	4.3 ± 0.6	3.8 ± 0.7	0.685†
of driving*	(3-5)	(2-5)	(3-5)	(2-5)	0.365†
or univing	(5.5)	(20)	(5.5)	(2 0)	0.000
Self-reported	1.8 + 2.4	1.7 + 1.4	1.6 ± 1.4	1.7 ± 1.5	0.631†
accidents	(0-10)	(0-5)	(0-5)	(0-5)	0.883†
	(0 10)	(0, 0)	(0.0)	(0.2)	0.000.
Difficulty driving at	0.5 ± 0.5	0.5 ± 0.7	0.1 ± 0.3	0.8 ± 0.8	0.869†
night8	(0-1)	(0-2)	(0-1)	(0-2)	0.085†
ingit's	(0 1)	(0 -)	(0 1)	(0 -)	0.000.
Difficulty with left	0.3 ± 0.5	0.2 ± 0.6	0 + 0	0.4 ± 0.8	0.452†
turns with traffic8	(0-1)	(0-2)	(0-0)	(0-2)	0.155†
turns with durnes	(0 1)	(0 -)	(0 0)	(0 =)	0.100 +
Difficulty with	0.2 ± 0.4	0.1 ± 0.4	0 + 0	0.2 ± 0.6	0.607*
highway driving8	(0-1)	(0-2)	0 = 0	(0-2)	0.440^{+}
ingiting antitings	(0 1)	(0 2)		(0 2)	0.1104
Difficulty driving	0.4 ± 0.7	0.2 ± 0.5	0 + 0	0.4 ± 0.5	0.355*
alone	(0-2)	(0-2)	0 _ 0	(0-2)	0.213*
4101103	(02)	(0 2)		(0 2)	0.210+

Table 3.2. Driving habits reported by patients with MCI and healthy controls

Note. Values reported in mean \pm standard deviation (range) format unless otherwise indicated. †p-value for healthy control versus all MCI patients comparison. ‡p-value for one-way ANOVA/Kruskal Wallis analysis (healthy control versus sd-MCI versus md-MCI comparison). *self-reported quality of driving is assessed on a 5-point Likert scale (1 = poor; 2 = fair; 3= average; 4 = good; 5 = excellent). §self-reported level of difficulty (0 = no difficulty; 1 = little difficulty; 2 = moderate difficulty; extreme difficulty).

n, number of participants; % = percentage of participants; MCI = mild cognitive impairment; sd-MCI = amnestic single-domain MCI; md-MCI = amnestic multiple-domain MCI

Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-report measure of anxiety and depression developed by Zigmond and Snaith (1983). The HADS was designed as a brief self-assessment scale to be utilized in outpatient general medical clinics to screen for clinically significant anxiety and depression (Zigmond & Snaith, 1983). The assessment consists of 14 items, with seven evaluating symptoms of depression (e.g. "I still enjoy the things I used to enjoy" and "I feel as if I am slowed down") and seven measuring symptoms of anxiety (e.g. "worrying thoughts go through my mind" and "I can sit at ease and feel relaxed"). Approximately half of the items on the inventory are reverse scored to prevent response bias. Each individual item is scored on a scale from 0 to 3, with a score of 0 corresponding to no endorsement of symptoms and a score of 3 corresponding to a high endorsement of that particular symptom of anxiety or depression. The total score on the HADS ranges from 0 to 21. Normative data suggests that those scoring between 0 to 7 should be classified as "normal", individuals scoring between 8 to 10 are classified as "borderline abnormal", and those scoring between 11 to 21 are classified as "abnormal". Various research studies have supported the clinical utility of the HADS as a measure of depression (Bocéréan & Dupret, 2014; Fong & Ho, 2014; C.-I. Hung, Liu, Wang, Yao, & Yang, 2012; Kjaergaard, Arfwedson Wang, Waterloo, & Jorde, 2014; Müller, Cieza, & Geyh, 2012; Turk et al., 2015) and anxiety (Bocéréan & Dupret, 2014; Fong & Ho, 2014; Müller et al., 2012; Turk et al., 2015).

In the current study, the HADS was administered to both healthy control participants and patients with MCI to identify and screen out any participants who may have had clinically significant levels of depression and anxiety.

The Montreal Cognitive Assessment (MoCA)

The MoCA was developed by Dr. Zaid Nasreddine as a screening tool for patients who present with mild cognitive complaints. Previous research suggested that the Mini-Mental Status Examination (MMSE), one of the most widely used screening tools for dementia, lacked the sensitivity necessary to identify patients with MCI (Nasreddine et al., 2005). Thus, the MoCA was developed as a tool to identify patients with MCI who typically score in the normal range of the MMSE (Nasreddine et al., 2005). The MoCA is scored out of 30, with a score of \geq 26 suggesting normal cognitive functioning and a score of <26 suggesting cognitive impairment associated with MCI, AD, or a related form of dementia. The MoCA assesses eight broad cognitive domains including: visuospatial/executive function (scores range from 0-5), naming (scores range from 0-3), attention (scores range from 0-6), language (scores range from 0-3), abstraction (scores range from 0-2), memory delayed recall (scores range from 0-5), and orientation (scores range from 0-6).

Research has confirmed the clinical utility and accuracy (i.e. high validity, specificity, sensitivity) of the MoCA in a variety of clinical populations, including MCI, AD, frontotemporal dementia (FTD), vascular dementia, vascular cognitive impairment (VCI), and stroke (Freitas, Prieto, Simoes, & Santana, 2014; Goldstein et al., 2014; Kaya et al., 2014; Lam, Middleton, et al., 2013; Schweizer, Al-Khindi, & Macdonald, 2012; Smith, Gildeh, & Holmes, 2007; Van Heugten, Walton, & Hentschel, 2015; Q. Xu et al., 2014). Furthermore, the MoCA has been recognized as an important clinical tool by the Canadian Consensus Conference for the Diagnosis and Treatment of Dementia Guidelines for Alzheimer's disease (Canadian Consensus on Diagnosis and Treatment of Dementia Working Group, 2007).

In the current study, the MoCA was used to screen healthy control participants for any potential underlying cognitive impairment. Any control participant who scored <26 on the MoCA (cut-off suggested by Nasreddine et al., 2005), was excluded from any further participation and any collected data were removed from the analysis. The MoCA was also used to confirm the subtypes (i.e. amnestic single-domain versus amnestic multiple-domain MCI) assigned by the geriatric psychiatrist at St. Michael's Hospital to the patients who were enrolled in the current study. The previous work of Lam and colleagues (2013) demonstrated that the MoCA subscores correlate with neuropsychological tests of the same domain. Specifically, memory (area under the receiver operating characteristic curve, AUC = 0.86), visuospatial (AUC = 0.79), and executive (AUC = 0.79) subscores were relatively sensitive to impairment in their respective domains. In the current study, the mean domain subscores of sd-MCI and md-MCI subgroups were compared to the mean domain subscores of healthy control participants. Previous research has confirmed the criterion validity of the MoCA subscores.

The Trail Making Test Part A (TMT-A) and Part B (TMT-B)

The TMT is measure of attention, speed, and mental flexibility (Strauss, Sherman, & Spreen, 2006). There are two parts to the evaluation. TMT-A requires participants to use a pen or pencil to connect 25 encircled numbers, which are randomly distributed across the sheet of paper, in the correct, ascending order (e.g. 1 to 2, 2 to 3, 3 to 4, 4 to 5, etc.) (Strauss et al., 2006). TMT-B requires participants to connect 25 encircled numbers and letters, which are randomly distributed across the sheet of paper, in alternating and ascending order (e.g. 1 to A, A to 2, 2 to B, 3 to C, etc.) (Strauss et al., 2006). All participants were administered a practice version of TMT-A and TMT-B before completing the experimental versions. The test administrator (M.A.H) was responsible for timing each exercise and, in the event of an error, directing the participant to the last correct item and asking him/her to continue from that point (Strauss et al., 2006). Scoring for TMT-A and TMT-B was reported in terms of time (in seconds) and the number of errors.

The TMT has been widely cited in the driving literature (Hird et al., 2016; Hird, Vetivelu, Saposnik, & Schweizer, 2014; Marshall et al., 2007). Some studies report the predictive utility of the TMT-A (Dawson et al., 2009; Grace et al., 2005; Hunt et al., 1993; Kawano et al., 2012) and TMT-B (Dawson et al., 2009; Kawano et al., 2012; Ott et al., 2003; Rizzo et al., 2001, 1997; Uc et al., 2006) in patients with AD and MCI, whereas other report little or no [i.e. not statistically significant (p>0.05) or low/weak correlation coefficient (r <0.5; Mukaka, 2012)] predictive utility (TMT-A: Ott, Festa, et al., 2008; Uc et al., 2006; TMT-B: Grace et al., 2005; Ott, Festa, et al., 2008; Uc et al., 2004, 2005). Thus, although some studies have shown success in predicting the driving performance of patients with MCI and AD using the TMT-A and TMT-B, results remain inconsistent. Given that too few studies have supported the reliability and validity of these measures, it is difficult to translate results into clinical recommendations.

In the current study, TMT-A was administered to patient and healthy control participants as a measure of attention, and TMT-B was administered to participants as a measure of executive function.

The Useful Field of View (UFOV)

The Useful Field of View (UFOV) is defined as the visual or spatial area that is required to complete a specific visual task (Ball & Owsley, 1993). The size of one's visual field can vary from person to person and as a function of task difficulty (i.e. the speed of presentation, the degree of similarity between the target and distractor stimuli) (Ball & Owsley, 1993). The UFOV was developed in response to the presence of visual attentional deficits in older adults that are not accurately identified using clinical measures and that often impact everyday abilities and tasks, including driving (Ball & Owsley, 1993; Wood & Owsley, 2014).

The UFOV measures visual awareness and it requires participants to detect, locate, and identify rapidly a target embedded in a complex environment (Ball & Owsley, 1993). There are three parts to the evaluation. For each part of the UFOV, the participant is presented with stimuli on the computer screen, and the time for which the stimuli are shown becomes shorter and shorter with each presentation. The program measures the point at which the participant can no longer accurately see all the information that is presented on the screen. Thus, the UFOV measures the presentation time at which the stimuli can be accurately (i.e. 75% accuracy) identified (Wood & Owsley, 2014). Processing Speed is the first subtest of the UFOV and involves the presentation of a central target without any other targets or distractors (Wood & Owsley, 2014). Divided Attention is the second subtest and involves the presentation of a pair of targets with one presented centrally and the other presented in the periphery along one of the eight cardinal directions (Wood & Owsley, 2014). Selective Attention is the third subtest, involving the same targets as the Divided Attention subtest with the addition of irrelevant distractor stimuli (Wood & Owsley, 2014).

The UFOV has been used as a tool to predict unsafe driving in a variety of populations, including older drivers (Classen, Wang, Crizzle, Winter, & Lanford, 2013; Wood, Chaparro, Lacherez, & Hickson, 2012), patients post-stroke (Akinwuntan et al., 2002; George & Crotty, 2010), and patients with AD (Dawson et al., 2009; Rizzo et al., 2001, 1997, Uc et al., 2004, 2005, 2006). Similar to the results of the TMT, it remains unclear whether the UFOV is an accurate predictor of driving performance within the AD population. Specifically, a few studies supported the UFOV as a predictor of simulator crashes and risky behaviours (Rizzo et al., 1997; Uc et al.,

2006) as well as on-road safety errors (Dawson et al., 2009), whereas others found that the UFOV was not predictive of these same variables (Rizzo et al., 2001; Uc et al., 2004, 2005). No study has investigated the ability of the UFOV to predict driving performance within the MCI population.

The UFOV (Version 6.1.4), including the Processing Speed, Divided Attention, and Selective Attention subtests, was administered to MCI patients and healthy controls as a measure of vision and attention.

3.1.4 Data Extraction and Analysis

3.1.4.1 Driving Simulator Data Extraction

All driving simulator data were extracted from the STISIM Drive® data files, which were automatically generated and saved at the end of each driving scenario run. All data were transferred to an Excel spreadsheet (Microsoft Office 2013) to increase the ease with which the data were analyzed. Some variables of interest were computed automatically by the STISIM Drive® software, including: length of run, number of speed exceedances (i.e. driving >5 km/h), number of centre line crossings, number of road edge excursions, the percentage of time spent out of the legal driving lane, and the percentage of time spent over the posted speed limit. Other variables were computed in excel including: number of collisions (i.e. the sum of pedestrians hit, vehicles hit, and off-road collisions), number of stop signs missed (i.e. failing to come to a stop at an intersection controlled by a stop sign), total number of errors (i.e. the sum of the individual errors across each scenario), standard deviation in speed, and number of errors (centre line crossings, road edge excursions, and collisions) during each turning condition (per one right turn, per one left turn, with traffic) throughout each scenario.

In the current study, the number of turning errors were reported as the average number of errors committed per one turn of each turning condition (i.e. average number of errors committed per one right turn, per one left turn, per one left turn with traffic, and per one turn in general). This was calculated by determining the number of errors committed by each participant during right turns, left turns, left turns with traffic, and all turns (Value 1). Second, the number of right turns, left turns, left turns with traffic, and total turns correctly executed by each participant was calculated (Value 2). For each turning condition, the number of errors per one turn was calculated by dividing Value 1 by Value 2. Finally, the number of errors per one turn was averaged for the control group and the MCI patient group. The reason for this calculation was two-fold: (1) there is a disproportionate representation of each turning type across the scenarios (i.e. the total number of right turns, left turns, and left turns with traffic is not consistent). (2) Some participants missed turns (i.e. went straight through the intersection) or turned in the incorrect direction (e.g. turned right instead of left). As a result, the total number of "correctly executed" turns (i.e. right turns, left turns, left turns with traffic, total turns) was variable across participants. Thus, the average number of errors committed per one turn of each type was calculated to provide the most accurate measure of turning errors.

All variables of interest were merged for Full Scenario 1 and Full Scenario 2 because the scenarios were highly similar in terms of driving tasks and length of run. Thus, errors were summed across the two scenarios.

3.1.4.2 Cognitive and Demographic Data Extraction

All cognitive and demographic data were scored and extracted into Excel spreadsheets. The TMT-A and TMT-B errors and time, MoCA total score and subscores, and demographic variables (i.e. age, sex, years of education, driving habits), were extracted manually from each participant's case report form (CRF). The UFOV was administered and scored using dedicated computer software. Thus, scores for each subtest (i.e. Processing Speed, Divided Attention, and Selective Attention) were automatically generated for each participant.

3.1.4.3 Statistical Analyses Using Statistical Package for the Social Sciences (SPSS) Software

All variables (i.e. driving simulator, demographic, and cognitive) were separated into MCI patient (i.e. including all MCI patients, patients with sd-MCI, and patients with md-MCI) and healthy control groups. The means and standard deviations of each variable above were computed for both the MCI groups and the healthy control group. All data were analyzed using SPSS software (IBM SPSS Statistics Version 23, 64-bit edition). The Kolmogorov-Smirnov test was used to assess the normality of each continuous variable of interest. Based on the results of the normality tests as well as homogeneity of variance, analyses comparing patients with MCI and healthy controls were run using an independent samples t-test (i.e. for normally distributed data, homogeneity of variance) or the Mann-Whitney U test (i.e. for not normally distributed data, no homogeneity of variance). In addition, all analyses comparing sd-MCI patients and md-MCI patients with healthy controls were run using a one-way ANOVA (i.e. for normally distributed data, homogeneity of variance) or the Kruskal–Wallis H test (i.e. i.e. for not normally distributed data, no homogeneity of variance), followed by post-hoc testing, with Bonferroni corrections for two comparisons (i.e. sd-MCI versus healthy controls and md-MCI versus healthy controls). For nominal data (e.g. sex), chi-square analyses with Bonferroni corrections were run. Most variables were not normally distributed (i.e. skewed distribution, small sample size) and, thus, more conservative, non-parametric tests were utilized for the majority of the variables in the current study.

Although the primary use of cognitive data was to compare the performance of patients with MCI and healthy controls, a secondary correlation analysis was run to determine whether the TMT-A, TMT-B, MoCA and UFOV were associated with simulated driving performance. Specifically, TMT-A time, TMT-B time, MoCA total score, UFOV Processing Speed, UFOV Divided Attention, and UFOV Selective Attention were correlated using the Spearman Rank Correlation (i.e. a non-parametric test of correlations), with total simulated driving errors (i.e. sum of collisions, stop signs missed, speed exceedances, centre line crossings, road edge excursions) and number of centre line crossings.

