

Task Switching Ability in Mild Cognitive Impairment

Marco Sinai

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ABSTRACT

Task switching ability in mild cognitive impairment

Marco Sinai, Ph.D.

Concordia University, 2009

There is growing evidence of executive function deficits in mild cognitive impairment (MCI) and task switching ability has been shown to predict MCI transition to Alzheimer's disease. We tested task switching ability using a cued task switching paradigm in 27 MCI patients. Sixteen patients could perform the task (MCI-able) and 11 could not (MCI-unable). Neuropsychological, electrophysiological, neuroanatomical, genetic, demographic, health-related data are presented for the MCI sub-groups and normal controls. The most significant finding of this study is that task-switching ability can be a powerful tool in characterizing this heterogeneous population. We found that most MCI patients exhibit some form of task-switching deficits, but to vastly different degrees. On the one hand there are individuals closer to the normal aging end of the cognitive spectrum; these individuals may present with memory deficits relative to their normal age peers but can compensate these with quasi-intact executive functions and have a high probability of remaining dementia free as long as their executive functions remain adequate. On the other side of the spectrum, there are individuals who perform poorly on executive tasks as well as having significant episodic memory deficits. These individuals appear to have a high probability of developing AD or dying within four years.

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GENERAL INTRODUCTION

A universally held opinion is that with aging comes inevitable cognitive decline. This opinion is supported by decades of research confirming a modest slowing of information processing and the ability to multitask (Park, 1999). Thankfully, normally aging individuals succeed in compensating for these modest declines through the accumulation of knowledge and experience, becoming more efficient and productive in their work. At the opposite end of the cognitive aging spectrum, dementia has been described, in the words of the illustrious neurologist John Hughlings Jackson (1985), as “the fourth depth of dissolution... at the bottom, there is no person, but only a living creature”. The most common form of dementia is Alzheimer’s disease (AD) which ranks fourth, behind cancer, cardiovascular, and respiratory disorders, as the most common cause of death in Canada (Health & Welfare Canada, 1995) and one of the most frequently cited fears in the elderly.

Having defined the ends of the cognitive aging spectrum, what remains is the middle, the vast area between age-appropriate cognitive function and dementia. Defining this middle ground has been and remains a challenging task, in part because of a loose association between the neuropathologic features of AD and their behavioral expression. On one hand, there are individuals who have lived long, dementia-free lives but who are found to have widespread neuropathological AD upon autopsy; on the other hand, there are patients who exhibit severe cognitive deficits consistent with AD, but who show only modest neuropathological features of AD (Ritchie & Touchon, 2000). This dissertation can be seen as a contribution to the continuing effort of defining this middle ground by examining the ability of mild cognitive impaired patients to switch between two tasks.

The following introductory section begins with a short consideration of Alzheimer's disease (AD) followed by a more detailed description of mild cognitive impairment (MCI) that includes a brief historical perspective of the attempts to define prodromal stages of dementia, and a review of the epidemiological literature pertaining to MCI. Third, executive function and task-switching are defined and the brain correlates of task-switching are described. Finally the literature on the extent to which executive functions in general and task-switching in particular are affected in MCI is reviewed.

Alzheimer's disease

Alzheimer's disease (AD) is a degenerative brain disorder characterized by neocortical atrophy, neuron and synapse loss, and the abnormal accumulation of neurofibrillary tangles (NFTs) and neuritic plaques (Braak & Braak, 1991). Studies have shown that the distribution of NFTs and neuritic plaques is generally correlated with the pattern of cognitive impairment observed in formal neuropsychological tests (Kanne, Balota, Storandt, McKeel, & Morris, 1998; Perry & Hodges, 2000). Concurrent with these pathological markers, important disruptions in the basal forebrain cholinergic system have been noted (Lawrence & Sahakian, 1995). The earliest pathologic changes appear in the transentorhinal cortex, spreading then to medial temporal lobe structures (hippocampus and entorhinal cortex). This stage of the disease is characterized behaviourally by mild anterograde episodic memory deficits (Hodges, 1998; Grober, Dickson, Sliwinski et al., 1999). Pathological markers then, spread to the association cortices of the frontal, temporal and parietal lobes (Coleman & Flood, 1987), affecting attention, executive function, semantic memory, language and visuospatial functions

(Arnold, Hyman, Flory, Damasio, & Van Hoesen, 1991). The primary motor and sensory cortices remain relatively spared.

By the time the patient receives the diagnosis, the progressive cognitive deterioration observed in AD distinguishes it from other disorders with high probability, but definitive diagnosis is done post-mortem with the confirmation of the presence of plaques and tangles. As a result, in-vivo diagnosis is preceded by the word “probable” pending autopsy confirmation. Two sets of criteria are commonly used in the clinical diagnosis of probable AD. The National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) guidelines requires that the patient first meets criteria for dementia, defined as a history of cognitive decline as ascertained by a clinical examination and psychometric testing. After this criterion is met, the NINCDS-ADRDA and Diagnostic and Statistical Manual of Mental Health Disorders (DSM-IV; American Psychiatric Association, 2000) systems are identical and require that the patient show cognitive decline from previous levels and presence of dysfunction in episodic memory and in at least one other cognitive domain. Once cognitive deficits are clear enough to warrant diagnosis, the stage of the disorder is described as mild, moderate, and severe. However, it is generally agreed that explicit diagnosis is preceded by a long period, spanning several years, in which slow neuropathological changes undermine the functional and structural integrity of key brain areas (Amieva, Le Goff, Millet, et al., 2008). In this phase, cognitive changes are mild and sometimes difficult to distinguish from normal aging. Many terms have been used to refer to this “grey” area between normal aging and dementia but it will be referred to as mild cognitive impairment (MCI) here.

Mild Cognitive Impairment

The origins of the concept of mild cognitive impairment can be traced to the early '60s with the term "Benign Senescent Forgetfulness" (BSF), defined as the infrequent inability to recall minor past events (Kral, 1962). Although no formal criteria were proposed, the crucial aspect of BSF is that it described an age-related memory decline which did not cross the disease threshold. Age-Associated Memory Impairment (AAMI; Crook, Bartus, Ferris et al., 1986) was the first attempt to formally operationalize the concept of abnormal cognitive decline without dementia, defined as gradual onset of memory complaints substantiated by psychological performance tests (1.0 standard deviation below the mean test value, normed on young adults). However, these criteria present severe problems when the goal is to describe abnormal cognitive decline. For example, individuals with a life-long poor performance, and others whose cohort effects, such as low education or unfamiliarity with test-taking, may result in low scores without necessarily reflecting abnormal decline. Although efforts were made to improve the criteria by requiring age appropriate standardization and the broadening to impairments in other cognitive domains with the development of the concept of Age-Associated Cognitive Decline (AACD; Levy et al., 1994), the concepts of AAMI and AACD have largely been superseded. As is apparent from their acronyms, BSF, AAMI, and AACD all emphasize that cognitive decline, even abnormal, is associated with the aging process. An alternative approach is to consider abnormal cognitive decline as a precursor to disease. The concept of "Cognitive Impairment No Dementia" (CIND) is an effort to provide a framework flexible enough to include both cognitive decline, not necessarily restricted to memory, that nonetheless remains within the lower boundaries of normal function, and

abnormal cognitive decline which may be a harbinger of future dementia (Canadian Study of Health and Aging; CSHA, 2000). Although CIND remains in use, it has not received as much attention as the concept of Mild Cognitive Impairment (MCI). The popularity of the MCI concept is possibly due to the fact that its explicit aim is to characterize and define a group of individuals with a high risk of developing dementia. In this respect, the concept of MCI does not concern itself with normal or abnormal cognitive decline, but is focused on dementia detection.

The original MCI criteria were proposed by Petersen, Smith, Waring, et al. (1999) and included: 1) presence of subjective memory complaints, 2) preserved general intellectual functioning as estimated by performance on a vocabulary test, 3) demonstration by cognitive testing of a memory impairment but no deficits in other cognitive functions, 4) intact abilities to perform daily living, and 5) absence of dementia. Considerable evidence (Grundman, Petersen, Ferris, et al., 2004; Palmer, Wang, Backman, et al., 2002; Petersen, Smith, Waring et al., 1999) suggested that MCI described a group of individuals at an increased risk of developing AD with a conversion rate of approximately 12% per year compared to 1% for the general population. However, these studies also raised considerable debate regarding the validity of the original proposed criteria. First, results showed that one cannot simply regard patients with memory problems as necessarily destined to develop AD as most studies have concluded that not all individuals identified with MCI appear to progress to AD and that a substantial minority ranging from 20 to 25% revert to normal status even after a 6 to 10 year follow-up (Busse, Hensel, Gühne, Angermeyer, & Riedel-Heller, 2006; Fisk & Rockwood, 2005; Ganguli, Dodge, Shen, & DeKosky, 2004; Ingles, Fisk, Merry, &

Rockwood, 2003; Palmer, Wang, Bäckman, Winblad, & Fratiglioni, 2002). Second, it has been argued that focusing on memory impairment alone is too restrictive, excluding cases who have deficits in other cognitive areas, and in so doing may omit a large number of cases that may develop AD or other forms of dementia such as vascular dementia. This latter argument is particularly compelling in view of the evolving parallel concept of Vascular Cognitive Impairment (VCI). It has been proposed that VCI is made up of three categories, those with vascular dementia (VD), those with mixed VD and AD, and those with vascular cognitive impairment that do not meet criteria for dementia (Vascular CIND; Erkinjuntti and Rockwood, 2003). It has long been maintained that VD and AD have different cognitive profiles with AD presenting with predominantly episodic memory deficits in contrast to the predominantly executive and processing speed decline observed in VD cases (Ballard, Stephens, McLaren, Wesnes, & Kenny, 2003; Desmond, 2004; Graham, Emery, & Hodges, 2004; Ingles, Boulton, Fisk, & Rockwood, 2007; Jokinen, Kalska, Mäntylä et al., 2006; Kramer, Reed, Mungas, Weiner, & Chui, 2002).