3.2 Results

In total, 27 patients with MCI and 25 healthy controls were recruited for the current study. Five patients with MCI (18.5%) and five healthy control drivers (20.0%) were unable to complete the driving simulation due to simulator sickness. Therefore, one group (i.e. patients and controls) was not disproportionally affected by simulator sickness. Although reported rates of simulator sickness are quite variable across studies, the rates observed were consistent with ranges of simulator sickness reported in the literature (10-80%; Mullen et al., 2010). Thus, the driving and cognitive performance of 22 patients with MCI and 20 healthy control participants were compared.

3.2.2 Demographic and Cognitive Presentation

As reported in Table 3.1 (Demographic Information, section 3.1.2), patients with MCI (including all MCI patients, sd-MCI patients, and md-MCI patients) did not significantly differ from healthy controls in terms of mean age, mean education, or sex frequency. Patients with MCI reported a similar number of years of driving experience (45.9 vs. 44.3), number of hours driving per week (6.1 vs. 6.8), and accidents (1.7 vs. 1.8) as healthy control participants. Furthermore, there was no significant difference between the MCI subtypes (i.e. sd-MCI and md-MCI) and healthy control participants across all self-reported driving variables (Table 3.2). Parametric tests were used when data were normally distributed and there was homogeneity of variance (i.e. independent samples t-test, one-way ANOVA); in cases where these assumptions were violated, non-parametric tests were used (i.e. Mann-Whitney U, Kruskal Wallis).

The MoCA results of participants are reported below in Table 3.3. Overall, patients with MCI performed worse than healthy control participants on the overall score of the MoCA (23.9 vs. 27.9, U = 15.00, p < 0.001), the visuospatial executive subscore of the MoCA (3.8 vs. 4.5, U = 100.5, p = 0.013), the attention subscore of the MoCA (5.1 vs. 5.9, U = 93.50, p = 0.007), and the memory delayed recall subscore of the MoCA (2.4 vs. 4.3, U = 67.00, p<0.001). The Kruskal

Wallis H Test revealed a significant difference between MCI subtypes and healthy controls on total MoCA score ($X^2 = 24.053$, p < 0.001) as well as the visuospatial/executive ($X^2 = 7.136$, p = 0.028), attention ($X^2 = 9.684$, p = 0.008), abstraction ($X^2 = 10.206$, p = 0.006), and memory delayed recall ($X^2 = 12.478$, p = 0.002) subscores of the MoCA. Post-hoc testing revealed that patients with sd-MCI performed significantly worse than healthy controls on the MoCA overall (24.1 vs. 27.9, U = 5.50, p < 0.001) and the memory delayed recall portion of the MoCA (2.2 vs. 4.3, U = 30.50, p = 0.004). Furthermore, patients with md-MCI performed significantly worse than controls on the MoCA overall (23.7 vs. 27.9, U = 9.50, p < 0.001) as well as the attention (5.0 vs. 5.9, U = 42.00, p = 0.03), abstraction (1.2 vs. 1.9, U = 43.00, p = 0.034), and the delayed recall (2.6 vs. 4.3, U = 36.50, p = 0.012) subscores of the MoCA. Although patients with md-MCI tended to perform worse than healthy controls on the visuospatial/executive subscore of the MoCA, results did not maintain significance after adjusting for multiple comparisons (3.6 vs. 4.5, p = 0.074).

As expected, patients with sd-MCI (i.e. amnestic single domain impairment) performed significantly worse compared to healthy controls on the memory delayed recall domain of the MoCA, but not on other the other domains (i.e. attention, visuospatial/executive, abstraction, language, etc.). Furthermore, patients with md-MCI (i.e. amnestic domain MCI with impairment in additional cognitive domains) performed significantly worse compared to healthy controls on the abstraction and attention domains, in addition to the memory delayed recall domain.

	TT 1/1		1 1 (0)	1 1 101	1
	Healthy	All MCI	sd-MCI	md-MCI	p-value
	Controls	Patients	Patients	Patients	
	(n = 20)	(n = 22)	(n = 11)	(n = 11)	
MoCA Total Score	$27.9 \pm 1.2^{\rm a}$	23.9 ± 2.0	$24.1\pm1.5^{\rm b}$	23.7 ± 2.4^{b}	<0.001 †
(/30)	(26-30)	(20-27)	(22-27)	(20-27)	<0.001 ‡
Memory (/5)	4.3 ± 1.0^{a}	2.4 ± 1.7	2.2 ± 1.7^{b}	$2.6\pm1.7^{\rm b}$	<0.001 †
	(2-5)	(0-5)	(0-5)	(0-5)	0.002‡
Visuospatial/ Executive	$4.5\pm0.9^{\rm a}$	3.8 ± 0.8	$3.9\pm0.7^{\rm a}$	3.6 ± 0.9^{a}	0.013 †
Function (/5)	(2-5)	(3-5)	(3-5)	(3-5)	0.028‡
Naming (/3)	2.9 ± 0.5^{a}	2.8 ± 0.4	2.9 ± 0.3^{a}	2.7 ± 0.5^{a}	0.566†
	(1-3)	(2-3)	(2-3)	(2-3)	0.279‡
Language (/3)	2.6 ± 0.5^{a}	2.2 ± 1.0	2 ± 1.1^{a}	2.4 ± 1.0^{a}	0.392†
	(2-3)	(0-3)	(0-3)	(0-3)	0.327‡
Attention (/6)	$5.9\pm0.3^{\rm a}$	5.1 ± 0.9	$5.3\pm0.8^{a,b}$	5.0 ± 1.0^{b}	0.007 †
	(5-6)	(3-6)	(4-6)	(3-6)	0.008‡
Abstraction (/2)	1.9 ± 0.3^{a}	1.5 ± 0.7	$1.8\pm0.4^{a,b}$	1.2 ± 0.7^{b}	0.110†
	(1-2)	(0-2)	(1-2)	(0-2)	0.006‡
Orientation (/6)	$6.0\pm0^{\mathrm{a}}$	5.9 ± 0.2	$5.9\pm0.3^{\rm a}$	6.0 ± 0^{a}	0.812†
		(5-6)	(5-6)		0.280‡

Table 3.3. Mean score of all patients with MCI, sd-MCI, md-MCI, and healthy controls on the MoCA and domains subscores of the MoCA

Note. Values reported in mean \pm standard deviation (range) format. MoCA = Montreal Cognitive Assessment. †p-value for healthy control versus all MCI patients comparison (independent samples t-test/Mann-Whitney U). ‡p-value for one-way ANOVA/Kruskal Wallis analysis (healthy control versus sd-MCI versus md-MCI comparison). When statistical assumptions were met, parametric tests were utilized (independent samples t-test/ANOVA); when assumptions were violated, non-parametric tests were used (Mann-Whitney U/Kruskal-Wallis). Post-hoc results (statistical values and p-values) are reported in-text. . ^{a,b}Superscripts denote whether a significant difference emerged between MCI subtypes (md-MCI and sd-MCI) and healthy controls (i.e. shared superscripts indicated no significant difference at p = 0.05).

MoCA domain subtests: Memory: delayed recall; Visuospatial/executive function: TMT-B, cube copy, clock drawing; Naming: naming three animals; Language: sentence repetition, verbal fluency; sentence repetition; Attention: digit span forward and backward, letter "A" tap, serial sevens; Abstraction: similarities.

The results from the remaining cognitive tests and questionnaires are reported below in Table 3.4. Overall, patients with MCI performed significantly slower compared to healthy controls on TMT-A (35.2 s vs. 23.0 s, U = 92.00, p = 0.017) and TMT-B (88.3 s vs. 51.9 s, U = 93.00, p = 0.017) 0.018). Performance on the subtests of the UFOV, TMT-A errors TMT-B errors, HADS Anxiety, HADS depression, and HADs Total (Anxiety + Depression) did not significantly differ between MCI patients and controls. The one-way ANOVA and Kruskal Wallis H Test analyses revealed a significant difference between MCI subtypes and healthy controls on TMT-A time ($X^2 = 8.563$, p = 0.014), TMT-B time (X^2 = 7.459, p = 0.024), HADS Anxiety (F = 4.483, p = 0.021), HADS Depression (F = 7.515, p = 0.003), and HADS Total ($X^2 = 8.641$, p = 0.013). Post-hoc analyses demonstrated that patients with sd-MCI did not perform significantly worse than healthy controls on any of the above measures. In contrast, patients with md-MCI performed significantly worse than healthy controls on TMT-A time (41.5 s vs. 23.0 s, U = 34.00, p = 0.008), TMT-B time (111.9 s vs. 51.9 s, U = 38.00, p = 0.016), HADS Anxiety (8.0 vs. 4.0, p = 0.020), HADSDepression (5.9 vs 2.8, p = 0.014), and HADS Total (13.9 vs. 6.8, U = 23.00, p = 0.016). Despite this tendency for patients with md-MCI to perform worse than healthy controls on the HADS, with two patients scoring in the "abnormal" range on HADS Anxiety, all cases of clinical anxiety and depression were deemed and confirmed to be stable by the referring geriatric psychiatrist.
	Healthy	All MCI	sd-MCI	md-MCI	p-value	
	Controls	Patients	Patients	Patients		
	(n = 20)	(n = 22)	(n = 11)	(n = 11)		
TMT-A time (s)	23.0 ± 5.8^{a}	35.2 ± 21.0	$27.6\pm10.5^{\mathrm{a,b}}$	41.5 ± 25.6^{b}	0.017 †	
	(11.1-32.8)	(15.8-109.0)	(18.5-52.4)	(15.8-109)	0.014‡	
TMT-A errors	$0\pm0^{\mathrm{a}}$	0.1 ± 0.4	0.1 ± 0.3^{a}	$0.2\pm0.4^{\mathrm{a}}$	0.442*	
		(0-1)	(0-1)	(0-1)	0.221‡	
TMT-B time (s)	$51.9\pm23.6^{\rm a}$	88.3 ± 71.8	$59.4 \pm 19.6^{\mathrm{a,b}}$	$111.9\pm90.1^{\rm b}$	0.018 †	
	(25.9-107.5)	(36.3-320.0)	(36.3-89.45)	(41.7-320)	0.012‡	
TMT-B errors	$0.5\pm0.8^{\mathrm{a}}$	0.5 ± 1.1	0.2 ± 0.4^{a}	0.8 ± 1.5^{a}	0.988^{+}	
	(0-3)	(0-5)	(0-1)	(0-5)	0.514‡	
UFOV	24.2 ± 16.4^{a}	40.0 ± 54.1	25.1 ± 11.3^{a}	53.5 ± 73.0^{a}	0.199†	
Processing Speed	(17-87)	(17-213)		(17-213)	0.425‡	
UFOV Divided	62.6 ± 65.7^{a}	143.9 ± 148.5	$91.6\pm65.3^{\rm a}$	$191.4 \pm$	0.091†	
Attention	(17-257)	(17-500)	(17-47)	187.2 ^a	0.236‡	
				(17-500)		
UFOV Selective	$167.8\pm95.9^{\rm a}$	226.2 ± 126.4	$268.1 \pm$	$173.9 \pm$	0.121†	
Attention	(47-420)	(57-500)	128.1ª	109.9 ^a	0.061‡	
			(57-500)	(63-417)		
HADS Anxiety	4.0 ± 2.4^{a}	6.5 ± 4.4	$4.0\pm2.3^{a,b}$	8.0 ± 4.8^{b}	0.079^{+}	
	(0-9)	(0-16)	(1-7)	(0-16)	0.021‡	
HADS	2.8 ± 2.5^{a}	4.4 ± 2.8	$2.0\pm1.5^{\rm a,b}$	5.9 ± 2.3^{b}	0.104†	
Depression	(0-9)	(0-9)	(0-4)	(3-9)	0.003‡	
HADS Total	6.8 ± 4.4^{a}	10.8 ± 6.7	$5.7\pm3.6^{a,b}$	13.9 ± 6.3^{b}	0.092†	
	(0-18)	(0-23)	(0-10)	(4-23)	0.013‡	

Table 3.4. Mean score of all patients with MCI, sd-MCI, md-MCI, and healthy controls on the TMT-A, TMT-B, UFOV, and HADS

Note. Values reported in mean \pm standard deviation (range) format. HADS = Hospital Anxiety and Depression Scale; TMT = Trail Making Test; UFOV = Useful Field of View. †p-value for healthy control versus all MCI patients comparison (independent samples t-test/Mann-Whitney U). ‡p-value for one-way ANOVA/Kruskal Wallis analysis (healthy control versus sd-MCI versus md-MCI comparison). When statistical assumptions were met, parametric tests were utilized (independent samples t-test/ANOVA); when assumptions were violated, non-parametric tests were used (Mann-Whitney U/Kruskal-Wallis). Post-hoc results (statistical values and p-values) are reported in-text. . ^{a,b}Superscripts denote whether a significant difference emerged between MCI subtypes (md-MCI and sd-MCI) and healthy controls (i.e. shared superscripts indicated no significant difference at p = 0.05).

3.2.3 Driving Simulator Performance

3.2.3.1 Experimental Driving Scenarios (Full Scenario 1 & Full Scenario 2)

Driving Performance of Patients all Patients with MCI

The first aim of this study was to investigate and identify the driving behaviours characteristic of patients with MCI (n = 22) as a whole (i.e. combining all subtypes of MCI together) by identifying areas and degrees of impairment relative to healthy control drivers (n = 20).

Table 3.5 lists a summary of the main results of Full Scenario 1 and Full Scenario 2. Parametric tests were used when data were normally distributed and there was homogeneity of variance (i.e. independent samples t-test); in cases where these assumptions were violated, non-parametric tests were used (i.e. Mann-Whitney U). On average, it took approximately 24 minutes for healthy control participants (24.25 minutes) and MCI patients (24.31 minutes) to complete Full Scenario 1 and 2. The Mann-Whitney U test revealed that patients with MCI committed significantly more errors over the simulated driving run (i.e. the sum of collisions, centre line crossings, road edge excursions, stop signs missed, speed exceedances) compared to healthy control drivers (20.0 vs. 9.9, U = 123.00, p = 0.014). However, the only individual errors that reached statistical significance were related to lane maintenance. Patients with MCI committed significantly more centre line crossings (5.4 vs. 1.9, U = 132.50, p = 0.025) and spent a significantly greater percentage of time out of the legal driving lane (2.3 vs. 0.3, U = 115.00, p = 0.008) compared to healthy control drivers (Figure 3.1).

titel and conditions			
	Healthy Controls	All MCI Patients	p-value
	(n = 20)	(n = 22)	
Collisions	0.3 ± 0.7	0.9 ± 2.1	0.332
	(0-2)	(0-10)	
Speed exceedances	6.2 ± 5.4	7.5 ± 4.9	0.276
-	(0-18)	(0-17)	
Centre line crossings	1.9 ± 2.1	5.4 ± 9.2	0.025
	(0-7)	(0-45)	
Road edge excursions	0.4 ± 0.8	3.9 ± 9.0	0.131
	(0-2)	(0-36)	
Stop signs missed	1.0 ± 1.4	2.3 ± 2.1	0.051
	(0-4)	(0-7)	
Total errors	9.9 ± 5.1	20.0 ± 20.7	0.014
	(1-19)	(2-104)	
% time out of the legal	0.3 ± 0.4	2.3 ± 5.7	0.008
driving lane	(0-1.7)	(0-26.2)	
% time over the speed	2.1 ± 2.0	2.7 ± 2.1	0.326
limit	(0-7.49)	(0.1-7.8)	
SD in speed	16.2 ± 6.1	19.8 ± 1.6	0.078
	(4.8-23.4)	(17.3-22.4)	
Right turn errors*	0.07 ± 0.11	0.13 ± 0.15	0.195
	(0-0.33)	(0-0.5)	
Left turn errors*	0.04 ± 0.09	0.12 ± 0.22	0.246
	(0-0.25)	(0-0.75)	
Left turn + traffic errors*	0.07 ± 0.08	0.13 ± 0.22	0.284
	(0-0.25)	(0-0.75)	
Total turning errors*	0.07 ± 0.06	0.13 ± 0.15	0.083
-	(0-0.21)	(0-0.7)	

Table 3.5. Driving simulator results of Full Scenario 1 & Full Scenario 2 for patients with MCI and controls

Note. Values reported in mean \pm standard deviation (range) format. SD = standard deviation; Total errors = sum of collisions, speed exceedances, centre line crossings, road edge excursions, and stop signs missed. *turning errors include: collisions, centre line crossings, road edge excursions.



Figure 3.2. Maintenance of proper lane positioning across patients with MCI and healthy controls in terms of average (A) number of centre line crossings and (B) percentage of time out of the legal driving lane. A significant difference was found between patients with MCI and healthy controls across both variables. Standard errors are represented in the figure by the error bars attached to each column. *p<0.05, **p<0.01.

Although results did not reach statistical significance for the remaining individual error types (i.e. road edge excursions, stop signs missed, speed exceedances, percentage of time over the posted speed limit, and standard deviation in speed), patients with MCI committed each type of error more than healthy control participants, and the within-group variability (i.e. the standard deviation) of the MCI group was high across all variables of interest.

Patients with MCI committed almost twice as many turning errors as healthy control drivers (0.13 vs. 0.07 errors per turn); however, these results did not reach statistical significance. Furthermore, although patients with MCI committed more errors than healthy controls across all driving conditions, including right turns (0.13 vs. 0.07 errors per turn), left turns (0.12 vs. 0.04

errors per turn), and left turns with traffic (0.20 vs. 0.07 errors per turn), these results also did not reach statistical significance.

Driving Performance of Patients with sd-MCI and md-MCI

Given the heterogeneous presentation of MCI and that patients can demonstrate varying areas and degrees of cognitive impairment, the second aim of the study was to investigate whether certain areas and degrees of simulated driving impairment were characteristic of two prominent subtypes of MCI – individuals with amnestic sd-MCI (n = 11) and individuals with amnestic md-MCI (n = 11). The simulated driving performance of these subtypes was compared to that of cognitively healthy control drivers (n = 20). Parametric tests were used when data were normally distributed and there was homogeneity of variance (i.e. one-way ANOVA); in cases where these assumptions were violated, non-parametric tests were used (i.e. Kruskal-Wallis test).

Please refer to Figure 3.2 below for a comparison of total driving errors across healthy controls, all patients with MCI, patients with sd-MCI, and patients with md-MCI. The Kruskal-Wallis test revealed a significant difference between MCI subtypes and healthy controls in the number of total driving errors committed ($X^2 = 6.769$, p = 0.034), centre line crossings committed ($X^2 = 8.141$, p = 0.017), and percentage of time out of the legal driving lane ($X^2 = 8.206$, p = 0.017). Post-hoc testing revealed that patients with sd-MCI did not perform significantly worse than healthy control drivers on any driving variable of interest. In contrast, patients with md-MCI committed significantly more errors overall (25.4 vs. 9.9, p = 0.024), more centre line crossings (8.2 vs. 1.9, p = 0.010), and spent a greater amount of time out of the legal driving lane (3.9 vs. 0.3, p = 0.010) compared to controls. These results suggest that the significant results found between MCI patients as a whole compared to healthy controls (i.e. lane maintenance behaviour, total driving errors) was likely driven by differences between the md-MCI group and healthy controls.



Figure 3.3. Average number of driving errors (collisions + centre line crossings + speed exceedances + road edge excursions + stop signs missed) across all patients with MCI, patients with sd-MCI, patients with md-MCI, and healthy controls. A significant difference was found between all MCI and healthy controls and with md-MCI and healthy controls, but not sd-MCI and healthy controls. This suggest the significant difference found between MCI patients as a whole and healthy controls was driver by the md-MCI group and not the sd-MCI group. Standard errors are represented in the figure by the error bars attached to each column. *p<0.05.

Please refer to Figure 3.3 for a comparison of turning errors across healthy controls, patients with sd-MCI, and patients with md-MCI. When investigating turning behaviour, the Kruskal-Wallis test demonstrated a significant difference between MCI subtypes and healthy controls on average number of errors committed during more cognitively demanding left turns with traffic ($X^2 = 9.731$, p = 0.008), but not more routine right turns ($X^2 = 3.850$, p = 0.146) and left turns ($X^2 = 1.345$, p = 0.510). The results of post-hoc testing revealed that patients with md-MCI committed significantly more errors than controls during left turns with traffic (0.21 vs. 0.07 errors per turn, p = 0.028); however, patients with sd-MCI committed a similar number of errors as controls

during left turns with traffic (0.04 vs. 0.07 errors per turn, p = 0.451). A summary of the main variables of interest for the control versus MCI subtype analysis across Full Scenario 1 and Full Scenario 2 is reported in Table 3.6 below.



Figure 3.4. Average number of errors (collisions + centre line crossings + road edge excursions) per turn across right turns, left turns, left turns with traffic, and all types of turns for healthy control participants, patients with sd-MCI, and patients with md-MCI. A significant difference was found between patients with md-MCI and healthy controls on the number of errors committed during left turns with traffic. No significant difference was found between patients with sd-MCI and healthy controls across any turning condition. Standard errors are represented in the figure by the error bars attached to each column. *p<0.05.

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	Healthy	sd-MCI	md-MCI	p-value
	Controls	Patients	Patients	
	(n = 20)	(n = 11)	(n = 11)	
Collisions	0.3 ± 0.7^{a}	$0.4\pm0.5^{\mathrm{a}}$	1.4 ± 2.9^{a}	0.485
	(0-2)	(0-1)	(0-10)	
Speed	$6.2\pm5.4^{\mathrm{a}}$	$8.6\pm5.4^{\mathrm{a}}$	6.4 ± 4.4^{a}	0.377
exceedances	(0-18)	(1-17)	(1-13)	
Centre line	1.9 ± 2.1^{a}	$2.6 \pm 2.4^{a,b}$	$8.2 \pm 12.5^{\mathrm{b}}$	0.017
crossings	(0-7)	(0-8)	(0-45)	
Road edge	0.4 ± 0.8^{a}	1.2 ± 1.9^{a}	$6.6 \pm 12.3^{\mathrm{a}}$	0.278
excursions	(0-2)	(0-6)	(0-36)	
Stop signs missed	1.0 ± 1.4^{a}	$1.9\pm2.2^{\mathrm{a}}$	$2.7\pm2.1^{\mathrm{a}}$	0.082
	(0-4)	(0-6)	(0-7)	
Total errors	$9.9\pm5.1^{\mathrm{a}}$	$14.7\pm7.8^{\mathrm{a,b}}$	$25.4\pm27.9^{\mathrm{b}}$	0.034
	(1-19)	(5-28)	(2-104)	
% time out of the	0.3 ± 0.4^{a}	$0.7\pm0.7^{\mathrm{a,b}}$	3.9 ± 7.8^{b}	0.017
legal driving lane	(0-1.7)	(0-2.1)	(0-26.2)	
% speed over the	2.1 ± 2.0	3.2 ± 2.0	2.1 ± 2.2	0.162
speed limit	(0-7.49)	(0.4-6.5)	(0.1-7.8)	
SD in speed	16.2 ± 6.1	20.4 ± 1.4	19.2 ± 1.5	0.067
	(4.8-23.4)	(17.7-22.4)	(17.3-21.8)	
Right turn errors*	0.07 ± 0.11^{a}	0.09 ± 0.13^{a}	$0.17\pm0.15^{\rm a}$	0.146
-	(0-0.33)	(0-0.33)	(0-0.5)	
Left turn errors*	$0.04\pm0.09^{\rm a}$	0.11 ± 0.20^{a}	0.12 ± 0.24^{a}	0.510
	(0-0.25)	(0-0.5)	(0-0.75)	
Left turn + traffic	$0.07\pm0.08^{\rm a}$	$0.04\pm0.06^{a,b}$	$0.21\pm0.21^{\text{b}}$	0.008
errors*	(0-0.25)	(0-0.12)	(0-0.75)	
Total turning	0.07 ± 0.06^{a}	$0.08\pm0.06^{\rm a}$	$0.18\pm0.19^{\rm a}$	0.061
errors*	(0-0.21)	(0-0.17)	(0.04-0.7)	

Table 3.6. Driving simulator results of Full Scenario 1 & Full Scenario 2 for patients with sd-MCI, patients with md-MCI, and controls

Note. Values reported in mean \pm standard deviation (range) format. SD = standard deviation; Total errors = sum of collisions, speed exceedances, centre line crossings, road edge excursions, and stop signs missed. p-value reported for one-way ANOVA/Kruskal Wallis analysis. When statistical assumptions were met, parametric tests were utilized (ANOVA); when assumptions were violated, non-parametric tests were used (Kruskal-Wallis). Post-hoc results (statistical values and p-values) are reported in-text. . ^{a,b}Superscripts denote whether a significant difference emerged between MCI subtypes (md-MCI and sd-MCI) and healthy controls (i.e. shared superscripts indicated no significant difference at p = 0.05). *turning errors include: collisions, centre line crossings, road edge excursions. One participant with MCI (participant 8) differed from the group and was potentially an "outlier" in terms of the total number of errors committed (i.e. 104 errors versus a group average of 20.0) as well as number of centre line crossings committed (i.e. 45 centreline crossing versus a group average of 5.4), and thus may have had greater difficulty than the remainder of the group in terms of simulator performance. However, this individual (1) did not differ from the group cognitively or in terms of mood (anxiety or depression), did not have any visual disturbances, or present with any co-morbidities of concern, (3) did not self-report greater difficulty with real-world driving performance or the simulated driving session and held a valid driver's license, and (4) all driving simulator results remained significant (including analyses comparing: MCI patients vs. controls, sd-MCI vs. controls, md-MCI vs. controls). Thus, we opted to (and were justified in) keep this individual's data in the analysis. Note that this individual did not participate in the fMRI portion of the study (i.e. Chapter 4 of the current thesis) as the participant stated that he/she does not enjoy undergoing MRI scans.

3.2.3.2 Associations between Cognitive Test Scores and Driving Errors in Patients with MCI

The primary purpose for administering the cognitive tests was to report and compare the scores of patients with MCI and healthy controls. A secondary analysis was run to assess the relationship between scores on cognitive tests and driving performance, including the mean completion times for TMT-A and TMT-B as well as the mean scores of the UFOV subtests (i.e. Processing Speed, Divided Attention, and Selective Attention) and MoCA total score. These scores were correlated with mean number of total errors and number of centre line crossings committed by patients with MCI. Given that the correlation analyses were a secondary aim of the study, total errors and number of centre line crossings were selected retrospectively, given that these were the two areas of driving in which patients with MCI performed worse compared to controls. Results are reported below in Table 3.7. Results of the Spearman rank correlation coefficient suggested a significant association between total driving errors and TMT-A time ($r_s = .448$, p = 0.048), UFOV Processing Speed ($r_s = 0.516$, p = 0.017), and UFOV Divided Attention ($r_s = .511$, p = 0.018) in patients with MCI. Among patients with sd-MCI, results revealed a significant correlation between UFOV Processing Speed and total driving errors ($r_s = .773$, p =

0.009). In patients with md-MCI, a significant relationship emerged between UFOV Processing Speed and total driving errors ($r_s = .605$, p = 0.049) as well as number of centre line crossings ($r_s = .666$, p = 0.025), and between UFOV Divided Attention and total driving errors ($r_s = .632$, p = 0.037).

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	All MCI Patients (n = 22)	sd-MCI Patients (n = 11)	md-MCI Patients $(n = 11)$	
Total Driving Errors				
MoCA	095	075	250	
TMT-A time	. 448 †	.151	.276	
TMT-B time	.418	.227	.555	
UFOV Processing Speed	.516 †	.773‡	.605 †	
UFOV Divided	.511 †	.354	.632 †	
Attention UFOV Selective Attention	.370	.152	.588	
Centre Line Crossings				
MoCA	.027	.224	236	
TMT-A time	.304	.061	.179	
TMT-B time	.298	.367	.486	
UFOV Processing	.157	.107	.666 †	
UFOV Divided	.387	.307	.573	
UFOV Selective Attention	.141	.125	.324	

Table 3.7. Associations between cognitive test scores and of total driving errors and centre line crossings in all patients with MCI, patients with sd-MCI, and patients with md-MCI

Note. All values represent Spearman rank correlation coefficients. \dagger indicates significance at p<0.05. \ddagger indicates significance at p<0.01. Total errors = sum of collisions, speed exceedances, centre line crossings, road edge excursions, and stop signs missed

3.3 Discussion

Results from the current study confirm the results of previous research (Devlin et al., 2012; Frittelli et al., 2009; Kawano et al., 2012; Wadley et al., 2009), which suggest that patients with MCI demonstrate difficulty during some aspects of driving, including lane maintenance (Wadley et al., 2009), whereas patients are able to maintain performance at a relatively equivalent level to controls during other aspects of driving. Furthermore, this represents the first study to identify driving behaviours that may be characteristic of two prominent subtypes of MCI, those with amnestic single-domain impairment and those with amnestic multiple-domain impairment. The results of the current study found specific differences in simulated driving performance between these two subtypes of MCI, demonstrating that patients with md-MCI may exhibit greater driving difficulty than patients with sd-MCI, relative to healthy controls, in general, as well as during more cognitively demanding aspects of driving. Furthermore, the driving performance of certain subtypes of MCI (i.e. in the case of the current study, the md-MCI group), may be responsible for the results when you look at the group as a whole (i.e. all patients with MCI together). A discussion specific to each of the hypotheses outlined at the beginning of this thesis (Chapter 2, section 2.2) is detailed below.

3.3.1 Hypothesis 1: Total Errors in Patients with MCI

The results of the current study showed that patients with MCI committed over twice as many simulated driving errors compared to healthy controls (mean = 20.0 vs. 9.9 errors; includes collisions, centre line crossings, road edge excursions, stop signs missed, and speed exceedances). These results are congruent with the first hypothesis outlined in Chapter 2, which predicted that patients with MCI would demonstrate a greater number of total errors than healthy control drivers. However, although patients with MCI committed all types of individual error more than healthy control participants (e.g. collisions, speed exceedances, stop signs missed, centre line crossings, road edge excursions), these results did not reach statistical significance, with the exception of centre line crossings.

Thus, results revealed that the patients with MCI in the current sample had particular difficulty in terms of lane control, as patients with MCI performed significantly worse compared to controls across two separate measures of lane maintenance: number of centre line crossings and percentage of time spent out of the legal driving lane. These findings are consistent with previous research investigating the on-road driving performance of patients with MCI (Wadley et al., 2009). Specifically, Wadley and colleagues (2009) evaluated the on-road performance of 46 patients with MCI and 56 healthy controls. Results suggested that patients with MCI may demonstrate impairment across aspects of driving similar to those identified in the current study, including global rating of driving performance and lane control (Wadley et al., 2009), which were evaluated on a 5-point Likert scale (1= evaluator took control of the car, 2 = unsafe, 3 = unsatisfactory, 4 = not optimal, 5 = optimal) by a certified driving rehabilitation specialist. Furthermore, this finding that patients may be at risk for difficulty in lane control is particularly important, as Ott and colleagues (2012) previously identified that maintenance of proper lane position emerged as a factor critical to safe driving during naturalistic driving involving older adults both with and without cognitive impairment.

3.3.2. Hypothesis 2: Turning Errors in Patients with MCI

Given the subtle nature of the cognitive deficits that are associated with MCI, it was expected that patients would be able to maintain performance during less cognitively demanding aspects of driving, such as right turns, but not during more demanding aspects of driving, such as left turns with oncoming traffic, which require a more extensive set of cognitive and brain resources (Callan et al., 2009; Schweizer et al., 2013).

The results of the current study did not support the above hypothesis. Although patients with MCI committed approximately twice as many simulated driving errors as controls during right turns and approximately three times as many simulated driving errors as controls during left turns, both with and without traffic, results did not reach statistical significance. Again, similar results were obtained during an on-road assessment (Wadley et al., 2009). Wadley and colleagues (2009) rated performance (i.e. from not optimal to optimal) of patients with MCI

during right turns and left turns (not specified whether this included turns with and/or without traffic). Results suggested that patients with MCI were not more likely to receive a less than optimal rating than healthy control drivers during right turns. Patients with MCI were more likely to receive a less than optimal rating compared to controls during the left turn condition; however, after adjusting for age and sex, this result was no longer statistically significant (Wadley et al., 2009).