In an attempt to address these concerns, a new set of criteria was developed as depicted in Figure 1 (Winblad, Palmer, Kivipelto et al., 2004). At the heart of the new classification is the recognition that the MCI construct is a heterogeneous entity. A distinction is made between impairment isolated to one cognitive domain and impairment in multiple domains. A second distinction is made between individuals presenting with episodic memory deficits and those presenting with deficits in any other domain than episodic memory. The resulting two by two matrix yields four MCI subcategories. The original MCI is now referred to as amnesic MCI-single domain (aMCI-s), whereas the new categories are: amnesic MCI multiple domain (aMCI-md) characterized by a

predominant amnesic deficit but concurrent with deficits in other cognitive domains, nonamnesic MCI–single domain (naMCI-s), whose principal feature is objective cognitive decline in one cognitive domain that is not memory, and nonamnesic MCI–multiple domain (naMCI-md) defined as deficits on multiple domains that are not related to memory. The new classification was designed to improve predictive validity with regard to the identification of patients that will subsequently develop dementia. It was hypothesized that aMCI-s is specifically the prodromal form of AD, that aMCI-md will develop into AD and/or vascular dementia (VD), and that naMCI-s and naMCI-md would evolve into VD or other forms of dementia (Winblad et al., 2004). Unfortunately, although plausible, these hypotheses were by-and-large not borne out by subsequent research.

Comparing amnesic versus nonamnesic MCI, studies agree that naMCI is more prevalent than aMCI (Fischer, Jungwirth, Zehetmayer, et al., 2007; Lopez, Becker, Jagust et al., 2006). However, Fischer et al. (2007) found that although a higher proportion of aMCI patients converted to AD, an equal number of naMCI patients also developed AD (although their prevalence rate was lower due to their larger population) and could not find a clear association between MCI subtype and dementia type. Thus, the hypothesis that aMCI is the prodromal phase of AD whereas naMCI is the prodromal phase of VD is not supported for now as both aMCI and naMCI can convert to AD. As mentioned previously, the neuropsychological dissociation between AD and VD has often been cited. However, recent reports have brought into question this dissociation. First, increasing evidence suggests an overlap between VD and AD brain pathology with up to a third of cases showing pathology consistent with the other dementia and that varying

degrees of vascular pathology is present in the majority of AD patients (de la Torre, 2002). Second, recent studies suggest a similar pattern of cognitive deficits in the preclinical phases of VD and AD patients with prominent episodic memory, executive function and cognitive slowing (Fahlander, Wahlin, Almkvist, & Bäckman, 2002; Laukka, Jones, Small, Fratiglioni, & Bäckman, 2004; Meyer, Xu, Thornby, Chowdhury, & Quach, 2002).

Turning now to the comparison of single versus multiple affected cognitive domains, most studies have focused on amnesic MCI. First, the prevalence of aMCI-s appears to be low compared to aMCI-md (Loewenstein, Acevedo, Agron, et al., 2007; Lopez et al., 2006; Nordlund, Rolstad, Hellström, et al., 2005). Further, and contrary to expectations, compared to individuals with isolated memory deficits, patients with deficits in more than just episodic memory were found to have an increased risk of developing AD (Artero, Petersen, Touchon, & Ritchie, 2006; Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001; Rasquin, Lodder, Visser et al., 2005; Tabert, Manly, Liu, et al., 2006), had higher mortality rates (Hungerfund, Roberts, Slusser, et al., 2007), and had lower episodic memory scores (Loewenstein et al., 2006). Only one study (Ravaglia, Forti, Maioli et al., 2006) reports a higher survival curve for aMCI-md compared to aMCI-s. Although the authors report a significant difference in baseline MMSE between converters and nonconverters, they unfortunately do not provide global functioning status differences by MCI types, leaving open the possibility that the aMCI-s group may have had significantly lower baseline scores on the mini mental state examination (MMSE; Folstein, Folstein, & McHugh, 1975) scores compared to the other subtypes thus confounding the results. In sum, there appears to be some consensus that

MCI patients with deficits in more than just episodic memory are at higher risk of developing AD and of mortality. The most affected cognitive domain outside of episodic memory has been shown to be attention and executive functions in general with particular emphasis on task-switching ability. However, before this growing literature is reviewed, the concept of executive function and task-switching will be described.

Executive functions

Whereas most authors agree that the essential feature of “executive control” refers to the capacity to plan, initiate, carry out, and monitor complex, goal-oriented behavior (Lezak, Howieson, & Loring, 2004; Royall, Lauterbach, Cummings et al., 2002; Stuss & Benson, 1986), a defining characterization of executive functions remains elusive. At least three problems contribute to this state of confusion. The first difficulty stems from the inherent nature of executive functions which is to organize and control other functions such as memory, attention, and motor response. As such, executive functions are never seen in isolation but rather emerge “on top” of the primary functions, complicating the task of measuring them. The second source of confusion, related to the first, has to do with the various techniques used in assessing executive functions. Historically, executive functions have been linked to the frontal lobe and the two terms have been and are still used interchangeably. The clinical tests that have been traditionally used to assess executive functions such as the Tower of London (ToL) and the Wisconsin Card Sorting test (WCST) were first popularized by showing their sensitivity to frontal lobe damage (e.g., Milner, 1963). Unfortunately, recent evidence has shown that damage in nonfrontal brain areas can also lead to deficits in these executive tasks. What is not clear, however, is whether this is due to non-frontal areas being

important in executive control, or whether failures are due to impairment in primary functions needed to perform the test.

Finally, these inherent difficulties are complicated further by the fact that the same term is often used for very different concepts. For example, in the cognitive literature, “working memory” refers to, as will be described in detail below, a model that encompasses many other executive functions; in other words, working memory is an umbrella under which other control functions operate. In contrast, the term is used in a more restrictive way in the neuroscience literature to refer to the ability to maintain and manipulate information “online”. The two uses of the term are not necessarily at odds, as the ability to hold information in real time may require other control functions, but it is used in very different contexts to refer to quite different concepts in different literatures. Despite these challenges, several models have emerged in an effort to define and organize executive functions into coherent frameworks. Two of these are presented next in some detail as they are particularly influential to this date.

The question of the relative influence of internal and external factors on the control of behavior has been hotly debated since the beginnings of modern psychological research. The behaviorist school of thought has traditionally ascribed most control of behavior to environmental factors external to the organism, whereas the cognitive school of thought has allowed far more endogenous control of behavior, emphasizing the role played by internal representations, stored as memory traces in the central nervous system, thought to override or modulate the influence of external stimuli (Jenkins, 1979). One model that has attempted to reconcile top-down and bottom-up contributions to the control of behavior is the Attention-to-Action (ATA) model proposed by Norman and

Shallice (1986). While going about his or her daily functioning, a person is continually confronted with stimuli coming from the environment. As a stimulus enters the central nervous system by the sensory channels, it has the potential to activate several task sets (i.e., action patterns). A task-set is a set of cognitive rules needed to perform a task, which can be compared to a computer program. The stimulus is the input data and behavior is the output. Usually, the behavior that emerges as dominant is selected by a rapid and automatic process called “contention scheduling”. This mechanism can be considered an example of bottom–up processing and does not require any top-down executive processes. However, “contention scheduling” cannot account for the complete range of behavior control. Sometimes an environmental stimulus is novel, ambiguous, or too complex and the system cannot automatically resolve the conflict between two or more task-sets. In this case, an executive system, the Supervisory Attentional System (SAS) steps in to guide behavior in a slow, flexible, and deliberate manner by biasing one task-set over another depending on the demands of the situation. The intentional and endogenous nature of the SAS makes it an excellent model of executive processes. The ATA model is able to account for a wide range of behaviors, including the behavior of frontal lobe patients. For example, when confronted with an object (e.g., a comb), some patients with known frontal lesions are compelled to perform the stereotypical action most commonly associated with this object (e.g., combing their hair) even if this action may not be appropriate at the time (utilization behavior; Lhermitte, 1983; Shallice, Burgess, Schon, & Baxter, 1989). The patient seems unable to override the dominant response. Yet another example of behavior typical of patients with frontal lesions is their inability to modify their behavior despite being aware that it is not optimal in that

particular circumstance. The tendency to perseverate in the face of clear negative feedback suggests the patient cannot override previously learned responses (Milner, 1963). In all these cases the behavior is conceptualized as a failure of endogenous control to inhibit the dominant task-set.

Another influential model that has invoked the role of central executive control is Baddley's working memory model (Baddeley, 2000; Baddeley & Della Sala, 1996). Working memory has been regarded as a basic cognitive function underlying executive control and refers to the ability to hold information "online" and manipulate it in real time. In this model, working memory is fractionated into four separate but interrelated systems: an attentional controller, called the central executive, and three subsidiary slave systems, the visuo-spatial sketchpad, which holds and manipulates visual images, the phonological or articulatory loop, which performs a similar function for speech-based information, and the episodic buffer, whose function is to link information across domains to form integrated units of visual, spatial, and verbal information. Although in the original formulation the nature of the "central controller" was implicitly unitary, the model was designed to be flexible enough to allow for the central executive to be fractionated into component processes. Baddeley proposed at least four separate functions of the central executive: the ability to divide attention between two or more tasks (i.e., divided attention), the ability to selectively attend one source of information and inhibit irrelevant distractors (i.e., selective attention), and the ability to shift between tasks (i.e., task-switching), as well as coordination between the slave systems (Baddley, 2000, 2003).

The fractionation of separable, although not totally independent executive functions has received support from several studies using factor analysis with various populations (Huizinga, Dolan, & van der Molen, 2006; Hull, Martin, Beier, et al., 2008; Miyake, Friedman, Emerson, et al., 2000; Willcutt, Pennington, Boada, et al., 2001; see Royall, 2002 for review). Miyake et al. (2000) tested whether three basic executive functions, inhibition, working memory updating, and shifting can be viewed as distinct functions or as parts of a more unified central executive. The authors defined inhibition as the ability to override dominant or prepotent responses when required. The authors make a distinction between response inhibition that is viewed as a deliberate act of control, and other forms of inhibition that act at the stimulus level such as reactive inhibition mechanisms outside of the individual control such as negative priming. Working memory updating, refers to the monitoring and processing of incoming information and the continuous updating of its relevance to the task at hand. This function goes beyond the simple “online” maintenance of information and requires the active manipulation of information in working memory. Finally, shifting refers to the ability to rapidly switch between two tasks or mental sets. As will be discussed in much detail in the next section, the switch cost derived from the task switching paradigm is thought to be an index of control processes involved in shifting mental sets.