The results reported by Wadley and colleagues (2009) for the left turn condition, as well as the left turn results of the current study, did not reach statistical significance likely due to the high degree of cognitive, and consequently driving performance, variability inherently present within the MCI population. This variability within the MCI group is likely the result of one key factor, which is the inherent heterogeneous presentation of MCI. Specifically, patients with MCI can present with varying degrees and areas of cognitive impairment, which likely translate to varying degrees and areas of driving impairment. Thus, it could be that certain patients within the MCI population, and certain subtypes of MCI, demonstrate deficits in certain aspects of driving relative to cognitively healthy drivers, particularly more cognitively demanding aspects of driving (e.g. left turns with oncoming traffic). Conversely, other subtypes may not exhibit increased impairments at all, or exhibit impairments during different aspects of driving. For example, those with amnestic sd-MCI may be able to maintain driving performance comparably well to healthy controls, whereas those with md-MCI, who exhibit impairment in cognitive domains that have been repeatedly shown to be implicated in safe driving (e.g. attention, executive function, visuospatial ability) may exhibit difficulties in driving situations that require the integration of these functions (e.g. turning at a high traffic intersection). The current study sought to address this issue by investigating the simulated driving performance of individuals with amnestic sd-MCI and md-MCI.

3.3.3. Hypothesis 3: Driving Profiles of sd-MCI and md-MCI

Given the heterogeneous cognitive presentation of patients with MCI (Albert et al., 2011; Petersen, 2004), the current study sought to identify whether the amnestic single-domain and multiple-domain subtypes of MCI exhibit different areas and degrees of difficulty during simulated driving relative to cognitively healthy adults. To our knowledge, this represents the first study to investigate the driving impairments (using either on-road or simulated driving assessments) characteristic of various subtypes of MCI. It was hypothesized that patients with md-MCI would exhibit greater driving difficulty compared to controls, particularly during more cognitively demanding aspects of driving (e.g. left turns with traffic) and that patients with sd-MCI would perform comparably well to controls across the driving variables and conditions of interest. This prediction was driven by the presence of more widespread cognitive deficits (e.g. attention, executive function, in addition to memory) that are characteristic of the md-MCI group. Furthermore, previous research has suggested that patients with md-MCI, particularly those with memory impairment (i.e. amnestic md-MCI), may be at the greatest risk of functional decline of all subtypes (K. R. Kim et al., 2009).

The results of the current study confirmed the above hypothesis. Post-hoc testing revealed that patients with md-MCI committed significantly more overall errors compared to healthy controls (i.e. collisions, centre line crossings, road edge excursions, stop signs missed, speed exceedances). Relative to cognitively healthy drivers, patients with md-MCI committed 2.56 times the number of errors during the experimental driving simulation. Specifically, patients with md-MCI may be at a particularly high risk of driving difficulty in lane control. This is supported by the results showing that patients with MCI committed over four times as many centre line crossings as healthy controls and spent a significantly greater percentage of time out of the legal driving lane compared to controls (3.9% versus 0.3%). In addition, post-hoc analyses revealed that patients with md-MCI committed significantly more errors than controls during left turns with traffic. In contrast, patients with sd-MCI did not differ significantly from controls across any of the driving variables of interest (i.e. total driving errors, collisions, centre line crossings, turning errors, etc.), results did not reach statistical significance.

The results of the current study suggest that patients with sd-MCI and md-MCI exhibit differing degrees of driving difficulty during compared to cognitively healthy drivers. Furthermore, the different patterns of driving behaviour observed between subtypes is masked when you look at all MCI patients together. When looking at the MCI patient group as a whole, results suggested that patients with MCI in general may be at risk of driving difficulty, particularly during lane

maintenance. However, the subtype analysis revealed, that patients with sd-MCI showed minor to no difficulties (i.e. results did not reach statistical significance) relative to controls across most aspects of driving, whereas patients with md-MCI showed more significant difficulties relative to controls, particularly during lane maintenance (i.e. increased number of centre line crossings and time out of the legal driving lane) and demanding left turns with traffic (i.e. increased number of lane deviations and collisions per turn). The discrepant driving profiles that emerged for sd-MCI and md-MCI patients may be a key factor contributing to the lack of significant results as well as the apparent variability in the turning analysis conducted for all patients with MCI (sd-MCI + md-MCI patients). The high degree of within group variability present in this analysis, which was identified as a factor likely contributing to the lack of significant results for left turns with traffic condition, is likely the result of combining sd-MCI and md-MCI in the analysis.

3.3.4 Cognitive Associations of Driving Performance

TMT-A was moderately associated ($r_s = .448$) with total driving errors in all patients with MCI (sd-MCI + md-MCI); UFOV Processing Speed was strongly associated ($r_s = .516-.773$) with driving errors in patients with MCI (sd-MCI + md-MCI), sd-MCI, and md-MCI; and UFOV Divided Attention was strongly associated ($r_s = .511-.632$) with driving errors in patients with MCI (sd-MCI + md-MCI) as well as patients with md-MCI. Previous research has supported the predictive utility of TMT-A (Grace et al., 2005; Kawano et al., 2012; Ott, Festa, et al., 2008) and the UFOV (Rizzo et al., 1997; Uc et al., 2006) in predicting driving performance in patients with AD and MCI, including simulated driving performance (Kawano et al., 2012; Rizzo et al., 1997). Specifically, Kawano, Iwamoto, Iidaka, and colleagues (2012) reported a significant positive correlation between TMT-A and performance on a car-following task in patients with a-MCI and healthy older drivers (a-MCI, n = 12; older adults, n = 26), although it was not specified whether these patients were single-domain or multiple-domain amnestic. This finding is consistent with the current results, which suggest a moderate correlation between TMT-A and driving errors in patients with amnestic single-domain and multiple domain MCI (sd-MCI + md-MCI). Despite this, other studies have reported small or not significantly significant correlations between TMT-

A (Uc et al., 2006) as well as the UFOV (Rizzo et al., 2001; Uc et al., 2005) and driving performance.

Thus, there a high degree of variability in the results of cognitive predictors of driving performance within the population of AD and MCI across research studies (Bennett, Chekaluk, & Batchelor, 2016). This has been reported for both individual tests as well as batteries and composite scores (Bennett et al., 2016). Due to variability in the results of associations between cognitive test scores and driving errors in this study and previous research, as well as the lack of evidence-based cut-off scores (Bennett et al., 2016), it is not possible to directly translate results into a clinical setting. Thus, there remains no single tool or combination of tools, with sufficient reliability, sensitivity, or specificity, available to assist healthcare professionals in determining when individual patients with MCI require a formal driving assessment. Despite this, the current results suggest that recognizing the inherent variability of the MCI population and differentiating between different subtypes of MCI to reduce this heterogeneity is an important advancement in the current literature. Identifying specific areas and degrees of driving impairment that are characteristic of different subtypes of MCI may be an important first step in the ultimate development of valid tools that can be implemented in a clinical setting.

3.3.5. Limitations

Although the current study offers important insight into the driving performance of patients with MCI, there are a few methodological limitations. It is important to note that despite separating sd-MCI and md-MCI patients, a high degree of within-group variability remained present for both MCI subtypes. This was demonstrated by a consistently larger standard deviation observed in the sd-MCI and md-MCI groups relative to the healthy control group. There are a couple of important factors likely contributing to this persistent variability. First, for both patients with sd-MCI and patients with md-MCI, the degree of cognitive impairment within each of the respective cognitive domains is unique to each patient and variable across patients. For example, each patient with sd-MCI likely had a different degree of memory impairment. Second, unique to the md-MCI group, patients within this subtype may have exhibited cognitive impairment in

different cognitive domains (e.g. attention versus visuospatial function) as well as impairment in a different number of domains (e.g. impairment in two versus three or more domains). Thus, even though separating subtypes of MCI accounted for some of the variability inherently characteristic of the MCI population, variability remains a critical factor influencing results within both the amnestic sd-MCI and amnestic md-MCI subtypes.

The presence of a small sample size is a limitation observed in the vast majority of the driving literature, particularly studies assessing the driving performance of patients with MCI. The current study is no exception. In addition, despite the fact that Wadley and colleagues (2009) obtained similar results to the current study in terms of the driving performance of MCI patients as a whole, it will be important to attempt to replicate the current results that suggest different driving profiles for various subtypes of MCI, using on-road assessments as well as other types of driving simulators (i.e. stationary, immersive simulators). The current study provided preliminary evidence regarding the driving profiles unique to amnestic sd-MCI and amnestic md-MCI patients. It will be important for future research to validate these profiles as well as determine those characteristic of other subtypes of MCI (e.g. executive sd-MCI, non-amnestic md-MCI, etc.) as well as patients with early AD. In particular, a large-scale longitudinal study, using both on-road and simulator technology, would be important to determine the extent to which driving performance may deteriorate over time in patients with MCI. This would involve assessing the driving performance, over time, of various subtypes of MCI (sd-MCI, md-MCI, aMCI, na-MCI), including those maintain diagnostic criteria for MCI and those who go on to develop AD or related dementia.

Finally, driving simulation has been scrutinized for being an invalid representation of driving performance and it has been speculated that the validity of driving simulation depends on the fidelity of the driving simulator. Despite this, the results of other studies have shown that driving simulators are highly related to on-road driving performance (Bedard et al., 2010). Furthermore, validation studies have supported the utility of three-screen (Bedard et al., 2010) and one-screen driving simulators (Gibbons et al., 2014), similar to the one used in the current study, as well as using driving simulation to evaluate lane control (Mayhew et al., 2011) and turning behaviour (Shechtman et al., 2009). In addition, driving simulation can expose patients to complex, and

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potentially dangerous situations in a standardized and safe environment. Thus, driving simulation may represent the ideal technology for isolating the subtle driving impairments that are related to mild deficits in cognitive function that may go otherwise undetected using on-road assessments. Nevertheless, it would be important to replicate the current results using fully immersive driving simulation as well as on-road assessments.

Chapter 4

Investigating the Brain Activation Patterns of Patients with MCI during Simulated Driving Tasks

No screening assessment tool has been consistently demonstrated to be an accurate predictor of driving within the population of MCI. Given this, coupled with the multifaceted nature of driving and the heterogeneous presentation of MCI, it is important to understand the changes in brain activation that are associated with MCI, as well as the different subtypes of MCI, across various aspects of driving (i.e. from more routine to more cognitively demanding driving situations).

Previous fMRI research in cognitively healthy individuals has consistently identified that multiple brain regions are recruited during driving, including parietal, occipital, motor, premotor, cerebellar, and frontal regions (Calhoun et al., 2002; S. C. Chung et al., 2014; Graydon et al., 2004; Hirth et al., 2007; H. S. Kim et al., 2014; Y.-O. Li et al., 2012; Mader et al., 2009; Schweizer et al., 2013; Spiers & Maguire, 2007; Uchiyama et al., 2003). A few studies have used fMRI and driving simulation in healthy individuals to investigate the brain regions recruited during turning (Callan et al., 2009; Schweizer et al., 2013; Spiers & Maguire, 2007). Schweizer and colleagues (2013) exposed young healthy participants to a variety of turning conditions, including more routine right and left turns without oncoming traffic to more demanding left turns at a high traffic intersection. Right and left turns without oncoming traffic were associated with greater activation in posterior brain regions, including occipital, parietal, motor, and cerebellar regions compared to straight driving, with greater activation observed during left turns than right turns. Executing left turns with oncoming traffic was associated with greater activation in these posterior brain regions as well as increased activation in medial and anterior regions, including the superior frontal gyrus and the cingulate cortex (Schweizer et al., 2013). Furthermore, Callan and colleagues (2009) reported that resolving uncertainty in decision making at busy intersections among cognitively healthy adults was associated with increased activation in the anterior cingulate and the amygdala. Thus, executing more cognitively complex driving

manoeuvres, such as turning at high traffic intersections, is associated with recruitment of a more extensive set of brain regions, including both posterior and anterior regions.

This represents the first study to identify the brain activation patterns that are characteristic of patients with MCI, as well as to provide preliminary evidence of the activation patterns of the amnestic single domain (sd-MCI) and amnestic multiple-domain (md-MCI) subtypes of MCI, during different simulated driving conditions of varying levels of complexity. Identifying the brain regions involved in these manoeuvres (Chapter 4) will be important for understanding which brain networks (that are related to driving) are affected by MCI.

4.1 Experimental Materials and Methods

4.1.1 Statement of Ethical Approval

Ethical approval for the current study was obtained from the Research Ethics Board (REB) at St. Michael's Hospital, Toronto Canada under REB 16-036 titled, "Investigating the driving behaviour and underlying neural networks in aging cohorts and patients with neurological conditions". All participants provided written informed consent before participating in the research study.

4.1.2 Participants

Sixteen (16) patients with MCI (mean age = 67.3; mean years of education 15.1; Male = 81.2%), including six patients with amnestic sd-MCI (mean age = 68.3; mean years of education = 15.3; Male = 66.7%) and ten patients with amnestic md-MCI (mean age = 66.7; mean years of education 14.9; Male = 90%) were recruited from the Memory Disorders Clinic at St. Michael's

Hospital. For comparison, 16 age- and sex-matched cognitively healthy controls mean age = 66.2; mean years of education 16.0; Male = 81.2%) were recruited from the community.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for this part of the study were highly similar to the inclusion and exclusion criteria outlined in Chapter 3 with two exceptions. One additional inclusion criterion was fMRI-compatibility. Potential patients or healthy control participants with any contraindications to 3.0 T MRI (e.g. claustrophobia, metal implants including stents and hip replacements) were excluded from the fMRI and driving session. In addition, potential participants with significant hearing loss were excluded. Participants were required to comprehend turning instructions over the loud noise of the fMRI data acquisition and respond correctly. Thus, it would not be possible to complete the experimental driving sessions with significant hearing loss.

4.1.3 Experimental Procedures

The experimental design aimed to combine fMRI and a fully immersive fMRI-compatible driving simulator to compare the brain activation of patients with MCI, including individuals with amnestic sd-MCI (n = 6) and amnestic md-MCI (n = 10) as well as healthy control participants across driving tasks of various levels of complexity, including right and left turns without traffic as well as left turns with oncoming traffic. Both patients with MCI and healthy controls completed four driving scenarios in the MRI, including two training sessions and two experimental sessions. The entire session took approximately 1.5 hours to complete. The session involved: (1) the pre-scanning procedure (30 minutes) and (2) the fMRI and driving simulation session (one hour).

4.1.3.1 Pre-Scanning

Before the fMRI and driving session began, all participants were shown a brief PowerPoint presentation on what to expect during the MRI session along with detailed instructions from the research personnel. The presentation included pictures and detailed descriptions of the set-up. Furthermore, instructions were provided on how to manipulate the equipment. Descriptions of each of the scanning sequences and driving tasks were given. Participants were reminded of the importance of keeping one's head as still as possible during imaging. In addition to the presentation, participants reviewed their MRI screening form with the MRI technologist. If participants required corrected vision, then MR-compatible glasses were prepared with the appropriate prescription.

4.1.3.2 fMRI and Driving Simulation Session

After the participant entered the MRI room, the research personnel described and explained the equipment. After lying down in the magnet bore, the distance of the accelerator and brake pedals was adjusted for optimal participant comfort. The participant was asked to press down on the accelerator and the brake pedal to become comfortable with the weight necessary to accelerate and brake properly. The steering wheel was adjusted so that it was in a comfortable position, and the research personnel guided the participant through an example of a right and left turn procedure. Pads were placed under the arms and elbows of each participant to increase comfort and minimize limb motion that could potentially translate to head motion. Sponges were placed in the spaces of the head coil to help minimize head motion. An adjustable mirror was placed on the MRI head coil. Looking through the mirror allowed participants to see a screen in which the driving scenarios (Figure 3.1) were projected using an Avotec Incorporated high resolution projector (model SV-6011, Avotec Incorporated). The participant was then instructed on the emergency call bell and was fitted with the fMRI head set (Avotec Incorporated, Conformal HeadsetTM). The headset made it possible for the research personnel to communicate with the participant between each imaging procedure and for the participant to hear the audio instructions during the simulated driving scenarios.

The driving scenarios (i.e. including both training and experimental sessions) were standardized across all participants, including both patients with MCI and healthy controls. All participants were presented with the same intersections (i.e. including type and location), audio instructions, levels of traffic, length of runs, etc. During the driving simulator scenarios, the audio instructions (e.g. turn left at the stop sign") were embedded into the scenarios and were presented to participants approximately 100 metres (i.e. between 5-10 seconds) before each event (e.g. an intersection controlled by a stop sign). Driving variables of interest that were collected by the STISIM software during the fMRI and driving session included: collisions, whether participants turned the appropriate direction at each intersection, and when each turn started and ended.

fMRI Training Sessions

The purpose of the two training sessions were for the participants to become familiar and comfortable with the driving simulator and fMRI equipment, including the steering wheel, accelerator, brake, the virtual reality environment within the MRI, and the sound system. Both training sessions were approximately 6-7 minutes in length. During the first training session, no fMRI data were collected. This allowed the participants to acclimate to the equipment with feedback provided by the research personnel. The first training session involved straight driving with some turning without any oncoming traffic. During the second training session, the structural scan was acquired (see section 4.1.3.3 below). This session allowed participants to become comfortable using the driving simulator while an MRI sequence was being run. The second training session involved straight driving as well as right turns, left turns and left turns with oncoming traffic. All participants reported feeling comfortable with the equipment and the virtual reality environment prior to moving to the experimental sessions.

fMRI Experimental Sessions

After the training sessions, the fMRI experimental driving sessions were administered. Both experimental sessions were approximately 10-12 minutes in length. The experimental driving sessions were synchronized in time, using a trigger, so that when fMRI data acquisition began, the driving scenario started automatically (i.e. time point "0" was the same for both the fMRI data and the driving simulation data). Between each of the training and experimental sessions,

the research personnel ensured that the participants felt comfortable, felt able to proceed to the next scenario, and that the headset was adjusted to an appropriate volume.

The experimental sessions were highly similar to the second training session and involved straight driving as well as executing right and left turns both with and without oncoming traffic (i.e. including other vehicles as well as pedestrians). Each turning condition was separated by approximately 10-15 seconds of straight driving, which served as the baseline condition in the statistical analyses. Participants were exposed to 4-7 variations of each type of turning condition.

4.1.3.3 fMRI Sequencing Protocol and Data Acquisition

The MRI scanning procedures were conducted at St. Michael's Medical Imaging Department in a research-dedicated 3.0 T Siemens Magnetom Syngo Skyra scanner with a 20-channel head coil. All sequences were acquired by a certified MRI technologist. Imaging acquisition took approximately 30-40 minutes to collect. The anatomical scan was acquired with T1-weighted imaging (MPRAGE; echo time (TE) = 2.54 ms, TR = 2000 ms, 176 slices, thickness = 1.0 mm, gap = 0 mm, field of view (FOV) = 256 mm, $1.0 \times 1.0 \times 1.0$ voxels). Functional task-based (i.e. driving simulation) MRI was acquired using T2*-weighted fast echo-planar images (EPI; echo time (TE) = 30.0 ms, TR = 2000 ms, 32 slices, thickness = 4.0 mm, gap = 0.5 mm, field of view (FOV) = 200 mm, $3.1 \times 3.1 \times 4.0$ voxels).

4.1.4 Data Extraction and Analysis

Using the program MRIconvert, all Digital Imaging and Communications in Medicine (DICOM) image files that were collected by the MRI system were converted to Neuroimaging Informatics Technology Initiative (NIfTI) files. Functional MRI (BOLD) data pre-processing and analyses were conducted using Preprocessing OptimizatioN Toolkit (PRONTO) software, which provides the fast optimization of preprocessing pipelines and analyses of BOLD fMRI (Churchill, Oder, et al., 2012; Churchill, Yourganov, et al., 2012; *PRONTO User's Manual (v 8.5)*, n.d.). The

PRONTO algorithm detects the set of preprocessing steps that is best suited for a particular dataset and optimizes the reproducibility of post-processing analysis results (*PRONTO User's Manual* (v 8.5), n.d.; Strother et al., 2002). The results of previous research suggest that PRONTO significantly improves signal detection, the reliability of brain activations, and the sensitivity of brain-behaviour correlations (Churchill, Oder, et al., 2012; Churchill, Yourganov, et al., 2012; *PRONTO User's Manual* (v 8.5), n.d.).

Prior to pre-processing and analyzing the fMRI data, the onset and durations for each turning condition (i.e. right turns, left turns, and left turns with oncoming traffic) were extracted for both experimental sessions by research personnel. The time points were double checked to ensure that there were no errors. These timing data were converted to PRONTO format and included the following information: the unit in which task onset/duration was measured (i.e. seconds), the time between scan volumes (i.e. TR = 2000 ms), the type of task paradigm (i.e. event-related design), name of each condition (e.g. right turns, left turns, left turns with traffic), onsets for each event within each condition (in seconds), and durations of each event within each condition (in seconds). Straight driving served as the baseline condition in the current analysis. Thus, brain activation of each turning condition was compared to straight driving.

4.1.4.1 Pre-Processing of fMRI Data

An in-house script was used to perform pre-processing and analyses. All scripts were run using Matlab. A pipeline file was created for the fMRI dataset. This file specified: the name and location of the unprocessed fMRI data to be optimized, the name and location for the final processed and optimized outputs, the number of image volumes dropped at the start and end of each fMRI data acquisition run (first and last two TRs), the name and location of the task textfiles (see section 4.1.4 above), and the name and location of the 3D structural brain image.

PRONTO was used to test all combinations of a set of 12 preprocessing steps and to identify the optimal pipeline (i.e. the one that gives the highest quality output data) for the current dataset. Thus, multiple pipeline options were tested to ensure that the pipeline chosen optimized output data quality. The current analysis utilized a standard, conservative pipeline (i.e. a single

conservative set of pre-processing steps across participants). This type of pipeline is highly similar to standard fMRI processing pipelines. The conservative pipeline minimizes potential noise confounds with minimal concern for signal optimization (*PRONTO User's Manual (v 8.5)*, n.d.). The pre-processing steps that were utilized include: rigid-body motion correction with optimal reference for volume section, basic outlier censoring, slice-timing correction, spatial smoothing, temporal linear detrending, and motion parameter regression. Preprocessing steps include both AFNI (Analysis of Functional NeuroImaging; R. Cox, 1996) and in-house developed functions. Spatial normalization of participants to an anatomical template was conducted using FMRIB Software Library (FSL). A General Linear Model (GLM) analysis was conducted, which generated group masks that were used for post-hoc analyses. Based on the results of quality control analyses, data that were preprocessed using the conservative pipeline were chosen for post-hoc analyses.

4.1.4.3 Post-Hoc Analyses

Post-hoc analyses involved one-sample bootstrap procedures to identify the brain activation patterns characteristic of patients with MCI, cognitively healthy controls, patients with sd-MCI, and patients with md-MCI. Analyses were conducted and brain activation maps were generated for the right turn, left turn, and left turn with traffic conditions for the one-sample procedures. The appropriate cluster size threshold for the current sample of participants was determined using FSL. Thus, voxels were subsequently adjusted for multiple comparisons at a false discovery rate (FDR) of q = 0.05 with a minimum cluster size of 34. Visual comparisons were made between healthy controls and patients with MCI (including subtypes of sd-MCI and md-MCI). Images were generated and localization of activation was achieved using MRIcron software (Rorden, 2015). Montreal Neurological Institute and Hospital (MNI) coordinates (X, Y, and Z) and peak levels of activation were obtained for each activated region. The Automated Anatomical Labelling (AAL) atlas was used to identify the regions of interest.

4.2 Results

4.2.1 Demographic and Cognitive Data

Statistical analyses revealed no significant difference between patients with MCI (including all patients, sd-MCI patients, and md-MCI patients) and healthy controls on mean age, mean years of education, sex, driving experience (i.e. years of experience and hours of driving per week), or number of self-reported accidents. Demographic information is reported in Table 4.1.

A comparison of cognitive profiles was conducted between patients with MCI who took part in the fMRI experiment (Chapter 4) and the patients with MCI who only completed the behavioural experiment (Chapter 3). Although there was a high degree of overlap between participants who completed the two experiments, this analysis was conducted to ensure that the participants who completed the behavioural experiment only, and were unable to undergo the fMRI experiment (e.g. due to the claustrophobia), did not differ significantly from the patients who underwent fMRI. Results suggested that there was no significant difference between the behavioural group (n = 22) and the fMRI group (n = 16) on mean age, number of years of driving experience, hours per week spent driving, TMT-A time, TMT-B time, MoCA total score, or any of the MoCA subtest scores. Furthermore, no individual MCI participant who only completed the behavioural experiment obtained cognitive scores greater than 2.5 standard deviations above or below the mean scores of the MCI patients who completed fMRI.

	Healthy	All MCI	sd-MCI	md-MCI	p-value
	Controls	Patients	Patients	Patients	
	(n = 16)	(n = 16)	(n = 6)	(n = 10)	
Age, years	66.2 ± 10.1	67.3 ± 10.2	68.3 ± 9.3	66.7 ± 11.2	0.969†
	(47-83)	(50-85)	(59-85)	(50-83)	0.915‡
Education, years	16.0 ± 2.3	15.1 ± 2.9	15.3 ± 3.3	14.9 ± 2.8	0.361†
	(12-20)	(12-20)	(12-20)	(12-19)	0.586‡
Sex, n (%) Male	13 (81.2%)	13 (81.2%)	4 (66.7%)	9 (90%)	1.000†
					0.512‡
Driving experience,	48.3 ± 11.7	46.8 ± 9.9	48.7 ± 6.2	45.7 ± 11.7	0.699†
years	(16-65)	(30-64)	(43-60)	(30-64)	0.811‡
Driving experience,	6.2 ± 6.3	6.2 ± 4.6	6.8 ± 2.8	5.8 ± 5.6	0.642†
hours/week	(0-20)	(0-15)	(3-10)	(0-15)	0.640‡
Self-reported	1.1 ± 1.1	1.5 ± 1.3	1.3 ± 1.2	1.6 ± 1.4	0.491†
accidents	(0-3)	(0-5)	(0-3)	(0-5)	0.743‡
MoCA Total Score	28.1 ± 1.1^{a}	$24.2\pm1.4^{\text{b}}$	23.8 ± 1.5^{b}	$24.4\pm1.4^{\text{b}}$	0.000†
	(26-30)	(22-27)	(22-26)	(22-27)	0.000;
Note. Values reported	in mean ±	standard deviation	n (range) fo	ormat. MoCA =	Montreal

Table 4.1. Demographic characteristics of patients with MCI and healthy controls

Cognitive Assessment. †p-value for healthy control versus all MCI patients comparison (independent samples t-test/Mann-Whitney U). ‡p-value for one-way ANOVA/Kruskal Wallis analysis (healthy control versus sd-MCI versus md-MCI comparison). When statistical assumptions were met, parametric tests were utilized (independent samples t-test/ANOVA); when assumptions were violated, non-parametric tests were used (Mann-Whitney U/Kruskal-Wallis). Post-hoc results (statistical values and p-values) are reported in-text. ^{a,b}Superscripts denote whether a significant difference emerged between MCI subtypes (md-MCI and sd-MCI) and healthy controls (i.e. shared superscripts indicated no significant difference at p = 0.05). *self-reported quality of driving is assessed on a 5-point Likert scale (1 = poor; 2 = fair; 3= average; 4 = good; 5 = excellent). §self-reported level of difficulty (0 = no difficulty; 1 = little difficulty; 2 = moderate difficulty; extreme difficulty).

n, number of participants; % = percentage of participants; MCI = mild cognitive impairment; sd-MCI = amnestic single-domain MCI; md-MCI = amnestic multiple-domain MCI

4.2.2 Functional MRI Activation during Driving Simulation

All one-sample bootstrap procedures (i.e. for patients with MCI, healthy controls, patients with sd-MCI, and patients with md-MCI) revealed reliable and significant activation patterns in regions previously identified as being recruited during various driving tasks (Callan et al., 2009; Just et al., 2008; Schweizer et al., 2013), including parietal, occipital, motor, premotor, supplemental motor, cerebellar, and frontal regions, across one or more driving conditions.

4.2.2.1 Brain Activation Patterns of Patients with MCI Relative to Healthy Control Drivers

Right Turns

One sample bootstrap analyses revealed significant positive activation in multiple brain regions in both healthy controls and patients with MCI, particularly in posterior and medial brain areas (Figure 4.1). Specifically, both patients and controls showed significant positive activation, bilaterally, in the cerebellum; superior, middle, and inferior occipital lobes; inferior and superior parietal lobes; fusiform gyrus; calcarine fissure; lingual gyrus; anterior and middle cingulum; pre- and post-central gyri; supplemental motor areas; precuneus; cuneus; putamen; thalamus; insula; as well as the right inferior and middle temporal lobes, right middle and orbitofrontal cortex, right superior frontal cortex, and the right triangular portion of the inferior frontal gyrus.

Patients with MCI showed significant positive activation in multiple regions in which controls did not demonstrate positive activation, including: the left inferior, middle, and superior temporal cortex; the left middle and inferior orbitofrontal cortex; and the left superior frontal cortex. Furthermore, compared to cognitively healthy drivers, individuals with MCI showed more recruitment of the cerebellum (primarily the left), the right middle temporal cortex, the left middle and inferior occipital lobes, left calcarine fissure, and the left supplemental motor area. Furthermore, cognitively healthy drivers showed negative activation bilaterally in the middle and superior temporal lobes, the inferior occipital cortices, as well as the triangular portion of the

inferior frontal gyri. Patients with MCI showed no negative activation. Healthy controls exhibited more recruitment of the right lingual gyrus compared to patients with MCI.



Figure 4.1. One sample bootstrap activation maps of cognitively healthy controls (top row) and patients with MCI (bottom row) during right turns. Patients with MCI demonstrated more positive activation compared to healthy controls, primarily in posterior and medial brain areas (e.g. occipital, temporal, cerebellar regions) as well as a few frontal regions (left middle and inferior orbitofrontal cortex). Patients with MCI exhibited less negative activation relative to healthy controls in temporal and occipital regions. Images are represented as axial slices (z = 24, -4, 36, 16, and 56 in MNI coordinates). Positive activation is represented in red scale (3.0 to 5.0) and negative activation in represented in blue scale (-3.0 to -5.0). L = left side of the brain; R = right side of the brain; MNI = Montreal Neurological Institute.

Left Turns without Traffic

Across left turns without oncoming traffic, one sample bootstrap analyses revealed significant positive activation in multiple brain regions in both healthy controls and patients with MCI (Figure 4.2). Specifically, both patients and controls showed significant positive activation bilaterally in the cerebellum; superior, middle, and inferior occipital lobes; superior, middle, and inferior temporal lobes; inferior and superior parietal lobes; fusiform gyrus; calcarine fissure; lingual gyrus; middle cingulum; pre- and post-central gyri; supplemental motor areas; precuneus; cuneus; putamen; thalamus; superior and middle frontal cortex; the inferior and middle orbitofrontal cortex as well as the right insula, right triangular portion of the inferior frontal gyrus, and left anterior cingulum.

Drivers with MCI demonstrated significant positive activation relative to controls (i.e. who did not demonstrate significant positive activation) in the left superior medial frontal cortex, right anterior cingulum, and the left insula. Compared to cognitively healthy drivers, individuals with MCI appeared to show more positive activation (i.e. larger peak activation) in multiple brain regions, including the left superior occipital cortex, the right inferior parietal cortex, left calcarine fissure, bilateral postcentral gyri, and bilaterally in the supplemental motor area. Controls exhibited negative activation bilaterally in the middle and superior temporal lobes and the inferior occipital lobes as well as the left middle frontal cortex and the right triangular portion of the inferior frontal gyrus. Patients with MCI showed no negative activation. Healthy controls showed a larger peak activation in the left middle temporal lobe compared to drivers with MCI.



Figure 4.2. One sample bootstrap activation maps of cognitively healthy controls (top row) and patients with MCI (bottom row) during left turns without oncoming traffic. Patients with MCI demonstrated more positive activation compared to healthy controls, primarily in posterior and medial brain areas (e.g. occipital and parietal regions, insula) and, to a lesser extent, in frontal regions (e.g. anterior cingulum, superior medial frontal cortex). Patients with MCI exhibited no negative activation whereas to healthy controls showed negative activation in temporal, occipital, and frontal regions. Images are represented as axial slices (z = 24, -4, 36, 16, and 56 in MNI coordinates). Positive activation is represented in red scale (3.0 to 5.0) and negative activation in represented in blue scale (-3.0 to -5.0). L = left side of the brain; R = right side of the brain. MNI = Montreal Neurological Institute.