Miyake and colleagues (2000) showed that, whereas the three functions were clearly separable, they did share a substantial portion of the variance suggesting the existence of a control mechanism common to all executive functions. Although it is not clear what this common factor may be, one candidate is the capacity to actively maintain and suppress working memory representations (Engle, Tuholski, Laughlin, & Conway,

1999) a basic ability common to all tasks used by Miyake et al. (2000). Further, the authors tested which of the three basic functions was associated with common measures of executive functions such as the WCST, Tower of Hanoi (a variant of the ToL test), Random Number Generation, Operation Span, and Dual Task. Results showed that WCST loaded most strongly on the task switching factor, the Tower of Hanoi test loaded most on the inhibition factor, the random generation task loaded on both the inhibition and working memory updating factors, the Operation Span task loaded heavily on the updating factor, whereas the Dual Task did not significantly load on any of the three factors suggesting it may require a yet unspecified control function or that the ability to perform two tasks simultaneously may be a fundamental executive function independent of inhibition, shifting, and updating. These four fundamental executive functions, although commonly cited in the literature are by no means exhaustive. Several authors have proposed other basic functions such as Concept Generalization and Planning (Royall et al., 2002) and others have proposed other important executive functions such as Volition, Planning, Purposeful Behaviour, and Self Monitoring (Lezak et al., 2005). Although important contributions to the field, it can be argued that these formulations are too broad, possibly reducible to more fundamental functions, and difficult to operationalize.

Of the executive functions just described, task switching is consistently identified as a significant latent variable in factor analysis (Huizinga, et al., 2006; Hull, et al., 2008; Miyake, et al., 2000; Salthouse, Fristoe, McGuthry, & Hambrick, 1998; Willcutt, et al., 2001). Indeed, the ability to switch flexibly between tasks, locations or objects is emerging as one of the most ubiquitous cognitive functions, implicated not only in spatial

and visual tasks but also in motor tasks (Rushworth, Hadland, Paus, & Sipila, 2002) and language (Gurd, Weiss, Amunts, & Fink, 2003; Jackson, Swainson, Mullin, Cunnington, & Jackson, 2004). Perhaps because of this ubiquity and importance in everyday life, task switching has been identified as one of the earliest non-episodic memory functions to be affected in AD (Amieva, Phillips, Della Sella, & Henry, 2004; Parasuraman & Haxby, 1993; Perry & Hodges, 1999). Further, if one considers the process of switching from one task to another, it involves a series of events such as disengaging from the old task, engaging the new task, recognizing the stimulus, and evaluating it, that may involve a combination of control processes that can be affected in AD and MCI. Identifying the affected components has obvious clinical benefit as these can be the target of therapy and can increase our understanding of these disorders.

Task-switching

The cognitive domain that most overlaps with executive functions is attention. The concept of attention refers to the ability to focus on a stimulus or set of stimuli, sustain this effort or shift it to another behaviorally appropriate set of stimuli. According to Posner and Petersen (1990), attention can be subdivided into four functions which require varying degree of executive control: sustained, selective, divided, and alternating attention. Sustained attention refers to the ability to focus on one task over a period of time, selective attention refers to the ability to filter out irrelevant information and focus on relevant stimuli, divided attention refers to the ability to carry out more than one task at a time, and alternating attention refers to the ability to shift rapidly between one task and another.

There are several ways to measure the ability to shift attention. The most widely used experimental method used in the study of attention shifting is the covert attention paradigm developed by Posner (1980). In this paradigm, the participant is asked to fixate a central cross while stimuli are presented in peripheral vision. Trials usually begin with the presentation of a cue that attracts the participant's attention to one location (i.e., left or right of the fixation cross). After a brief interval, a target is presented, either in the same location as the preceding cue (i.e., a valid trial), or in the opposite location (i.e., invalid trials). The basic finding is that invalid trials tend to be slower than valid trials and has been interpreted as the time it takes for the "mind's eye" to shift attention from one location to another (Posner, 1980).

In the clinical literature, two tests in particular are known to be standard measures of shifting abilities. The first is the Wisconsin Card Sorting Test (WCST), a neuropsychological test that requires participants to shift their attention from one stimulus dimension to another in a seemingly unpredictable fashion. The Trails B test is another cognitive measure of set shifting that is commonly used in neuropsychological batteries. In this test, participants must connect points on a sheet of paper alternating between numbers and letters in ascending order. Their performance is compared to the Trails A test in which the subject must connect only numbers or letters.

Somewhat akin to the Trails B test, the task switching paradigm requires the test taker to alternate between two tasks although, as will become apparent in the following discussion, there are important differences between the two tests. Jersild (1927) pioneered the study of what is known today as "task switching" by comparing reaction times in blocks where subjects had to switch between performing two tasks

(heterogeneous blocks) with reaction times in blocks where subjects performed the same tasks in isolation for the whole block (homogeneous blocks). Jersild found that when subjects were required to switch between two tasks that were related to each other (e.g., adding six and subtracting three), they took more time to complete heterogeneous blocks than homogeneous blocks. However, when subjects were asked to switch between very different tasks (e.g., naming an antonym and subtracting three) no switch cost was found. Jersild also manipulated task complexity by comparing the switch cost when switching between simple tasks (i.e., adding and subtracting a single digit number) and the switch cost when switching between more difficult tasks (i.e., adding and subtracting two digit numbers) and found that the size of the switch cost was sensitive to task complexity.

Spector and Biederman (1976) replicated Jersild's results and concluded that the principal determinant of switch costs is the extent to which a stimulus is able to determine the appropriate task. The more ambiguous a stimulus (i.e., a stimulus that can evoke more than one response is ambiguous), the larger the switch cost. In one experiment (Experiment 4), participants switched between the same tasks as in a previous experiment, but this time the tasks to be performed were shown concurrently with the stimulus (i.e., the task was cued). Results showed that the switch cost was dramatically reduced, reinforcing the authors' conclusion that the principal determinant of switch costs is the extent to which a stimulus is able to determine the appropriate task.

One potential problem of the blocked design used by Jersild (1927) and Spector and Biederman (1976), is that in homogeneous blocks, subjects can simply attend to the present stimulus, but in heterogeneous blocks, subjects must also keep track of past trials to know when to switch tasks. This extra working memory requirement present in

heterogeneous but not in homogeneous blocks may account for some of the switch cost. Also, between-block reaction time differences could be due to differences in arousal, motivation, and fatigue. In order to address these concerns, Rogers and Monsell (1995) developed the “alternate runs” paradigm where participants are required to switch between two tasks (switch trials) or repeat the previous task (repeat trials) in the same block. For example, on the first trial the subject is asked to decide whether the letter in the stimulus “K9” is a vowel or a consonant. On the next trial the subject is again asked to decide whether the digit in the stimulus “3L” is odd or even. This is considered a switch trial because the subject has been asked to switch from categorizing the letter to categorizing a digit. On the next trial, the subject is asked whether the digit in the stimulus “A5” is odd or even. This is considered a repeat trial because the subject is asked to make a decision along the same dimension as the previous trial. The difference in average reaction time (RT) between switch trials and repeat trials (switch trial RT – repeat trial RT) is the switch cost (Rogers & Monsell, 1995). It is important to note that Rogers and Monsell’s “switch cost” is not the same as Jersild’s, which is now referred to as the “alternation cost” (Meiran, 2000). By introducing this “within block” contrast, Rogers and Monsell’s procedure essentially splits the cost of alternating between two tasks into two basic costs (Figure 2). The first, as just described, is a within block cost called the “switch cost”, and the second, referred as the “mixing cost” compares performance between repeat trials within heterogeneous blocks (i.e., mixed blocks) with repeat trials within homogeneous blocks (i.e., single task blocks; Kray & Lindenberger, 2000; Meiran, 2000; Rubin & Meiran, 2005).

Mixing Cost

Early conceptualizations of the mixing cost assumed that, contrary to the transient trial-to-trial effects that act on the switch cost, mixing cost effects would be due to more sustained factors (Los, 1996). Some of the proposed processes included the extra attentional resources during mixed as opposed to single task blocks and reflects the requirement of keeping more than one task set active in working memory, akin to a dual task situation (Kray & Lindenberger, 2000; Mayr, 2001; Meiran et al., 2000). In recent years, however, evidence has been presented that raises doubts regarding this account. Rubin and Meiran (2005) hypothesized that if working memory was the determining factor behind mixing costs, increasing the task load from two to three tasks should increase the mixing cost. However, results showed that mixing costs did not appear to be affected by working memory demands but rather, they were modulated by the nature of the stimuli. In blocks in which stimuli were only associated with one task (i.e., univalent stimuli) mixing costs were negligible whereas when stimuli were associated with both tasks (i.e., bivalent stimuli), mixing costs were sizeable. In essence this manipulation confirms what Jersild (1927) and Spector and Biderman (1976) had already observed; that switch costs only arise in situations of task ambiguity or overlap. The significance of Rubin and Merian's finding, however, is that mixing costs appear to also be due to transient, trial-by-trial factors and not to more sustained factors such as working memory load as could be reasonably assumed.

Thus, the mixing cost and the switch cost reviewed next appear to be affected by more similar factors than previously thought. Nevertheless, these two costs have been clearly differentiated in both fMRI (e.g., Braver, Reynolds, & Donaldson, 2003) and ERP

studies (e.g., Goffaux, Phillips, Sinai, & Pushkar, 2006) and both report clear functional differences. For example, Braver et al. (2003) showed that mixing cost contrasts tend to activate exclusively frontal regions whereas switch cost contrasts tend to activate frontal and parietal regions. Further, an interesting aspect of the mixing cost is that it appears to be affected by aging far more than switch costs (Kray & Lindenberger, 2000; Mayr, 2001) and, inasmuch as MCI can be viewed as a form of accelerated aging, it may yield significant group effects in the current study.

Switch Cost

The introduction of the alternating runs paradigm (Rogers & Monsell, 1995) generated considerable research activity aimed at elucidating the nature of the switch cost (i.e., the contrast between repeat and switch trials within a mixed block). The review that will follow will center around two main themes that represent the two main hypotheses on the nature of the switch cost. On the one hand is the view that the switch cost is due to time consuming control processes required to change the system's configuration from one task to another. On the other hand, is the view that the switch cost is the product of interference from previous tasks. Importantly, this latter account does not contend that task switching does not require control processes but simply that the switch cost is not due to executive mechanisms. In their extreme forms, these two views could be seen as mutually exclusive; however, one should keep in mind that they are an oversimplification of the concepts formulated in fifteen years of research. There is however a reason for explicitly shining the spotlight on the contribution of memory processes in task switching given that this thesis' population of interest, MCI is partially defined by their episodic memory deficits.