Left Turns with Oncoming Traffic

Across left turns with oncoming traffic, one sample bootstrap analyses revealed significant positive activation in multiple brain regions in both healthy controls and patients with MCI (Figure 4.3). Both patients and control groups showed significant positive activation bilaterally in the cerebellum; superior, middle, and inferior occipital lobes; middle and inferior temporal

lobes; inferior and superior parietal lobes; fusiform gyrus; calcarine fissure; lingual gyri; middle cingulum; anterior cingulum; pre- and post-central gyri; supplemental motor areas; precuneus; cuneus; putamen; thalamus; superior frontal cortices; and the inferior orbitofrontal cortices as well as the right superior temporal lobe, right insula, right middle frontal cortex, the left middle orbitofrontal cortex, the right triangular portion of the inferior frontal gyrus, and the left superior medial frontal cortex.

Patients with MCI showed significant positive activation in multiple medial and frontal regions in which controls did not demonstrate significant positive activation, including: the left superior temporal cortex, the left middle frontal cortex, the right middle orbitofrontal cortex, the left superior orbitofrontal cortex, the right superior medial frontal cortex, the left triangular portion of the inferior frontal gyrus, and the left insula.

Compared to cognitively healthy drivers, patients with MCI exhibited greater positive activation (i.e. a larger peak activation), bilaterally, in the left cerebellum, right fusiform, right middle occipital lobe, left superior occipital lobe, the bilateral inferior and superior parietal cortex, bilaterally in the middle cingulum, the left anterior cingulum, the left lingual gyrus, the bilateral precuneus, the right post-central gyrus, and the left precentral gyrus. Controls demonstrated significant negative activation bilaterally in the middle and superior temporal lobes as well as the inferior occipital lobes. Patients with MCI showed no negative activation. Controls demonstrated a larger peak activation compared to patients with MCI in the right calcarine fissure.



Figure 4.3. One sample bootstrap activation maps of cognitively healthy controls (top row) and patients with MCI (bottom row) during left turns with oncoming traffic. Patients with MCI demonstrated significant positive activation compared to healthy controls, primarily in medial (e.g., superior temporal cortex, insula) and frontal regions (e.g. middle and superior medial frontal cortex, orbitofrontal cortices, triangular portion of the inferior frontal gyrus). Patients with MCI exhibited less negative activation relative to healthy controls in temporal and occipital regions. Images are represented as axial slices (z = 24, -4, 36, 16, and 56 in MNI coordinates). Positive activation is represented in red scale (3.0 to 5.0) and negative activation in represented in blue scale (-3.0 to -5.0). L = left side of the brain; R = right side of the brain. MNI = Montreal Neurological Institute.

4.2.2.2 Brain Activation Patterns of Single-Domain and Multiple-Domain MCI Relative to Healthy Control Drivers

Preliminary analyses were conducted to look at the brain activation patterns of patients with sd-MCI (n = 6) and md-MCI (n = 10). Across all turning conditions (i.e. right turns, left turns, left

turns with oncoming traffic), patients with sd-MCI tended to show significant positive activation in which controls did not or a greater positive peak activation relative to cognitively healthy control drivers. This positive activation was observed in brain regions previously identified as being involved in driving (temporal, parietal, frontal regions). In contrast, patients with md-MCI tended not to show significant positive activation in regions in which controls demonstrated significant positive activation as well as lower peak activation relative to controls.

Right Turns

Both patients with sd-MCI and md-MCI demonstrated activation in areas similar to cognitively healthy adults (see Figure 4.4)—cerebellar (bilateral); fusiform (bilateral); inferior, middle, and superior occipital (bilateral); inferior, middle, and superior temporal (bilateral); inferior and superior parietal (bilateral); putamen (bilateral); thalamus (bilateral); insula (left); calcarine fissure (bilateral); lingual gyri (bilateral); cuneus (bilateral); pre- and post-central gyri (bilateral); supplemental motor (bilateral); middle cingulum (bilateral); precuneus (bilateral); and superior frontal (bilateral) regions. Controls exhibited negative activation bilaterally in the middle and superior temporal lobes as well as the inferior occipital lobes.

Patients with sd-MCI showed significant positive activation in multiple brain regions, primarily medial and frontal areas, in which controls did not demonstrate significant positive activation, including: the left inferior, middle, and superior temporal cortex; bilateral middle frontal cortex, the bilateral middle orbitofrontal cortex, the left inferior orbitofrontal cortex, bilateral superior frontal cortex, bilateral medial superior frontal cortex, and the left triangular portion of the left inferior frontal gyrus. Furthermore, patients with sd-MCI showed a larger peak activation compared to healthy control drivers in the left cerebellum, right middle and superior temporal cortex, bilateral putamen, bilateral thalamus, bilateral insula, right triangular portion of the inferior frontal gyrus, left lingual gyrus, bilateral anterior cingulum, bilateral cuneus, bilateral precuneus, bilateral pre- and post-central gyri, and the right supplemental motor cortex.

In contrast, patients with md-MCI did not exhibit significant positive activation in anterior brain regions in which controls did, including the anterior cingulum, the right inferior orbitofrontal

cortex, and the right triangular portion of the inferior frontal gyrus. Patients with md-MCI also showed a lower peak activation in the right cerebellum, right superior occipital cortex, right putamen, right pre- and post-central gyri, and right insula. However, patients with md-MCI showed a higher peak activation relative to controls in the left inferior and superior temporal cortex and the superior frontal cortex.


Figure 4.4. One sample bootstrap activation maps of cognitively healthy controls (top row), patients with single-domain (sd-) MCI (middle row), and patients with multiple-domain (md-) MCI (bottom row) during right turns. Patients with sd-MCI demonstrated a greater peak activation compared to healthy controls, primarily frontal and medial regions (e.g. middle frontal cortices, orbitofrontal cortices, anterior cingulum, middle cingulum). Patients with md-MCI demonstrated a lower peak activation compared to healthy controls in multiple brain areas (e.g. inferior occipital lobe, cerebellum, anterior cingulum). Patients with sd-MCI and md-MCI exhibited less negative activation relative to healthy controls in temporal and occipital regions. Images are represented as axial slices (z = 24, -4, 36, 16, and 56 in MNI coordinates). Positive activation is represented in red scale (3.0 to 5.0) and negative activation in represented in blue scale (-3.0 to -5.0). L = left side of the brain; R = right side of the brain. MNI = Montreal Neurological Institute.

Left Turns without Traffic

Both patients with sd-MCI and md-MCI, as well as healthy controls, exhibited activation in regions similar to the right turn (see Figure 4.5). Furthermore, similar to right turns, during left turns without oncoming traffic, patients with sd-MCI showed significant positive activation in multiple brain areas relative to controls, particularly in frontal (e.g. superior medial, middle frontal brain regions, etc.) and medial regions (e.g. insula). In addition, patients with sd-MCI showed a larger peak activation relative to controls in multiple brain areas (i.e. frontal, medial, and posterior), including the bilateral cerebellum; bilateral inferior, right middle, and right superior temporal cortex; right inferior, bilateral middle, and left superior occipital cortex, the right inferior and bilateral superior parietal cortex; bilateral superior frontal cortex; right triangular portion of the inferior frontal cortex; right under cortex; right middle orbitofrontal cortex; right middle and right superior frontal cortex; right precentral gyrus; bilateral supplemental motor area; and right precuneus.

Also similar to the right turning condition, during left turns without oncoming traffic, patients with md-MCI did not exhibit significant positive activation relative to controls primarily in medial and frontal regions, including the left superior temporal cortex and the right middle frontal cortex. Patients with md-MCI also showed a lower peak activation than controls in the middle temporal cortex, right inferior occipital cortex, as well as the left inferior and superior parietal cortex. However, patients with md-MCI showed a higher peak activation relative to controls in the right middle and left superior occipital cortex, the right inferior parietal cortex, and the right superior frontal cortex.



Figure 4.5. One sample bootstrap activation maps of cognitively healthy controls (top row), patients with single-domain (sd-) MCI (middle row), and patients with multiple-domain (md-) MCI (bottom row) during left turns without traffic. Patients with sd-MCI demonstrated significant positive activation in regions controls did not, including primarily frontal and medial regions (e.g. middle frontal cortex, superior medial frontal cortex, anterior cingulum, insula). Patients with md-did not exhibit significant positive activation in anterior and medial regions in which healthy controls did (e.g. middle frontal, superior temporal cortices). Images are represented as axial slices (z = 24, -4, 36, 16, and 56 in MNI coordinates). Positive activation is represented in red scale (3.0 to 5.0) and negative activation in represented in blue scale (-3.0 to - 5.0). L = left side of the brain; R = right side of the brain. MNI = Montreal Neurological Institute.

Left Turns with Oncoming Traffic

Both patients with sd-MCI and md-MCI, as well as healthy controls, exhibited activation in regions similar to the right and left turning conditions without oncoming traffic (see Figure 4.6). Relative to healthy control drivers, patients with sd-MCI showed significant activation in multiple anterior brain regions in which controls did not, including the left middle frontal cortex, the right middle and bilateral superior orbitofrontal cortex, left triangular portion of the inferior frontal cortex, bilateral inferior frontal operculum, and right superior medial frontal cortex as well as the left insula. Thus, compared to the left turns without traffic condition, patients with sd-MCI showed significant positive activation in more frontal brain regions compared to healthy controls. Patients with sd-MCI also showed a higher peak activation in the right cerebellum; bilateral fusiform; right inferior, right middle, and left superior temporal cortex; left middle and right superior occipital cortex; bilateral inferior and superior parietal cortex; right superior and middle frontal cortex; bilateral inferior orbitofrontal cortex; right triangular portion of the inferior frontal gyrus; left superior medial frontal cortex; right putamen; right thalamus; right insula; bilateral anterior and middle cingulum; bilateral supplemental motor area; right postcentral gyrus; the right cuneus; and bilateral precuneus. Patients with sd-MCI showed a lower peak activation relative to controls in the right calcarine fissure and the left cuneus.

Patients with md-MCI did not exhibit significant positive activation in multiple brain regions relative to controls, including posterior (e.g. right inferior occipital cortex), medial (left inferior temporal, left putamen), and frontal brain regions (e.g. left superior medial frontal cortex, right anterior cingulum, left superior frontal cortex, left middle and inferior orbitofrontal cortex). Thus, compared to the left turn without traffic condition, patients with md-MCI did not exhibit positive activation in more brain regions, primarily frontal, relative to controls. Patients also demonstrated a lower peak activation in the left fusiform, right lingual gyrus, left postcentral gyrus, and right precentral gyrus relative to controls. However, patients with md-MCI also showed significant positive activation in regions in which controls did not (i.e. left middle frontal cortex, left superior orbitofrontal cortex, left insula).



Figure 4.6. One sample bootstrap activation maps of cognitively healthy controls (top row), patients with single-domain (sd-) MCI (middle row), and patients with multiple-domain (md-) MCI (bottom row) during left turns with oncoming traffic. Patients with sd-MCI demonstrated significant positive activation in multiple regions in which healthy controls did not, primarily frontal regions (e.g. middle frontal cortex, orbitofrontal brain regions). Patients with md-MCI failed to demonstrate significant positive activation in multiple roccipital cortex), medial (inferior temporal cortex), and frontal regions (e.g. anterior cingulum, middle and inferior orbitofrontal regions, frontal superior regions). Patients also showed significant positive activation in frontal (superior orbitofrontal cortex) and medial regions (e.g. insula) in which controls did not. Images are represented as axial slices (z = 24, -4, 36, 16, and 56 in MNI coordinates). Positive activation is represented in red scale (3.0 to 5.0) and negative activation in represented in blue scale (-3.0 to -5.0). L = left side of the brain; R = right side of the brain. MNI = Montreal Neurological Institute.

4.3 Discussion

This study is the first to (1) identify the brain activation patterns characteristic of patients with MCI during simulated driving and (2) explore the activation patterns that are associated with different subtypes of MCI, including amnestic sd-MCI and amnestic md-MCI. Results revealed that patients with MCI, including single-domain and multiple-domain subtypes, demonstrate systematic differences in brain activation compared to cognitively healthy drivers and suggest that patients with sd-MCI and md-MCI may exhibit different patterns of brain activation, unique to each subtype, across simulated driving conditions of varying levels of complexity. Furthermore, the extent of deviation in activation between patients with MCI and controls appeared to increase across driving conditions of increasing complexity (i.e. from right turns, to left turns, to left turns with oncoming traffic). A discussion specific to each of the hypotheses outlined at the beginning of this thesis (Chapter 2) is detailed below:

4.3.1 Hypothesis 1: Reliable Activation Patterns in Patients and Controls

It was hypothesized that both patients with MCI and cognitively healthy controls would exhibit reliable activation in brain regions previously identified as being recruited during driving (Callan et al., 2009; S. C. Chung et al., 2014; Just et al., 2008; Schweizer et al., 2013). The results of the current study confirmed this hypothesis, demonstrating reliable brain activation for both patients and controls in occipital, parietal, cerebellar, motor (including premotor and supplementary motor), temporal, and frontal brain areas across all simulated driving conditions (i.e. right and left turns without oncoming traffic, left turns with oncoming traffic). Both patients and controls exhibited reliable positive activation across turning conditions in predominantly the occipital, parietal, temporal, motor, cerebellar, and frontal regions as well as the precuneus, thalamus, and the cingulum; whereas healthy controls exhibited reliable negative activation across turning conditions, predominantly in the middle and superior temporal lobes as well as the inferior

occipital lobes. This finding supports the highly complex nature of driving, suggesting that performing both routine and complex driving maneuvers requires the integration of brain regions that have been implicated in motor control (e.g. primary motor cortex, cerebellum), attention (e.g. precuneus, cingulum), visuospatial function (e.g. occipital and parietal regions), and executive function (e.g. frontal brain regions).

These areas of activation are highly congruent with the previous work of Schweizer and colleagues (2013), which identified the neural activation patterns associated with various turning conditions in healthy, young adults (mean age = 25.8 years). Furthermore, these 16 healthy young drivers (Schweizer et al., 2013) demonstrated increased and more widespread activation in multiple brain regions as driving conditions increased in complexity (i.e. from right turns to left turns to left turns with traffic to left turns with traffic and audio distraction). Similar results were obtained in the cognitively healthy older, the MCI patient (i.e. when observed as a whole), and the sd-MCI patient groups of the current study across right turns, left turns, and left turns with oncoming traffic. In particular, the healthy control and patient groups in the current study appeared to demonstrate a greater recruitment (i.e. significant positive activation) of frontal brain regions across conditions, particularly left turns with oncoming traffic. This recruitment of frontal brain regions during left turns with oncoming traffic was more substantial in patients with MCI relative to controls.

4.3.2 Hypothesis 2: Activation Patterns Characteristic of Patients with MCI Relative to Healthy Controls

Across all turning conditions (right turns, left turns, and left turns with oncoming traffic), patients and controls exhibited positive activation in multiple overlapping areas (e.g. cerebellum, occipital lobes, parietal lobes, temporal lobes, fusiform and lingual gyri, calcarine fissure, the cingulum, cuneus, precuneus, pre- and post-central gyri, supplemental motor area, thalamus, putamen, superior frontal cortex, and orbitofrontal regions). Across all turning conditions, controls demonstrated negative activation in temporal (superior and middle) and occipital

(inferior) brain areas. Patients did not exhibit reliable negative activation across turning conditions.

Consistent with the hypothesis, patients with MCI demonstrated deviations in brain activation compared to healthy controls. In particular, patients with MCI showed significant positive activation in multiple brain regions in which controls did not, and this trend was consistent across turning conditions. Furthermore, compared to more routine turning conditions (right turns, left turns without traffic), significant positive activation was observed in a greater number of frontal brain regions of patients with MCI, relative to healthy controls, during left turns with oncoming traffic (i.e. 2-3 frontal regions during right and left turns versus 5 frontal regions during left turns with traffic). This suggests that patients with MCI recruit a more extensive set of brain resources relative to controls, particularly frontal brain regions, as driving tasks increase in cognitive complexity.