The debate over the nature of the switch cost started in earnest with the publication of two almost simultaneous papers (Allport, Styles, & Hsieh 1994; Rogers & Monsell, 1995). Allport and colleagues proposed that the switch cost (defined as the contrast between mixed and pure trials) could be mainly accounted for by factors related to previous trials, a form of pro-active interference that they term task-set inertia (TSI). In a series of experiments, they brought forward evidence for TSI involvement and against prominent executive processes involvement. In experiment 4, two stimulus ensembles made of two tasks each was used. One ensemble was incongruent Stroop color words where the participant was presented with words printed in different color ink (e.g., “blue” printed in red ink); participants were asked to either read the word (i.e., reverse Stroop task) or name the color of the ink (i.e., Stroop task). The other ensemble was a set of displays containing from 1 to 9 digits (i.e. 11111 or 77777777) where the subject was required to judge the value or the group size (less or more than 5). First, subjects were asked to switch between the reverse Stroop task and the digit value task. Then, subjects were asked to switch between the Stroop task and the group size task. Finally, subjects were asked to go back to switch between the reverse Stroop task and the digit value task. Switch costs for both the reverse Stroop task and the digit value task increased dramatically from the first to the third block. The TSI hypothesis can easily account for these results, as the activation of competing S-R mappings during the intervening block interfered with subsequent performance of the original tasks. At about the same time that Allport et al., were conducting their experiments, another team of researchers (Rogers and Monsell, 1995) were also independently working on task switching and reaching very different conclusions.

Rogers and Monsell proposed that the switch cost was due to the extra time needed to reconfigure the task-set ahead of a switch to a new task (i.e., internal control settings required to perform a given task). They gave the analogy of a signalperson who is tasked to move the lever at railroad intersections. Switching from track A to track B is time consuming and, if the next train (i.e., the next task) arrives too early, it will have to wait until the signal person has finished moving the lever (i.e., the new task-set has been configured). They reasoned that if this account was plausible, the switch cost would be eliminated by simply allowing participants more time to prepare between trials. Results showed that indeed the switch cost is reduced by increasing the inter stimulus interval (ISI) but it was not entirely eliminated. This fundamental result motivated their two-step model of task-set reconfiguration. The first step in the reconfiguration process involves an endogenous component (i.e., initiated by the participant) that can be prepared ahead of the upcoming task. The second step is an exogenous component that is stimulus triggered and completes the reconfiguration process. Rubinstein, Meyer, and Evans (2001) developed the two step theory further by hypothesizing the existence of two distinct executive processes involved in task switching. The first, “goal-shifting” can be prepared before the stimulus is presented, whereas the second, “rule-activation” requires the presentation of the stimulus. It should be noted though that the two theoretical perspectives are not mutually exclusive, that is, proactive interference and executive processes may both contribute to switch costs and evidence of this comes from cued task-switching paradigm. In this paradigm, the interval between the response on the present trial and next trial stimulus (RSI) is broken down into two components by the introduction of a cue that informs the subject what the dimension on the following trial

will be. Therefore, the RSI divides into the response-cue interval (RCI) which is the interval between the response on the previous trial and the cue for the current trial, and the cue-stimulus interval (CSI) which is the interval between the cue and the stimulus on the current trial. Evidence for the existence of passive interference comes from the observation that increasing the RCI decreases switch costs (Meiran, 1996). During the RCI, no cue has yet been given, and the subject is not yet able to prepare for the upcoming trial. Any reduction in switch cost must be due to a lingering effect from the previous trial. Evidence for advanced “task-set reconfiguration” comes from the observation that increasing the CSI (i.e., the interval between the cue and the stimulus) while keeping the overall RSI constant – thus controlling for passive decay effects – reduces switch costs substantially (Meiran, 1996).

While the debate on the nature of the switch cost continues to this day, some have suggested that it may not be the best indicator of the putative control processes involved in task switching. According to Altmann and Gray (2008), the switch cost is not an index of executive function but rather an indication of the time it takes for a new task to “settle” into the system. Altman refutes the idea that extra processes are expended on switch trials relative to repeat trials, suggesting instead that in both cases knowledge required to perform the task (i.e., task rules) has to be activated. However, during repeat trials, the rules are somewhat primed in the system and on switch trials these rules may be more difficult to activate due mainly to the need to resolve interference from the previously active task rules. A similar concept was brought forward by Mayr and Kliegl (2000) who proposed that much of what a subject can do to prepare for an upcoming task is to retrieve the task rules associated with the upcoming task from long term memory. In

experiment 3, subjects were asked to switch between two possible tasks chosen between two tasks with high task rules retrieval demands (arbitrary, recently learned episodic associations such as whether the word was originally presented in yellow or blue font or in the top or bottom half of the screen) and two tasks with low task rules retrieval demands (semantic based knowledge such as judging whether a noun is living/nonliving or large/small). A cueing paradigm was used where the RCI and CSI was manipulated as well as the information provided by the cue. The retrieval demand effect was present in conditions where the subject had little time to prepare and where the cues were not very explicit. However, when the task rules were presented on the screen along with the cues (i.e., explicit cue condition), no retrieval demand effect was found (i.e., semantic and episodic tasks had similar switch costs). Also, when subjects were allowed enough time to prepare (short RCI and long CSI), the retrieval demand effect disappeared even when the cue was not very explicit.

There are important differences between the alternate run paradigm and the cued paradigm that may crucially affect the switch cost. The most crucial difference is that in the alternate runs paradigm the task sequence is predictable and known in advance (i.e., the participant has to repeat a task and then switch to the next one and so forth) whereas in the cued paradigm, the task sequence is random. This basic difference forces the participant to adopt very different strategies. In the alternate runs paradigm, the participant knows in advance whether the next trial is a repeat or a switch. Thus, in preparation for a repeat trial, the participant will seek to simply maintain the just performed task activated in working memory; in contrast, when preparing for a switch trial, the participant will attempt to reconfigure the cognitive system, presumably

deploying extra control mechanisms. In a cued paradigm, the participant doesn't know if the next trial is a repeat or a switch. Therefore the optimal strategy is to adopt a "neutral stance" which would perhaps involve the deactivation of the just performed task. This strategy may have the consequence of making switch and repeat trials more similar to each other since the task set has to be reactivated even on repeat trials, and this may lead to generally smaller switch costs on cued paradigms. However, we selected this design because it has the advantage of being able to clearly separate endogenous versus exogenous components of task switching (i.e., cue related versus target related processes) and because it lends itself naturally to functional neuroimaging and electrophysiological investigations as will be reviewed in the next section. However, before moving on to the next section, a last effect observed in task switching paradigms, which concerns the ambiguity afforded by the target stimulus, will be briefly described.

Crosstalk Effect

In their landmark paper, Rogers and Monsell (1995) used compound stimuli composed of numbers and letters (e.g., A2, 3G) and asked participants to alternate between performing the number task (i.e., press left for even, press right for odd) and letter task (press left for letter, press right for consonant). One third of the targets also contained a neutral foil (i.e., an irrelevant character from a list of symbols not relevant to any of the two experimental tasks; e.g., "%E"). On non-neutral trials, target presentation will evoke both tasks resulting in "cross-talk" interference. Despite the fact that advanced preparation may be able to bias the system in favour of one task (e.g., the number task), both the number and letter tasks will be exogenously activated by the target and resources must be expended to suppress the irrelevant task. In a further step of the analysis, the two

non-neutral trials can be distinguished on the basis of response selection processes. Whereas both conditions evoke both task sets and in both conditions the inappropriate task set needs to be inhibited, on congruent trials, both stimuli (e.g., “E” and “4”) map onto the same response key (e.g., right button), whereas on incongruous trials, the two stimuli map onto different response keys. Thus, on incongruous trials, there is added interference at the response selection level which produces similar demands as in Stroop and Flanker tasks, with the important difference that in task switching experiments, the tasks associated with the compound stimuli are equivalent whereas in the Stroop and Flanker tasks one of the tasks is dominant. Nevertheless, the difference between congruent and incongruent trials can be seen as an index of response inhibition and stimulus-response (S-R) conflict.

Brain correlates of Task Switching

Posner and Petersen (1990) proposed the existence of two attentional networks that come together during the switching of attention. Although the model was designed to account for shifts in spatial locations, they provide a useful framework in which to understand brain activation during task switching in general. The posterior parietal system is required for the disengagement of attention from one stimulus and the engagement of attention to another whereas the frontal attentional system is involved in planning and task control. The frontal areas most often involved in task switching include the anterior cingulate and other medial prefrontal areas, which are important for response selection and resolution of conflict, and the dorsolateral prefrontal cortex which has been associated with working memory, or the ability to maintain and manipulate one or more active representations (Posner & Petersen, 1990). In the following review, evidence will be presented from lesion, imaging and ERP studies that sheds light on the role of each

attentional network in the different sub-processes thought to be required for efficient task-switching.

In one of the first studies exploring the neural substrates of task switching, Moulden, Picton, Meiran et al. (1996) employed ERPs to examine the brain mechanisms mediating task switching and found a left frontal sustained negativity evoked by a cue that indicated that a new task was going to occur. Also implicating frontal regions, Rogers, Sahakian, Hodges, et al. (1998) found increased switch costs in left frontal patients but only in conditions with high levels of interference, suggesting that left frontal areas are also involved in exogenous task set reconfiguration. In one of the first event-related fMRI studies of the brain areas involved in task preparation, Sohn, Ursu, Stenger, and Carter (2000) presented young healthy participants with pairs of two tasks that were either the same (task repetition) or different (task switch) from each other. In a further manipulation, on half of the trials, participants knew what task was going to be presented next (foreknowledge) and on the other half they were not (no foreknowledge). The reason for this manipulation is the hypothesis that both endogenous and exogenous control processes involve retrieval of information. In the conditions with foreknowledge, the participant will likely engage in effortful preparation for the upcoming trial when they know it will be a switch. But if the participant knows the upcoming trial is a repeat, they will simply maintain the task from the previous trial. Therefore, the authors predicted increased preparatory activity in the foreknowledge switch condition that would reflect activity associated with preparation before the upcoming task is presented. In conditions without foreknowledge of the upcoming task, participants will have to retrieve task rules on switch trials and this should result in increased activation in areas involved in both

endogenous and exogenous task set reconfiguration. Results showed that both dorsolateral prefrontal and posterior parietal areas were both involved in task preparation and execution, although their design could not rule out the possibility that the frontal activation was due to cue processing or to working memory demands due to the long RSI. In a further effort to isolate the brain areas uniquely involved in task preparation, Brass and von Cramon (2004) manipulated the number and types of cues presented to participants and occasionally presented cues not followed by a target. Using this method, they were able to show the importance of the dorsolateral prefrontal cortex and the intraparietal sulcus to task preparation processes and were able to establish that the prefrontal activations were not due to working memory demands or cue processing. These two studies and others (Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000; Ruge, Brass, Koch et al., 2005; Rushworth, Hadland, Paus, & Sipila, 2002; Sylvester, Wager, Lacey, et al., 2003) emphasize the co-operation between frontal and parietal cortices during both task preparation and response selection. Hence, it seems that prefrontal regions are involved in establishing and maintaining general task representations during the endogenous phase and selecting the appropriate response during the exogenous phase, whereas parietal regions are involved in the representation of the candidate S-R associations (Brass, Ulsperger, Knoesche, Von Cramon, & Phillips, 2005; Braver, Reynolds, & Donaldson, 2003; Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002 ; Corbetta & Shulman, 2002; Tomita, Ohbayashi, Nakahara, Hasegawa, & Mijashita, 1999; Wylie, Javitt, & Foxe, 2004). However, one important issue that is not addressed by these fMRI studies is the timing of the activation of anterior and posterior areas because the inability to decompose a trial-related BOLD response into sub-

components associated with separate within-trial events (cue and target) unless the events are separated by at least a few seconds.