In keeping with the current findings, studies using fMRI to investigate the brain regions recruited during cognitive testing (e.g. attention, executive function, visuospatial ability) in patients with MCI have consistently supported that MCI is associated with more extensive activation in multiple brain regions relative to healthy controls (Berger et al., 2015; Bokde et al., 2010; Clement, Gauthier, & Belleville, 2013; Leyhe et al., 2009; C. Li, Zheng, Wang, Gui, & Li, 2009; Yetkin, Rosenberg, Weiner, Purdy, & Cullum, 2006). Specifically, C. Li and colleagues (2009) investigated the fMRI activation patterns associated with Stroop test performance across patients with AD, patients with MCI, and healthy controls. Increased activation in the dorsal anterior cingulate, bilateral middle and inferior frontal gyri, bilateral inferior parietal lobule, and the bilateral insula was observed for MCI patients compared to controls (C. Li et al., 2009). Similarly, Clement and colleagues (2013) reported increased brain activation in frontal brain regions (i.e. the fronto-striatal network) in some MCI patients during a divided attention task. These results as well as the current results support the idea that some patients with MCI recruit a more extensive set of brain resources, including anterior brain regions, during cognitively oriented tasks, including the Stroop test, working memory tasks, the Clock Drawing Test (CDT), and driving.

The results of the current study also suggest that patients with MCI, relative to healthy controls, may recruit more brain resources (particularly more anterior regions) as driving conditions increase in complexity (i.e. from routine right and left turns to left turns with oncoming traffic). This tendency to exhibit greater activation in frontal regions as task conditions increase in demand is supported by the results of Berger and colleagues (2015). In this study, patients with AD and MCI demonstrated increased activation in the left prefrontal network and amygdala as a working memory task increased in difficulty (Berger et al., 2015).

The Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) model suggests that at lower levels of task demands, older adults may show overactivation relative to young adults, corresponding with preserved behavioural performance. However, when task demands surpass the amount of resources available, older adults will show underactivation relative to controls, and impaired performance (Angel et al., 2016). The same logic may apply when comparing individuals with MCI to cognitively healthy older adults; patients with MCI may show compensatory, overactivation in order to maintain task performance as well underactivation and behavioural impairment when task demand is too great. This has been supported in the MCI and cognitive function literature (Angel et al., 2016; Berger et al., 2015; Clement et al., 2013). The results of Clement and colleagues (2013) suggested that increased activation in the frontostriatal network was associated with better task performance among patients with MCI. Furthermore, a compensatory mechanism was supported in a study in which increased activation in prefrontal regions was observed as working memory tasks increased in complexity (Berger et al., 2015).

In the current study, the increased activation associated with MCI patients in general relative to controls as well as during tasks of increasing complexity may represent an attempt to compensate to maintain task performance. The turning behaviour results of Chapter 3 suggested that drivers with MCI did not commit significantly more errors compared to controls across any of the turning conditions (i.e. right turns, left turns, left turns with traffic). Thus, the apparent increase in recruitment of frontal brain resources may be compensatory in nature, in order to maintain task performance.

However, there may be other explanations for the apparent deviation in activation observed for the MCI patient group in the current study. An alternative explanation is that this additional recruitment of frontal brain resources was not task-relevant. Thus, rather than being compensatory in nature, the activation may have been unrelated to maintenance of performance. This explanation seems less likely, as patients with MCI showed additional recruitment in frontal brain regions (e.g. orbitofrontal, superior medial frontal cortex, and middle frontal cortex) that are associated with cognitive functions known to be associated with driving, including cognitive control, planning, and higher-order attention.

Finally, another explanation is that the observed increased recruitment of frontal resources was pathological and represented a decreased efficiency in task performance. Although patients with MCI did not commit significantly more turning errors compared to controls in Chapter 3, drivers with MCI committed more errors across all turning conditions, particularly during the left turn with oncoming traffic condition. Thus, alternatively, the deviation in brain activation of patients with MCI compared to healthy controls (i.e. increased activation) may represent a decrease in efficiency in driving performance (i.e. more subtle/minor difficulty, rather than overt driving difficulty), with the greatest decrease in efficiency being observed during more cognitively demanding aspects of driving (i.e. left turns with oncoming traffic).

4.3.3 Preliminary Results on Activation Patterns Associated with MCI Subtypes

The current results provide initial empirical evidence regarding the brain activation patterns that are associated with two subtypes of MCI—individuals with amnestic single-domain and amnestic multiple-domain impairment. These preliminary results suggest that different subtypes of MCI may be associated with considerably different brain activation patterns across driving conditions. Specifically, whereas patients with sd-MCI tended to show significant positive activation (across driving conditions) in multiple brain regions in which cognitively healthy individuals do not, patients with md-MCI tended to show the reverse pattern—failure to show significant activation in regions in which healthy controls demonstrate significant activation.

Patients with sd-MCI demonstrated significant positive activation in multiple brain regions relative to controls across all turning conditions, particularly in frontal (middle, superior medial, etc.) and medial regions (insula, temporal regions, etc.). Although this trend held across turning conditions, this increased activation, predominantly in anterior brain regions (middle frontal lobes, orbitofrontal regions, and superior medial frontal lobes) was more prominent in the more cognitively demanding left turn with oncoming traffic condition. Similar to patients with sd-MCI, patients with md-MCI did show significant positive activation in regions in which controls did not (e.g. left middle frontal cortex during left turns with traffic); however, in contrast to patients with sd-MCI, patients with md-MCI did not show significant activation in brain regions that were activated in healthy controls. This pattern was observed across driving conditions, primarily in medial and anterior brain regions, such as temporal regions and orbitofrontal regions. Similar to patients with sd-MCI, results were most pronounced during left turns with oncoming traffic. Thus, controls demonstrated significant positive activation in the greatest number of frontal brain regions, relative to patients with md-MCI, during left turns with traffic.

The increased frontal and medial recruitment observed for the sd-MCI may represent (1) a compensatory process (i.e. maintenance of task performance as discussed below), (2) activation that is not task-relevant (i.e. unrelated to the maintenance of task performance), or (3) increased functional changes corresponding with a decrease in efficiency of task performance. Research conducted by Clement and colleagues (2013) supports the compensatory hypothesis. Specifically, this group investigated the brain activation patterns that were differentially characteristic of higher cognitive functioning patients with MCI and lower cognitive functioning patients with MCI, relative to healthy controls, during divided attention and manipulation tasks. Consistent with the results of the current study, different brain activation patterns emerged for the higher cognitive functioning and lower cognitive functioning groups. Specifically, MCI patients with higher cognitive functioning showed increased activation in the left caudate and putamen, thalamus, bilateral anterior cingulate cortex, as well as the left middle, inferior, and superior frontal gyri during either the manipulation or divided attention task (Clement et al.,

2013). Furthermore, increased activation in frontal brain regions was associated with increased task performance, suggesting a compensatory process. These results are consistent with the sd-MCI group of the current study, whose cognitive deficits were less extensive (i.e. only amnestic impairment, higher MoCA scores), and who did not commit significantly more errors compared to healthy controls across any of the turning conditions.

Clement and colleagues (2013) also reported that patients with lower cognitive functioning showed decreased activation in the left inferior and middle frontal gyri as well as the left occipitotemporal regions. These results are similar to the md-MCI group of the current study, whose cognitive deficits were more extensive (i.e. multiple areas of cognitive impairment, lower MoCA scores) than those with sd-MCI and who showed less activation in anterior and medial brain regions across driving conditions, relative to healthy controls. Thus, the more extensive and wide-spread cognitive deficits that are characteristic of md-MCI may be more associated with failed recruitment of brain regions (relative to cognitively healthy individuals), whereas the unitary deficits associated with sd-MCI may be more associated with more extensive recruitment of brain regions (i.e. a greater number of brain regions, relative to cognitive to cognitively healthy individuals).

Alternatively, the md-MCI group may have shown more variable recruitment of brain regions that failed to reach statistical significance across the group, with the greatest variability during more cognitively demanding aspects of driving, such as making left turns with oncoming traffic. The sd-MCI group was fairly homogeneous and presented with only memory deficits. However, md-MCI is highly heterogeneous. Patients within the md-MCI group may have differed in which cognitive domains were affected in addition to memory (e.g. attention vs. language vs. visuospatial ability) and the number of cognitive domains affected (i.e. two vs. more areas of cognitive impairment). As a result, there may be variability in the underlying brain network changes across patients in this group. Thus, the tendency for patients with md-MCI to show less recruitment in regions that were significantly activated in healthy controls may reflect a more variable recruitment of brain regions among individuals that failed to reach statistical significance across the md-MCI group.

4.3.4 Limitations

This study represents an important a fundamental step in advancing the MCI and driving literature. The current results are the first to identify brain activation patterns that are characteristic of a group of patients with MCI, including the two amnestic subtypes of MCI—amnestic sd-MCI and amnestic md-MCI. Despite this important contribution to the literature, there are important methodological limitations that warrant discussion. Similar to Chapter 3, the current study is limited by its small sample size, particularly in the subtype fMRI analysis (i.e. 10 patients with md-MCI and 6 patients with sd-MCI). Furthermore, MCI is highly heterogeneous in nature—in terms of cognitive presentation (i.e. the areas and degree of cognitive impairment) and driving ability, as corroborated in the results of Chapter 3 (i.e. the high standard deviation consistently present in the MCI group, across driving variables of interest). Thus, given the small sample size of the current study, as well as the variable presentation of MCI, it is hard to generalize results beyond the current sample of MCI patients to the population in general. It is important for future research to confirm the results of the current study, particularly with a larger sample of patients with sd-MCI and md-MCI as well as in other subtypes of MCI (discussed further in Chapter 6: Future Directions).

The current study used fMRI to identify the brain activation patterns of patients with MCI during various turning conditions. Given the loud noise associated with MRI scanning, potential research participants with significant hearing loss were excluded from the current study. Hearing loss has been shown to be associated with MCI (F. R. Lin et al., 2011; Quaranta et al., 2014), and greater hearing loss is associated with greater impairment in cognitive functioning (F. R. Lin et al., 2011). Exclusion of participants with significant hearing loss in this study offers a potential confound, as those with the most significant degree of cognitive impairment may have been omitted. The exclusion of these patients limits the generalizability of the current results to patients with MCI who have significant hearing loss. Therefore, it is important to replicate the current results using other imaging modalities in which exclusion of potential participants with significant hearing loss is not warranted (e.g. EEG, fNIRS), to provide convergent validity.

Furthermore, individuals within the MCI patient groups (i.e. all MCI, md-MCI, sd-MCI) likely demonstrated variability in terms of brain activation. Increased variability would be expected in the MCI groups, as the cognitive profiles of individuals within the group are more heterogeneous compared to the healthy control group. Thus, certain individuals with MCI (and in particular, those with md-MCI) may have demonstrated unique patterns of brain activation across the turning conditions. Particularly for the md-MCI patient group, there is a possibility that increased activation was occurring for individuals within the group; however, the patterns of activation may have differed between individuals, leading to a lack of significant positive activation for the md-MCI group as a whole. However, for the MCI patient group as a whole as well as the sd-MCI group, even with potentially high variation, a significant pattern of activation still emerged amongst these groups (with proper FDR-adjustments for multiple-comparisons). Thus, even with high variability and statistical corrections, a pattern still emerged for the group as a whole as well as sd-MCI. A variability analysis would be important to determine (1) if variability was a factor contributing to the lack of significant positive activation observed in the md-MCI group, (2) whether divergent activation patterns were still prevalent for the MCI patient group as a whole as well as the sd-MCI group.

In addition, the MCI group (particularly those with md-MCI) scored higher on the HADS (total, anxiety, and depression), a measure of chronic anxiety and depression. Although all participants had controlled depression and anxiety, it would be important for a future study to add symptoms of anxiety and depression as a covariate in the fMRI analysis, to ensure that these symptoms were not contributing to, or driving, the observed patterns of activation. Furthermore, physiological data was not collected during the fMRI session as a measure of acute stress response. Although collecting this data does cause some interference with the driving task (i.e. monitor is placed on the participant's finger while he/she is driving), it might be important for future research to collect physiological data correct for this during the pre-processing analysis.

Despite the fact that fMRI is known for its exceptional spatial resolution, ability to acquire structural and functional images, excellent imaging depth, and moderate temporal resolution, MRI is highly susceptible to motion and other artifacts. To minimize the effects of motion, and consequently optimize data, procedures were implemented both during data acquisition and data

analysis. During data acquisition, participants were instructed on the importance of staying still during the scanning procedure, were given feedback on motion after the second training session (i.e. when structural imaging was acquired), and padding was placed between each participant's head and the head coil. Furthermore, multiple, robust pre-processing algorithms have been developed to correct for motion and other artifacts (e.g. physiological), which were implemented in the current analysis (Churchill, Oder, et al., 2012). Thus, extensive procedures were used to minimize motion artifacts.

Finally, similar to Chapter 3 of the current thesis, driving simulation has been repeatedly scrutinized for being inferior to real-world driving. This is particularly evident in the fMRI driving simulator set-up, which requires participants to lie down while they are driving. Thus, current activation results are only applicable to simulated driving. It would be important to replicate results on-road (i.e. open and closed course) as well as with fully immersive, fixed-based driving simulators using other imaging modalities, such as EEG and fNIRS.

Chapter 5 General Discussion

The results of the Chapter 3 demonstrated that patients with MCI committed significantly more overall errors during simulated driving. Further analysis showed that patients with MCI may be at particularly risk of difficulty when maintaining lane control, as demonstrated by committing significantly more centre line crossings and spending a greater amount of time out of the legal driving lane compared to a group of cognitively healthy drivers. Although patients with MCI committed more errors (collisions and lane deviations) than controls across all turning conditions (right turns, left turns, left turns with oncoming traffic), these results did not reach statistical significance. This finding is consistent with the results of previous research (Devlin et al., 2012; Frittelli et al., 2009; Wadley et al., 2009), which suggest that, when looking at patients with MCI overall as a group, patients with MCI most typically demonstrate minor driving impairments compared to cognitively healthy drivers, including during lane maintenance.

The behavioural results of Chapter 3 of patients with MCI, as a whole, coincide well with the neuroimaging results presented in Chapter 4. Specifically, the neuroimaging results of all patients with MCI suggest that patients exhibit significant positive activation in multiple brain regions, predominantly medial and frontal brain areas, relative to controls, as driving conditions increase in complexity (i.e. from right turns to left turns to left turns with oncoming traffic). Thus, together, the results of Chapter 3 and Chapter 4 suggest that this tendency to recruit a more extensive set of brain resources may represent a compensatory mechanism (Berger et al., 2015) and an attempt to maintain task performance. However, this is only a potential explanation, as the increased activation observed for the MCI patient group may have been unrelated to task performance or may have represented a decrease in efficiency in task performance.

Most importantly, the current results highlight the importance of looking at different subtypes of MCI separately when evaluating driving performance, as different patterns of driving behaviour

can emerge between subtypes. When looking at all MCI patients together, results suggested that MCI patients as a whole may experience driving difficulty, particularly in terms of lane maintenance. However, the results of the subtype analysis revealed that patients with amnestic MCI who exhibit multiple areas of cognitive impairment (i.e. those with md-MCI) may be at a greater risk of driving difficulty (compared to healthy controls), relative to patients who demonstrate impairment only in the domain of memory (i.e. those with sd-MCI). Specifically, this difficulty in driving performance observed for patients with md-MCI was particularly prominent during lane maintenance as well as more cognitively demanding aspects of driving, such as making left turns with oncoming traffic. These results are highly congruent with the preliminary brain activation patterns of these patient groups as well as the CRUNCH model of compensation. Specifically, patients with sd-MCI tended to demonstrate significant positive activation in more brain areas (predominantly medial and frontal regions) relative to healthy controls across all driving conditions, whereas patients with md-MCI failed to show significant activation in multiple brain regions (primarily anterior and medial regions) in which healthy controls demonstrate significant activation. Furthermore, these trends were most pronounced in patients during left turns with oncoming traffic, which is the most cognitively demanding driving condition that was investigated, as it requires judgement, visual attention, and decision-making. In particular, regions that patients with sd-MCI showed significant activation include the superior medial frontal cortex, orbitofrontal regions, as well as the middle frontal cortex, which are regions involved in higher-order attention, cognitive control, and planning.

Similar to the analysis looking at MCI patients in general, this greater recruitment of frontal brain regions observed in the sd-MCI group (relative to healthy control drivers) may represent a compensatory neural mechanism (Clement et al., 2013)—an attempt to recruit a more extensive set of brain resources to maintain task performance, as demonstrated by committing a similar number of errors across turning tasks, even as conditions increased in complexity. In contrast, the failure of md-MCI group to show significant activation in regions in which cognitively healthy drivers showed significant activation, may represent a failed attempt to compensate (Clement et al., 2013), resulting in task impairment (Angel et al., 2016), which is exacerbated as driving increases in complexity. The behavioural results of Chapter 3 support this, which showed that patients with md-MCI commit more errors than healthy controls across driving conditions, and

most considerably (i.e. reaching statistical significance) during the most cognitively demanding condition, left turns with oncoming traffic. Alternatively, however, individuals within the md-MCI group may have shown more variable recruitment of brain regions that failed to reach statistical significance across the group. Furthermore, the increased recruitment observed for the sd-MCI group may have been unrelated to task performance or may have represented a decrease in efficiency in task performance.

The current results highlighted the importance of separating different subtypes of MCI when evaluating driving performance, as different patterns emerged in terms of behavioural simulated driving performance as well as brain networks recruited during simulated driving. Providing empirical evidence regarding the driving behaviours characteristic of two prominent subtypes of MCI as well as the brain activation patterns associated with MCI during driving represents a fundamental step in advancing the MCI and driving literature. Currently there are no agreed upon guidelines or gold standard assessments to help healthcare professionals accurately assess the driving fitness of individuals with MCI. The current results provide a preliminary understanding of the underlying changes in brain networks associated with driving that are characteristic of MCI. These findings lay the foundation for future research in terms of validating current assessment tools (i.e. do the brain regions recruited during driving overlap with those recruited during cognitive tasks?) as well as guiding the development of objective driving assessment tools that better map onto the underlying brain changes associated with patients with MCI. The identification and implementation of these tools will be essential in assisting healthcare professionals to assess the driving ability of patients with MCI.

Chapter 6 Future Directions

This represents the first study to identify simulated driving behaviours that may be characteristic of different subtypes of mild cognitive impairment as well as the first study to identify the neural correlates of driving in patients with MCI. There are a few important next steps that need to be taken in order to advance the literature on, and ultimately improve the assessment of, driving performance in patients with MCI.

6.1 Confirming and Validating Areas and Degree of Driving Impairment Characteristic of MCI and Subtypes of MCI

Importantly, future-large scale research, using both driving simulation and on-road assessments, is required to confirm the results of the current study in terms of the areas and degree of driving difficulty characteristic of patients with MCI in general as well as the amnestic multiple-domain and single-domain subtypes of MCI. In addition, it will be important to identify and validate the areas of driving difficulty characteristic of other subtypes of MCI (e.g. single-domain executive and multiple-domains executive).

Driving is a highly complex and multi-faceted task. Furthermore, driving safely requires the integration of multiple cognitive domains as well as the corresponding brain regions. Importantly, not all aspects of driving are the same, nor do they recruit the same areas and degree of cognition or cortical activation. Research using fMRI and driving simulation has supported this, demonstrating that various aspects of driving are associated with specific and unique

patterns of brain activation. For example, the anterior cingulate cortex has been shown to be linked to performance on a car-following task (Uchiyama et al., 2003) as well as resolving uncertainty in decision-making at high traffic intersections (Callan et al., 2009). The superior parietal and occipital regions have been associated with planning and monitoring (Spiers & Maguire, 2007). Finally, the lateral prefrontal cortex has been associated with processing road traffic rules (Spiers & Maguire, 2007). The results of these fMRI and driving studies suggest that each aspect of driving differentially involves the recruitment of distinctive brain regions and, consequently, cognitive functions.

Given the complex nature of driving, coupled with the heterogeneous cognitive presentations of MCI, different subtypes of MCI are likely associated with different areas of driving difficulty. The results of the current study support this, suggesting that patients with amnestic md-MCI exhibit greater driving difficulty than cognitively healthy individuals, particularly during cognitively complex aspects of driving (e.g. making left hand turns at a busy intersection) as well as lane maintenance, whereas patients with amnestic sd-MCI do not exhibit significant impairment. It is critical for future research to confirm this as well as to identify the areas of driving difficulty characteristic of other subtypes of MCI. Specifically, a large-scale study should observe the driving profile characteristic of non-amnestic single-domain subtypes (e.g. singledomain executive) as well as the non-amnestic multiple domain subtype of MCI (e.g. multipledomain executive). For example, given that more complex aspects of driving (e.g. turning at a high traffic intersection, distracted driving; Callan et al., 2009; Schweizer et al., 2013) have been shown to be associated with recruitment of frontal brain regions, coupled with the fact that the frontal lobes have been repeatedly shown to be implicated in executive functions, it follows that patients with single-domain executive MCI may demonstrate impairment during more complex and demanding aspects of driving, including left turns at busy intersections.

6.1.1 Importance of Converging Results of On-Road and Simulator Assessments

Combining the results of driving simulation and on-road assessments to identify the driving performance characteristic of patients with MCI will have important implications. Both on-road evaluations and driving simulator assessments offer strengths in areas in which the other has limitations. For example, on-road assessments are limited in their ability to assess a driver's response to complex and potentially dangerous situations (e.g. distracted driving, collision avoidance, etc.), whereas driving simulation is capable of assessing these situations. Furthermore, despite the fact that driving simulation has been shown to be correlated with naturalistic driving (i.e. in a non-research setting that is not highly controlled) (Lew et al., 2005) and on-road driving performance (Bedard et al., 2010; Helland et al., 2013; Lundqvist et al., 2000; Mayhew et al., 2011; Shechtman et al., 2009), simulators have been scrutinized for being less realistic compared to real-world driving (E. Chung & Dumont, 2009; de Winter et al., 2009; Hallvig et al., 2013). In contrast to driving simulation, on-road tests have been shown to be direct measures of driving ability (Galski et al., 1992) that offer high face validity (Akinwuntan et al., 2005; Galski et al., 1992).

Using both on-road and simulated driving evaluations to identify the aspects of driving that patients with MCI (including various subtypes of MCI) consistently demonstrate difficulty as well as the aspects that are preserved will provide important convergent validity. It would also be important for these studies to use the results of on-road assessments to assess the validity of using driving simulation within the population of MCI. Ultimately, these results can be used to develop and implement comprehensive driving assessments (i.e. likely those that use both driving simulator and on-road assessment procedures), with high sensitivity and specificity, that assess a variety of key aspects of driving that patients are known to be at risk for impairment. This will be critical for isolating drivers with MCI who are at a risk for unsafe driving and, thus, identifying individuals who should have their license withdrawn or restricted.

In particular, the current study was limited in that some non-visual cues are lacking in the simulator (i.e. auditory, sensorimotor). These cues may be most relevant to one's performance during turning, braking, and lane control, which are areas of driving in which those with MCI demonstrated difficulty compared to healthy controls. There is the potential that the lack of these cues was more detrimental to the MCI group and contributed to the current results. Thus, replicating the results on road (i.e. where these non-visual cues are prominent, including the engines of oncoming vehicles), would be important in validating the results shown in the current study.

After the areas of driving in which a patient demonstrates difficulty have been identified using a validated driving assessment, targeted rehabilitation strategies (i.e. both cognitive and simulatorbased programs) can be developed and implemented on an individual basis, tailored to the unique presentation of each patient. For example, if a particular patient with MCI demonstrates difficulty with gap judgement and decision making at controlled intersections (e.g. left turns at traffic lights) on a validated driving assessment procedure, driving simulator-based rehabilitation strategies could be applied to help retrain this aspect of driving and improve the driving safety of the patient. After the rehabilitation procedures are completed, the patient can be re-assessed using the validated driving assessment. Driving is a significant source of independence and mobility for older adults. Offering effective rehabilitation programs to retrain driving ability in patients with MCI will potentially help reinstate the licenses of these patients and will be important for maintaining the autonomy of these individuals. Furthermore, demonstrating the level of responsiveness of patients with different subtypes of MCI will be important, as some groups (e.g. those with amnestic md-MCI due to underlying AD pathology) may have progressive conditions that make them unresponsive to the effects of training or in which training effects may only have short-term benefits.

6.1.2 Potential Policy Implications of Driving in Patients with MCI

Although current guidelines state that moderate to severe AD or related dementia is a contraindication to safe driving (American Medical Association, 2010; Canadian Medical

Assocation, 2012; Driver and Vehicle Licensing Agency, 2014), physicians and other healthcare professionals currently have no guidelines to help assess the driving safety of patients with mild AD or MCI. The results of the current study suggest that some patients with MCI, particularly individuals with md-MCI, may be at higher risk for driving difficulties. Furthermore, a recent meta-analysis conducted by Hird and colleagues (2016) showed that patients with very mild and mild AD (CDR = 0.5, 1.0) most commonly received a pass (or safe) rating on an on-road assessment; however, patients with AD had a fail rate 10 times greater than cognitively healthy drivers. These results suggest that even patients with mild Alzheimer's disease may be at risk of driving impairment and that there should be driving guidelines specific to this patient group. Despite this, however, there is currently a lack of data to inform driving guidelines in MCI and mild AD.

The absence of concrete guidelines is a huge issue that needs to be addressed, so that physicians and other healthcare professionals can better assess the driving safety of patients with MCI and mild AD. If specific areas of impairment are identified in MCI and its various subtypes, physicians and other healthcare professionals can ask patients and caregivers about these specific areas of driving and whether any self-reported difficulties are present. In cases in which the patient or caregiver report concern, or the physician suspects that performance in a certain aspect of driving may be compromised, patients can be referred for a comprehensive, validated assessment procedure conducted by a driving expert.

6.2 Isolating Brain Activation Patterns Associated with Driving and Driving Impairment in MCI and Subtypes of MCI

Exacerbating the issue of limited guidelines is the lack of objective, valid screening tools to assist physicians and other healthcare professionals in identifying patients who may be at an increased risk for driving impairment and, consequently, should be referred for a more comprehensive assessment of driving ability (Hird et al., 2016; Molnar et al., 2006). Thus, it is critical that future research identify accurate assessment tools with high sensitivity and specificity.

6.2.1 Confirming and Validating Current Results

The neuroimaging results of the current study represent the first step in addressing this issue. Specifically, the current study is the first to identify the brain activation patterns characteristic of patients with MCI, as well as explore those associated with different subtypes of MCI, across driving tasks of varying levels of complexity. Current results suggest that patients with MCI as a whole (significantly) activate more brain regions, particularly frontal brain regions, relative to controls. This significant activation in frontal brain regions was observed across all aspects of driving and increased during more cognitively demanding driving situations (i.e. left turns with oncoming traffic). Furthermore, preliminary results suggest that sd-MCI may be associated with greater recruitment of frontal and medial brain regions across driving conditions, whereas md-MCI may differentially be associated with less recruitment of frontal and medial brain regions with md-MCI to not show significant activation in brain regions that were significantly activated by healthy controls is due to variability in the recruitment of brain regions across the group.

It is critical for future research to confirm the generalizability of the current results in a larger sample of patients with MCI. This is particularly important for the amnestic sd-MCI and amnestic md-MCI subtypes of MCI due to the small sample size for each group in the current study. In addition, it would be important for future research to identify the neural activation pattern unique to non-amnestic single domain (e.g. executive-domain) and non-amnestic multiple domain subtypes of MCI. Furthermore, after isolating the brain activation patterns characteristic of the various subtypes of MCI, it would be important to determine if there are certain patterns and regions of activation consistent across all subtypes and, therefore, representative of MCI patients in general.

6.2.2 Neural Correlates of Actual Driving Impairment in MCI and Cognitive Associations with Activation Patterns

In addition to isolating the neural correlates of different aspects of driving (i.e. during turning, car following, etc.), it is essential that research explore the brain regions associated with actual driving impairment in patients with MCI as well as the various subtypes of MCI. Given that cognitive tools are needed to screen patients and identify individuals who are at risk for unsafe driving, it is essential to understand the brain regions that are implicated in actual driving impairment. Determining the brain regions and related cognitive functions that are associated with driving impairment would be an important next step in the isolating current cognitive tests and potentially the development of other assessment tools that are accurate and valid predictors of these driving impairments. The results of the behavioural portion of the current study (Chapter 3) as well as the results of Wadley and colleagues (2009) suggest that patients with MCI have difficulty in global driving performance as well as difficulties maintaining proper lane positioning. Current results suggested that patients with MCI, and more specifically, patients with md-MCI, commit more centre line crossings and spend a greater percentage of time out of the legal driving lane than cognitively healthy drivers. Given the low sample size in both studies, and consequently the low statistical power, future research is required to confirm the current results, further evaluate left turns to establish if this is an additional area of concern among patients, and identify other specific areas of impairment in patients with MCI and its subtypes.

Finally, performance on assessment tools that are repeatedly utilized in the cognitive impairment and driving literature could be correlated with the brain activation patterns that are associated with impaired driving performance to further assess their utility. Furthermore, new cognitive tools tapping into these brain regions could potentially be developed and validated. One important way to validate current tools, and guide the development of future tools, is to combine fMRI, tablet (F. Tam, Churchill, Strother, & Graham, 2011), and driving simulator technologies. This approach can be used to determine the extent to which the brain regions recruited during cognitive tests that are widely cited in the driving literature (e.g. TMT, Maze tests) map onto the brain activation patterns associated with driving impairment in patients with MCI and its subtypes.

Chapter 7 Conclusions

Currently there are no tools with sufficient sensitivity and specificity to assist healthcare professionals in assessing the driving fitness of patients with MCI. Identifying the brain activation patterns associated with simulated driving in patients with MCI represents a fundamental and first step in the ultimate development of valid screening tools that can be used in a clinical setting. This is the first study to identify the driving behaviours that may be characteristic of different subtypes of MCI as well as the first study to identify the neural correlates of simulated driving in patients with MCI. In the current study, patients with MCI, as a whole, committed more simulated driving errors overall and during lane maintenance. This behavioural finding is consistent with the neuroimaging results of the current study, which showed that patients with MCI exhibited increased activation in multiple brain regions, relative to controls, across turning conditions. In particular, patients with MCI showed increased recruitment of frontal resources (i.e. significant positive activation in more frontal regions relative to controls), predominantly during cognitively demanding left turns with oncoming traffic. Given that patients with MCI demonstrated minor difficulties rather than definitive impairment (i.e. results did not reach statistical significance) across turning conditions, this increased frontal activation may represent a compensatory mechanism (Clement et al., 2013) and an attempt to maintain driving performance, resulting in more mild rather than definitive driving impairment.

In addition, current results suggest that certain subtypes of MCI (i.e. amnestic sd-MCI and md-MCI) may be associated with different degrees of driving impairment and corresponding brain activation patterns. Specifically, individuals with md-MCI may be at risk for more substantial driving difficulty, particularly during more cognitively demanding aspects of driving (e.g. left turns with oncoming traffic, lane maintenance). Furthermore, patients with md-MCI failed to exhibit significant activation in multiple frontal and medial regions that were significantly

activated by cognitively healthy individuals across driving tasks. However, this finding was most pronounced during left turns with oncoming traffic, the condition in which this patients group exhibited the most substantial driving difficulty. In contrast, patients with sd-MCI did not perform significantly worse than cognitively healthy drivers across any of the investigated driving variables, and patients with sd-MCI tended to show significant positive activation in regions, predominantly medial and frontal regions, in which healthy controls did not. This increased recruitment of frontal brain regions was most pronounced during the left turn with oncoming traffic condition. Both these activation patterns (i.e. those associated with sd-MCI and md-MCI) may represent an attempt to compensate—potentially a successful compensation as demonstrated by recruitment of a more extensive set of brain resources in the sd-MCI to maintain task performance similar to healthy controls and a less extensive recruitment of resources in the md-MCI drivers, potentially representing an inability to compensate and resulting in behavioural driving impairment (Angel et al., 2016; Clement et al., 2013).

Future research is needed to: (1) confirm and validate the areas and degree of driving impairment characteristic of patients with MCI and its various subtypes (i.e. amnestic, non-amnestic, single-domain, multiple- domain) using both on-road and driving simulator assessments, (2) identify the brain activation patterns associated with actual driving impairment in patients with MCI, and (3) use these results to guide the development and validation of comprehensive driving assessment methods. These research directions will be important for identifying objective assessment tools, developing concrete driving guidelines, and developing targeted rehabilitation strategies to help physicians and other healthcare professionals assess and re-train driving ability in patients with MCI.

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