Another functional imaging technique that can complement fMRI findings is the event-related potentials (ERP). ERPs are limited in their ability to infer the precise brain area from which activity emanates because they represent the summation of electrical brain activity recorded at the surface of the scalp. However, what they lack in spatial resolution is made up by its excellent temporal resolution (time course of the activity) on the order of milliseconds, making it an ideal technique in the investigation of cognitive processes.

There is a rich tradition of using ERPs to study attentional functions and preparatory activity. When subjects are asked to flex the index finger at self-paced intervals, a slow increase in surface negativity starting 800-500 ms before the onset of the motor movement is observed, referred to as the Bereitschaftspotential (BP; Deecke, Bashore, Brunia, et al., 1984). The amplitude is maximal over cortical areas containing representations of the index finger. Negativity rises earlier and reaches higher amplitudes with increasing complexity of the movement. This negativity can be attributed to the preparation of the movement and not to the movement itself because (a) it precedes the movement itself, (b) it shifts from frontal to more central areas as the movement becomes automatic (i.e., over-learned), and (c) the negativity is observed even when the subject is asked to imagine the movement of the finger without overt behavior (Deecke et al., 1984). If cortical negativity is associated with preparatory activity, then tasks presented during periods of spontaneous high cortical negativity should be performed better than during periods of low cortical negativity (Potential-Related Event Paradigm; PRE).

Semantic task facilitation has been observed during periods of high parietal negativity (Stamm, Whipple, & Born, 1987). Also, delayed-response task facilitation (associated with frontal lobe activity) has been observed during periods of high frontal lobe negativity (Born, Whipple, & Stamm, 1982).

Another paradigm where a large negative wave can be observed is the Contingent Negative Variation (CNV) paradigm. When one stimulus (i.e., the warning, or signal stimulus) always precedes (or is conditionally related to) another (i.e., the imperative stimulus), a negative potential is observed between the two stimuli. This negativity is monophasic when the interval is less than 3 seconds and is biphasic when the interval between the two stimuli is more than 3 seconds. The monophasic CNV has been related to cortical priming and can be considered an index of preparation for the second stimulus (Walter, Cooper, Aldridge, McCallum, & Winter, 1964). There are strong parallels between the paradigms (BP, PRE, and CNV) designed to evoke Slow Negative Potentials (SNV), and the task switching paradigms (i.e., alternating runs and cuing paradigms) reviewed here. The CNV can be considered a good model of ERP activity during the cueing paradigm because of the use of an explicit cue. The cue is analogous to a warning signal and the target is analogous to an imperative stimulus. Cortical negativity preceding the target stimulus can be associated with degree of preparation and increased performance.

Accumulating evidence has demonstrated that task switching is associated with a number of different ERP waveform patterns. These can be divided into two major categories: cue-locked and target-locked activity. The most prominent component observed during the cue-locked interval is a sustained negative wave (i.e., CNV-like

activity) lasting until target presentation. There is disagreement in the literature on whether this negative shift is observed over frontal or parietal sites. One commonly observed pattern of activation is increased switch negativity at frontal sites during the latter part of the cue-target interval, accompanied by increased negativity over parietal sites on repeat trials (Lorist, Klein, Nieuwenhuis et al., 2000; Phillips, Poulsen, & Segalowitz, 2000; Poulsen, Luu, Davey, & Tucker, 2005). This pattern of activation supports the view that frontal regions are involved in top down control processes such as inhibition of previous task rules or retrieval and biasing of attention in favor of new task rules. According to this view, the parietal negative shift on repeat trials simply reflects the maintenance of the task set in working memory. However, several other ERP studies have failed to observe increased switch negativity at frontal sites but have recorded increased negative shift over parietal areas on repeat trials (Karayanidis, Coltheart, Michie, & Murphy, 2003; Goffaux, Phillips, Sinai, & Pushkar, 2006) making this the more consistent cue-locked effect to date. The functional significance of this posterior negativity has been investigated by Goffaux and colleagues (2006). Their first finding was that this posterior negativity was associated with performance on the upcoming trial; in other words, repeat trials that showed larger posterior negative shifts in the cue-locked interval resulted in faster reaction times. The authors raised the possibility that the enhanced negativity to repeat trials relative to switch trials could fully account for the observed behavioural switch cost. However, when they compared switch and repeat trials with similar reaction times, they still found a larger negative shift on repeat trials, suggesting that the posterior switch modulation reflects control processes differentially involved in switch and repeat trials.

Turning now to target-locked activity, the most commonly observed component is a general late positivity with maximal amplitude at midline centro-parietal sites, which resembles the P300. The P300 has historically been studied in oddball type tasks where the participant is confronted with a series of identical stimuli interspersed with infrequent odd targets. A positive going wave is typically observed approximately 300 to 600 ms after the presentation of the oddball stimulus. Two components have been dissociated: the first, referred as the P3a, is an early (300-400 ms) frontally distributed component that has been proposed to reflect attention shifts to relevant information (Schroger & Wolff, 1998); the second, referred to as the P3b is a later (350-600 ms) posteriorly distributed component that has been associated with working memory updating (Donchin & Coles, 1988). An alternative influential interpretation of the P3b is that its amplitude is enhanced by increased available working memory resources that can be deployed for stimulus evaluation (Johnson, 1984; Kok, 2001; Kramer and Spinks, 1991). Evidence for the sensitivity of the P3b to attentional capacity comes from divided attention studies in which participants are asked to perform two tasks at the same time but pay more attention on one task (the primary task) over the other (the secondary task). What is typically observed is an enhanced P3b to targets evaluated within the primary task. When the task roles are reversed, P3b amplitude also changes according to task saliency (i.e., the P3b is enhanced when the secondary task becomes the primary task; Kok, 2001; Kramer and Spinks, 1991).

Task switching experiments usually do not reveal P3a activity even though one would logically expect to observe it given that it has been hypothesized as an index of attention shifting. In contrast a target-locked posteriorly distributed P3b-like activity is

consistently recorded (Goffaux et al., 2006; Karayanidis et al., 2003; Lorist et al., 2000; Phillips et al., 2000). This component is enhanced during repeat relative to switch trials (Goffaux et al., 2006; Karayanidis et al., 2003; Lorist et al., 2000; Phillips et al., 2000; but see Poulsen 2005 for different interpretation) and largest during homogeneous block trials (Goffaux et al., 2006). Because of this graded enhancement ranging from switch trials to homogeneous block trials, this P3b-like activity has been interpreted as an index of the amount of resources allocated for target evaluation (Goffaux et al., 2006; Karayanidis et al., 2003; Lorist et al., 2000; Phillips et al., 2000). Further evidence in favor of the target-locked posterior positivity being related to stimulus processing comes from a study by Poulsen et al. (2005), in which crosstalk conditions were manipulated. Results showed enhanced P3b activity to neutral trials (i.e., no crosstalk condition) relative to congruous and incongruous trials and no difference between the latter two (i.e., crosstalk conditions). From a resource capacity perspective, the difference between neutral and non-neutral trials is that, in the former, the target affords only one task whereas in the latter two tasks are evoked and resources must be expended to resolve the interference from the competing foil in both congruent and incongruent conditions. Finally, the fact that the authors did not observe P3b differences between the two crosstalk conditions (which differ from each other on the basis of stimulus-response mapping conflict) is consistent with this ERP component being sensitive to stimulus evaluation rather than response related effects. It is very important not to confuse target-locked activity with response related processes. We have seen in our discussion of the switch cost that the exogenous, target-locked component of the switch cost is likely due to interference from previous stimulus-response mappings and reflects response related

processes. Therefore, the most important target-locked ERP component measured during task switching, the P3b, should not be considered an index of exogenous processes but rather an index of working memory resources available for stimulus evaluation.

Complementing behavioural measures with ERP analysis permits a more in-depth analysis of the control processes involved in task-switching. Cue-locked activity is likely associated with endogenous processes such as retrieval of task rules from long-term memory and their maintenance in working memory whereas target-locked activity is a sensitive marker of working memory capacity. The extent to which these and other executive functions are likely to be impaired in MCI is reviewed next.

Executive functions and MCI

Although AD has traditionally been considered a memory disorder, there is general agreement that executive function deficits are significant and may occur early in the disease and perhaps even in the preclinical phase of the disorder (Albert, Blacker, Moss, Tanzi, & McArdle, 2007; Backman, Jones, Berger, Laukka, & Small, 2005; Baddeley, Baddeley, Bucks, & Wilcock, 2001; Chen, Ratcliff, Belle et al., 2001; Perry & Hodges, 1999), and the extent to which executive functions are affected in AD has led some to consider it a hallmark of the disease along with episodic memory dysfunction (Duke & Kaszniak, 2000; Voss & Bullock, 2004). Given that individuals with MCI are at increased risk of developing AD, it would be reasonable to expect executive deficits in MCI patients, as mounting evidence appears to suggest. What follows is a review of studies that have examined executive functions in MCI. Although there is widespread, but not unanimous, agreement that executive dysfunction is common in MCI, there is considerable variation in opinion as to precisely which executive functions are affected in

MCI and how best to measure them. The review is organized in two sections: the first examines studies that compare the performance of MCI patients (or variants of MCI such as CIND) with normal controls on a variety of neuropsychological tests (see Tables 1 to 4). The second section reviews studies that look at the executive functions that best predict MCI conversion to AD.

Tables 1 to 4 are an effort to organize the conflicting pattern of results emerging in the literature. Following Miyake's CFA study (Miyake et al., 2000), four fundamental executive functions were retained: Dual Tasking (Table 1), Working Memory Updating (Table 2), Inhibition (Table 3), and Task Switching (Table 4). These four were selected because they are among the most reported and have been proposed as fundamental control functions. As can be seen by a quick glance through Tables 1 to 4, results are mixed for every function with some studies reporting deficits while others do not. These discrepancies can be due to at least two reasons. First, the tasks used may have placed subtly different cognitive demands on MCI participants leading to variation in results across studies. The second has to do with the heterogeneity of MCI; to aid comparison between studies, the tables include basic characteristics of the MCI sample (age and MMSE scores). However, even samples with approximately similar age, education, and MMSE scores can hide significant group differences; as discussed previously, a substantial minority (from 20 to 25%) of MCI patients is made up of individuals who will remain stable or even revert to normal cognitive status. Even slight differences in proportions of "healthy" MCI participants may alter results significantly and cause discrepant results between studies.

Dual Task

We start the review with the examination of dual tasking because it has a special place in the history of cognitive science since the observation that AD patients have deficits in dual task situations (Baddeley, Logie, Bressi et al., 1986) was one of the earliest empirical validations of the working memory model developed by Baddeley and Hitch (1974). A dual task paradigm is a procedure in which a participant is asked to perform two tasks simultaneously. Although there is consensus that AD patients in the moderate stages of the disease exhibit a decline in dual task performance, results are mixed when AD patients in earlier stages are tested (see Perry & Hodges, 1999 for a review). In MCI, evidence of dual task impairment is mixed. Whereas Belleville, Chertkow, and Gauthier (2007) as well as Johns, Phillips, Belleville et al. (2009) found that MCI patients have deficits on the Brown Petersen task (BPT), and Lopez et al. (2006) on the Baddeley dual task, three other studies did not show significant differences in similar dual task situations (Nordlund et al., 2005; Perry & Hodge, 2000; Silveri et al., 2008). In an effort to explain the different results obtained between the BPT and the other dual task paradigms, we can rule out differences in age or MMSE between the five samples; in fact, Belleville's sample was younger and together with the Johns' (2009) study had higher MMSE scores than the Perry and Hodge (2000) and the Silveri et al. (2008) samples. One remaining potential explanation of these discrepant results is that the tasks used were quite different from each other and may have varied sensitivity in detecting divided attention deficits in MCI patients. The BPT requires participants to recall series of auditorily presented trigrams after different time delays. During the delay, participants are asked to add one to a series of randomly presented numbers presented

orally by the examiner. In contrast, the other three studies employed either the Baddeley dual performance test (Della Sala, Baddeley, Papagno, & Spinnler, 1995) or the dual task test of the Test of Everyday Attention (TEA) battery. In both cases, participants have to perform a visual (or visuo-motor) and a verbal task with no memory rehearsal demands. There are two major differences between these tasks and the BPT. First, there is an important memory component present in the Brown Petersen task but not in the other dual task paradigms. Second, contrary to the other tasks, in the BPT both tasks are presented orally and may compete for sensory based channels rather than central resources. Therefore, it can be argued that the Della Sala and TEA dual task procedures are better measures of divided attention in MCI patients because the BPT has an important memory component that may be deficient in this patient group. This however does not explain Lopez et al. (2006) finding of impaired MCI performance on the Baddeley's dual task. It is interesting to note that Lopez distinguishes between MCI patients with isolated memory impairment (aMCI-s) and amnesic MCI patients with other impairments (aMCI-md) and found that dual task deficits were only present in aMCI-md patients. To sum up, it appears that dual task processing is spared in MCI patients with isolated memory impairments but may begin to be impaired in MCI patients with deficits in multiple cognitive domains.

Working Memory Updating

Working memory updating, refers to the monitoring and processing of incoming information and the continuous updating of its relevance to the task at hand. This function goes beyond the simple "online" maintenance of information and requires the active manipulation of information in working memory. There are several measures of

working memory updating capacity that have been tested in MCI patients. The most commonly used method is the ability to repeat a string of orally presented digits backwards (digit span backward). Two studies have failed to show differences between MCI and controls (Bisiacchi, Borella, Bergamaschi, Carretti, & Mondini, 2008; Kramer et al., 2006) whereas two other studies have shown significant differences (Grundman et al., 2004; Lopez et al., 2006). However, although statistically significant, Grundman et al. (2004) effects were quite small in terms of z score (.4), and Lopez et al. (2004) found the same pattern described in the previous section, with a significant difference between aMCI-md and controls, but no difference between aMCI-s and controls. Another commonly used measure of working memory is the Letter Number Sequencing test (LNS) in which the participant must reorder a string of randomly presented numbers and letters. Two studies have shown deficits in MCI patients on this test (Griffith, Netson, Harrell et al., 2006; Johns et al., 2009) but Belleville et al. (2007) did not find significant group differences on a verbal-only version of the test (Alphabetical recall; Baudot, 1992). Finally, on the N-back task, in which participants have to compare targets seen on the current trial with targets seen on previous trials, Borkowska, Drozd, Jurkowski, and Rybakowski (2007) found a significant difference between MCI patients and controls; however, the validity of this result is questionable because the MCI participants also showed significantly poorer scores on digit forward span (5.2 versus 7 for normal controls) which is unusual and may suggest deficits in short term memory rather than central executive processes in that sample. In sum, there is some evidence of deficits in the capacity of MCI patients to update working memory content although this evidence is confined to LNS.

Inhibition

The concept of inhibition is complex and multifaceted and may be subsumed by different cortical networks depending on what needs to be inhibited (Kok, 1999). For the purpose of this review, inhibition is defined as the ability to override dominant or prepotent responses when required. Perhaps the most widely used measure of response inhibition is the Stroop test. Many different versions of the Stroop test have been developed but in its original and most widely used form, participants are presented with color words printed in different colored ink (i.e., the word red written in blue ink) and are asked to name the color of the ink and refrain from reading the word. In order to perform the task, one has to inhibit the more dominant behaviour which is the tendency to read a word. Several studies have examined MCI performance on the Stroop task and results are mixed. Belleville et al. (2007) found no significant difference between MCI patients and controls on a validated short version of the color Stroop (Victoria Stroop; Regard, 1981). Duong, Whitehead, Hanratty, and Chertkow (2006) tested MCI patients on the Victoria Stroop and also found no significant difference, and on a picture naming Stroop test in which participants are presented with animal drawings with letter strings that were either the name of the animal in the picture (congruent condition) or the name of a different animal (incongruent condition). On this test the authors did find that MCI patients made more errors than controls on the incongruent condition and interpreted these results as evidence that inhibitory processes themselves are not impaired in MCI but become apparent when they involve situations of semantic retrieval. These results were supported by Nordlund et al., (2005) who also found no MCI deficits on the Victoria Stroop but significant group differences on a picture/naming Stroop task similar to Duong et al's

(2006). It therefore appears that the Victoria Stroop may not be sensitive enough to detect subtle MCI response inhibition deficits (but see Johns et al., 2009 for positive results). However, several studies have found MCI deficits on the long version of the color Stroop test (Kramer et al., 2006; Lopez et al., 2006; Perry et al., 2000; Traykov, Raoux, Latour et al., 2007).

Two studies have examined MCI performance in other modalities. Kaufmann, Ischebeck, Weiss et al. (2008) tested MCI performance on a numerical stroop task in which participants had to assess number magnitude on the basis of its numerical value or the actual physical size of the number. Results showed that MCI patients committed significantly more errors on conditions of maximal interference and that these errors tended to be due to fast responses (less than 200 ms) that the authors interpret as being indicative of inhibitory deficits. Zamarian, Semenza, Domahs, Benke, and Delazer (2007) asked participants to multiply two numbers when they saw the addition sign and to add two numbers when they saw the multiplication sign, and found a performance decrement in MCI patients relative to controls.

Although not as widely used as the Stroop, the Hayling test requires participants to finish a sentence with a word that doesn't fit the meaning of the sentence requiring the participant to inhibit context appropriate words that are automatically retrieved. Three studies have examined MCI performance on the Hayling test and whereas two studies reported no significant difference between MCI and controls (Belleville et al., 2007; Bisiacchi et al., 2008), one study (Johns et al., 2009) reports a clear difference between the two groups in the error rate with a large effect size (partial $\eta^2 = .58$). It is difficult to reconcile this very large effect with the negative results reported by Belleville et al.

(2007) since the identical procedure is used. Perhaps the fact that Johns et al. (2009) sample was significantly older may partly explain the difference. However, sample characteristics cannot account for the differences between the Johns' and Bisiacchi's studies because the latter sample was older, less educated and with lower MMSE than the former. Perhaps the differences could be attributed to the fact that the two studies used different scoring procedures and independently developed versions of the original test translated into different languages (i.e., French and Italian).

To sum up, there is mounting evidence that MCI patients exhibit response inhibition deficits and that these deficits are best assessed with the long version of the traditional color Stroop Test.

Task Switching

The most widely used test of switching ability is perhaps the Wisconsin Card Sorting Task (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993). In this test, participants are presented with four stimulus cards placed in front of them and a deck of card and are asked to match each deck card to one of the four key cards and is given feedback each time on whether they are right or wrong. The examiner changes the rules by which the deck cards should be sorted, without warning the participant, after ten correct responses. Nelson (1976) proposed a modified version of the test by making it considerably shorter (48 cards instead of 128), eliminating deck cards that can be classified according to more than one dimension, shortened the number of correct responses before a dimension shift (from 10 to 6) and notified the participants of dimension changes. Regardless of the version used, several measures can be extracted from the card sorting test. The most widely used ones are the number of categories

achieved, the number of perseverative errors (i.e., recorded when the participant persists in responding to a stimulus dimension that is incorrect) and the number of nonperseverative errors. Most studies examining MCI card sorting performance have used the modified version, perhaps because of its ease of use and shorter administration time, or a computerized shortened version of the original WCST (Heaton et al., 1993).

In general, most studies examining MCI performance on card sorting tasks report deficits in number of categories (Baudic, Barba, Thibaudet et al., 2006; Borkowska et al., 2007; Nagahama, Okina, Suzuki et al., 2003; Silveri et al., 2007) and/or perseverative errors (Baudic et al., 2006; Borkowska et al., 2007; Nagahama et al., 2003; Silveri et al., 2007; Traykov et al., 2007). Only two studies have failed to report significant differences between MCI and controls (Nordlund et al., 2005; Perry et al., 2000) but in both cases they only sample one card sorting measure, categories achieved (Perry et al., 2000) or number of correct responses (Nordlund et al., 2005), possibly decreasing the sensitivity of this test. In sum, there appears to be mounting evidence of MCI deficits in card sorting tasks, either the original or abbreviated versions, but that measurement of both perseverative errors and number of categories achieved is advisable to increase the sensitivity of the test. Although the ability to switch tasks is undoubtedly an important component of the WCST, it also relies on several other abilities such as the ability to form abstract concepts and to utilize feedback and for this reason it should not be considered as a “pure” test of switching ability.

Another widely used measure of switching ability is the Trail Making Test which, contrary to the WCST, measures rapid shifts between tasks. In this test, participant’s performance is measured on two parts of the test. In the first part, Trails A, subjects are

asked to connect numbered circles, randomly located across the page, in ascending order. In the second part of the test, Trails B, participants are asked to alternate between number and letters. Most studies examining MCI performance on Trail Making tests have reported significant deficits in time to complete Trails B compared to controls (Baudic et al., 2006; Kramer et al., 2006; Nordlund et al., 2005; Silveri et al., 2008). However, two studies have failed to detect significant differences (Lopez et al., 2006; Traykov et al., 2007) although Traykov et al. showed a trend toward significance ($p=.07$) and their sample had very high MMSE scores ($MMSE = 29$) suggesting it may have been a minimally impaired group of MCI patients. Lopez et al. (2006) actually found a significant difference between MCI and controls on the Trails B but the two groups also differed on the Trails A test and when the Trail Making ratio was compared (Trails B/Trails A), no difference was found suggesting that performance differences on the Trails B may not be due to switching difficulties but rather to processing speed and/or visual processing deficits in this MCI sample. In fact, this sample of MCI patients also showed severe deficits on the Raven matrices test, a measure that is often used as a premorbid estimate of nonverbal intelligence, suggesting that visual processing capacities may have been impaired in this MCI group. A less often used test of rapid attention shifting is the Visual Elevator from the TEA battery. In this test, participants have to count upwards and downwards following the movement of an elevator, requiring the rapid switch between arithmetical operations. Two studies (Perry et al., 2000; Silveri et al., 2008) have reported differences between MCI and controls on performance speed but not on error rate.

The tests reviewed so far are all taken from the clinical literature. To date only one study has examined MCI ability on a task switching paradigm. Belleville, Bherer, Lepage, Chertkow, and Gauthier (2008) asked participants to alternate between adding and subtracting two digits appearing on the screen. Although they found AD patients impaired on the task, MCI patients' performance was not significantly different from controls. Upon close examination of their procedure however, the study reveals several methodological limitations. First, the authors chose a set of stimuli that did not afford task overlap and allowed participants to respond orally (i.e., univalent response), creating an environment in which the literature reviewed above clearly predicts absence of, or very small switch costs. However, the authors still report a switch cost of approximately 50 ms for both MCI and controls. It is possible that the extra time taken on switch relative to repeat trials was due to the fact that switch trials were preceded by a cue which consisted of a centrally located "+" or "-" whereas repeat trials were not. It is possible that participants' attention was directed in the central location during switch trials and had to then be redirected to peripheral locations to process the targets. Therefore, it is doubtful that the switch cost measured in this study is a measure of any form of executive function, whether task preparation or resolution of proactive interference.

An important point raised by the Belleville et al. (2008) study is the differences and similarities between the task-switching paradigm and the Trail Making test. Both tests provide estimates of the cost of performing tasks in mixed blocks compared to single task situations. Whereas the task switching paradigm deducts performance on the single task block from performance on the mixed task block to arrive at the mixing cost, the Trail Making Test divides performance on Trails B and performance on Trails A to

arrive at the Trail Making ratio; although calculated differently, the two measures are conceptually similar and, as described earlier (see mixing cost section), is thought to be a measure of increased working memory demands during mixed blocks and of proactive interference¹. Support for this line of reasoning comes from a study that found a significant correlation between Trails B and task switching performance (Arbuthnott & Frank, 2000). However, the task switching paradigm allows for a more fine grained analysis of switching ability by comparing switch and repeat trials within mixed block conditions (i.e., the switch cost).

Executive Tests that Predict Conversion to AD

In the preceding section, the evidence in favor of executive deficits in MCI has been reviewed. Strong evidence has been accumulated suggesting that MCI is associated with deficits in response inhibition and switching ability. Although documenting group differences between MCI and controls is important in furthering our understanding of the gray area between normal cognitive aging and dementia, from a clinical perspective, what is most important is to determine which functions and tests can best predict imminent transition to dementia. We already reviewed evidence suggesting that MCI patients who have impairments beyond episodic memory are at increased risk of developing AD in the subsequent three to five years compared to MCI patients who have isolated memory impairments. We also discussed evidence implicating executive functions as the earliest and most frequently impaired cognitive domain after episodic memory. The next question to answer is what particular executive functions and tests are most sensitive to AD conversion.

¹ Since both the Trails B test and Belleville et al's (2008) design do not use ambiguous stimuli and bivalent responses, proactive interference is unlikely to be the source of the mixing cost.

Several studies have examined the usefulness of tests of executive function in predicting conversion to AD. Tierney, Szalai, Snow, et al. (1996) followed a group of MCI patients for 2 years and found that taken together, the RAVLT (Rey Auditory Verbal Learning Test; Rey, 1964) delayed recall and Mental Control (Wechsler Memory Scale Revised), a test that requires participants to recite overlearned strings of information (e.g., days of the week, months of the year) forward and backward had a modest sensitivity and excellent specificity in predicting AD converters. Bozoki et al. (2001) and Laukka et al. (2004) reported that MCI patients that converted to AD showed impaired performance on Block Design (Wechsler Memory Scale III; WMS III), a test that requires visuo-spatial integration and strategy, at baseline testing two and three years prior to diagnosis respectively. Also, several studies (Albert et al., 2001; Blacker et al., 2007; Chen et al., 2000; Daly et al., 2000) have shown that Trails B and verbal episodic memory are the most sensitive combination of tests for prediction of transition to AD. Curiously, although several studies have reported MCI deficits on the long version of the Stroop test, it does not appear to be a sensitive marker of AD conversion.

Overview of the project

The MCI and executive function literature reviewed above suggests that as a group, MCI patients are impaired in situations where they are required to alternate frequently between tasks and that Trails B appears to be a sensitive marker of MCI transition to AD. However, MCI performance on an experimental task switching paradigm has been limited so far to one study with important methodological flaws. In theory, the task switching paradigm is a more sensitive marker of executive control than other clinical tests widely used to assess task-switching ability (i.e., Trails B and WCST)

and, coupled with the use of electrophysiological measures, should allow for a better understanding of the different control processes required for effective task switching that are affected in MCI.

The overarching goal of this project was to examine task switching ability in MCI patients. The project is divided into two chapters that are manuscripts that have been submitted for publication. We set out to test MCI participants on a cued task switching paradigm; however, it quickly became apparent that a large minority of MCI participants were not able to perform the task. In Manuscript 1, we sought to characterize this MCI subset to better understand the factors associated with poor task switching ability. We were able to compare MCI patients that were not able to perform the task with MCI participants that could perform the task and with age-matched controls on neuropsychological, neuroanatomical, demographic, health related, and genetic data. Also, we were able to ascertain their diagnostic status at four year follow-up which allowed us to determine whether failing to perform this task was associated with increased risk of developing AD.

In the second manuscript we collected behavioural and event-related brain potential (ERP) measures from the MCI patients that were able to perform the task and from age-matched controls. This study is an in-depth analysis of the control processes that may become impaired in MCI.

The thesis then ends with a general discussion that attempts to integrate the findings from the two manuscripts followed by a discussion on how these results contribute to our understanding of mild cognitive impairment.

MANUSCRIPT 1

Task switching ability differentiates between two distinct groups of MCI patients.

Marco Sinai¹, Natalie A. Phillips^{1,2}, Howard Chertkow², and Noor Jehan Kabani³

¹ Department of Psychology/Centre for Research in Human Development, Concordia University, Montreal, Québec, Canada

² Lady Davis Institute for Medical Research/Jewish General Hospital, Montreal, Québec, Canada

³ Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada

Corresponding Author:

Natalie A. Phillips, Ph.D.
Centre for Research in Human Development,
Department of Psychology, Concordia University,
7141 Sherbrooke Street West,
Montréal, Québec, Canada, H4B 1R6
Phone: 514-848-2424 ext. 2218, fax: 514-848-4537
E-mail: Natalie.Phillips@concordia.ca

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Authors' Note

Marco Sinai, Department of Psychology/Centre for Research in Human Development, Concordia University, Montreal, Canada; Natalie A. Phillips, Department of Psychology/Centre for Research in Human Development, Concordia University; Lady Davis Institute for Medical Research/Jewish General Hospital, Montreal, Canada; Howard Chertkow, Lady Davis Institute for Medical Research/Jewish General Hospital, Montreal, Canada; and Noor Jehan Kabani, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada.

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Correspondence concerning this article should be addressed to Natalie A. Phillips, Ph.D., Centre for Research in Human Development, Department of Psychology, Concordia University, 7141 Sherbrooke Street West, Montréal, Québec, Canada, H4B 1R6, Phone: 514-848-2424 ext. 2218, fax: 514-848-4537, E-mail:

Natalie.Phillips@concordia.

Authors' Contributions

Marco Sinai: study design, subject recruitment, cognitive and medical data collection, data reduction and statistical analysis, interpretation, and write-up.

Natalie Phillips: study design, subject recruitment, statistical analysis, and interpretation.

Howard Chertkow: subject recruitment, cognitive and MRI data collection.

Noor Kabani: MRI data reduction and interpretation.

Abstract

There is evidence of executive function deficits in mild cognitive impairment (MCI). Task switching ability has been shown to predict MCI transition to Alzheimer's disease. We tested task switching ability using a cued task switching paradigm in 27 MCI patients. Sixteen patients could perform the task (MCI-able) and 11 could not (MCI-unable). Neuropsychological, neuroanatomical, genetic, demographic, health-related data are presented for the MCI sub-groups and normal controls. The three groups did not differ on age, gender, APO E4 frequency, and atherosclerotic risk factors. However, compared to the control group, the MCI-unable group had significantly lower scores on episodic memory and the Trails B test, and had smaller temporal and frontal lobes. In contrast, the MCI able group did not differ from the control group except on episodic memory tests. Further, a significantly larger proportion of MCI-unable patients transitioned to dementia or died compared to the MCI-able group at 4-year follow-up. We interpret these results as pointing to the presence of premorbid factors that may interact with AD pathology to accelerate cognitive decline.

Task switching ability differentiates between two distinct groups of MCI patients.

Although the earliest manifestation of cognitive dysfunction associated with AD is widely recognized to be episodic memory decline, increasing evidence points to a decline in attention and executive functions in early AD (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Baudic, Barba, Thibaudet, et al., 2006; Duke & Kaszniak, 2000; Perry & Hodges, 1999; Perry, Watson, & Hodges, 2000; Swanberg, Tractenberg, Mohs, et al., 2004). The development of new therapeutic agents for the treatment of AD symptoms, and the hope of a therapeutic breakthrough highlight the increasing importance of early diagnosis. Patients with mild cognitive impairment (MCI) are of particular interest in this regard because these individuals have been shown to be at greater risk for conversion to AD than their age peers in the general population. Estimates of MCI progression to AD are in the 10–25% per year range compared with healthy elderly controls who progress at a rate of 1–2% per year (Petersen & Negash, 2008; Petersen, Smith, Waring, et al., 1999; Petersen, Stevens, Ganguli, et al., 2001). However, this high risk population has proved to be highly heterogeneous, with a significant minority of MCI patients returning to a normal profile and another sizeable subgroup remaining stable even up to a ten-year follow-up (e.g., Ganguli, Dodge, Shen, & DeKosky, 2004). The ability to distinguish those MCI patients who are more likely to imminently progress to AD from those who will remain stable or will improve to normal status is of obvious clinical importance.

MCI was originally defined by the presence of symptomatic memory problems in conjunction with relatively preserved daily functioning (Petersen et al., 2001). However, the concept has evolved to encompass a variety of symptom clusters. In addition to the original “pure” form of amnesic MCI, which presents with relatively isolated episodic

memory deficits, other MCI subtypes have been identified. First, amnesic multiple-domain MCI is characterized by a predominant amnesic deficit but concurrent with deficits in other cognitive domains. Second, non-amnesic single-domain MCI, is defined as objective cognitive decline in one cognitive domain that is not memory. Finally, nonamnesic multiple domain MCI is defined as deficits on multiple domains that are not related to memory. This study focuses on amnesic MCI patients of both the single- and multiple-domain subtype; thus, reference to MCI patients in this paper implicitly assumes amnesic MCI.

There is evidence that MCI patients with deficits in multiple cognitive domains are at increased risk of transitioning to dementia relative to MCI patients with isolated episodic memory deficits. For example, Rasquin, Lodder, Visser et al., (2005) found very high negative predictive validity of the aMCI-s subtype, indicating that the chance of an MCI patient with isolated memory deficits to transition to AD in the following two years was low. Similarly, Artero, Petersen, Touchon, and Ritchie (2006) found that at two year follow-up, MCI patients with isolated memory deficits showed a less than 1% rate of AD conversion compared to a 13% rate of conversion for MCI patients with deficits in memory and other cognitive areas. Also, Bozoki, Giordani, Heidebrink et al (2001) found a 6% conversion rate for MCI patients with isolated memory loss compared to a 50% conversion rate for MCI patients with deficits in memory and other cognitive domains. Of all the non-memory cognitive domains affected in MCI, attention and executive function have been shown to be the best predictors of MCI conversion to AD (Albert, Moss, Tanzi, & Jones, 2001; Arnaiz, & Almkvist, 2003; Backman, Jones, Berger et al., 2005; Belleville, Chertkow, & Gauthier, 2007; Blacker, Lee, Muzikansky, et al.,

2007; Bozoki et al., 2001; Chen, Ratcliff, Belle et al., 2000; Daly, Zaitchik, Copeland et al., 2000; Fabrigoule, Rouch, Taberly et al., 1998; Kaufmann, Ischebeck, Weiss et al., 2008; Kramer, Nelson, Johnson et al., 2006; Perry, Watson, & Hodges, 2000; Rapp & Reischies, 2005; Ready, Ott, Grace, & Cahn-Weiner, 2003; Silveri, Reali, Jenner, & Puopolo, 2007; Traykov, Raoux, Latour et al., 2007; van der Flier, Van Den Heuvel, Weverling-Rijnsburger et al., 2002; Wylie, Ridderinkhof, Eckerle, & Manning, 2007; Zamarian, Semenza, Domahs, et al., 2007; Zhang, Han, Verhaegen, & Nilsson, 2007). Furthermore, it appears that only some attentional and executive functions are impaired early in the disease. One of these is task switching ability as evidenced by several studies showing MCI impairments on the Trail Making B test, a widely used clinical test of shifting abilities (Lopez, Becker, Jagust et al., 2006; Silveri et al., 2008; Zhang et al., 2007). Others have highlighted its ability to predict MCI conversion to AD (Albert et al., 2001; Chen et al., 2002; Daly et al., 2000; Blacker et al., 2007; Rapp & Reischies, 2005).

Task Switching

The task switching paradigm (e.g., Rogers & Monsell, 1995) has been widely used to study set-shifting in the experimental cognitive literature. We chose a cued task switching paradigm to explore impairment in MCI because it is a widely used experimental task that allows for the parcellation of attentional control such as the ability to multitask, goal-directed preparatory activity, and resolution of stimulus-response conflict (Allport, Styles, & Hsieh, 1994; Meiran, Chorev, & Sapir, 2000; Rogers & Monsell, 1995). In the cued task switching design, the order of each task to perform is random and the participant is cued on every trial as to what task to perform next. This

reduces task demands such as working memory relative to designs where the participant has to keep track of what task to perform next.

The broadest measure of switching ability is the contrast between repeat trials during blocks where the participant has to switch between two tasks (i.e., a mixed block of trials) and repeat trials in blocks where the participant has to perform only one task (i.e., a homogeneous block of trials); this contrast is referred to as the mixing cost. The cost, usually expressed in reaction time (RT) or error rates (ER), is believed to reflect the engagement of extra monitoring processes during mixed as opposed to single task blocks (Meiran et al., 2000) as well as decreased availability of cognitive resources due to the requirement of maintaining two tasks in working memory (Kray & Lindenberger, 2000). Second, the most widely studied aspect of the task switching paradigm is the contrast between trials where the participant must switch to a different task (i.e., a switch trial) and trials where the participant is allowed to repeat a task (i.e., a repeat trial) which has been termed the switch cost. This cost has been conceptualized as a composite of both endogenous top-down control processes and stimulus-driven bottom-up conflict resolution processes (Rogers & Monsell, 1995; Allport & Wylie, 2000).

Neural substrate of task switching

Converging evidence from fMRI and ERP studies, suggests that both frontal and posterior parietal regions are involved in task switching. Evidence from fMRI emphasize the cooperation between frontal and parietal areas during task switching. Whereas prefrontal regions are involved in establishing and maintaining general task representations during task preparation as well as selecting the appropriate response, parietal regions are involved in the representation of the candidate S-R associations

(Brass, Ulsperger, Knoesche et al., 2005; Wylie, Javitt, & Foxe, 2004). This view is supported by electrophysiological studies showing increased negativity at frontal and parietal sites (Goffaux, Phillips, Sinai, & Pushkar, 2006; Karayanidis, Coltheart, Michie, & Murphy, 2003) during task preparation.

Interestingly, similar brain regions have been implicated in MCI patients. Although structural Magnetic Resonance (MRI) techniques typically reveal atrophy in medial temporal lobe regions in MCI (DeCarli, Frisoni, Clark et al., 2007; deToledo-Morrell, Stoub, Bulgacova et al., 2004; Korf, Wahlund, Visser, & Scheltens, 2004; Wolf, Hensel, Kruggel et al., 2004), some studies have also highlighted regions of atrophy in parietal (i.e., posterior parietal lobes) and frontal lobes (i.e., medial frontal cortex; Pennanen, Testa, Laakso et al., 2005; Bell-McGinty, Lopez, Meltzer et al., 2005).

Current Study

Given the growing literature suggesting the presence of attention and executive function deficits in early AD and their tendency to predict MCI conversion to AD, we set out to examine task switching ability in patients with MCI. We did this in two ways. The first consists of a comparison between MCI participants and healthy normal controls using behavioural and electrophysiological measures to examine the timeline of task switching processes (see Sinai, Phillips, & Chertkow, submitted, for a discussion of those results). The second was to describe and understand the important differences we observed between the MCI patients who were able to perform the task adequately and those who were fundamentally unable to perform the task at all. This is the focus of the present paper. In other words, we observed that a substantial minority of MCI patients that we recruited could not perform the task (referred to below as the “MCI-unable”

group). This paper characterizes those MCI patients with severely impaired task switching abilities, in comparison with the subgroup of MCI patients who were able to perform the task successfully (referred to below as the “MCI-able” group) and normal controls. To this end, we present data on demographic and medical background, neuropsychological function, as well as genetic and neuroanatomical data.

With respect to medical factors, we expected the MCI-unable group to be further along in the disease process (i.e., longer time since diagnosis) relative to the MCI-able participants and, thus, may have developed deficits in executive function. We also examined atherosclerotic risk as it pertains to risk for vascular dementia. Several studies have shown that vascular disease has been associated with increased risk of AD pathology and more rapid cognitive decline in AD patients (Fein, Di Sclafani, Tanabe, et al., 2000; Kivipelto, Laakso, Tuomilehto, Nissinen, & Soininen, 2002; Launer, Ross, & Petrovitch, 2000; Mungas, Reed, Ellis, & Jagust, 2001; Vermeer, Prins, den Heijer, et al. 2003). Also, a recent study (Behl, Bocti, Swartz et al., 2007) found an association between cholinergic pathway hyperintensities and a decline in executive functions; we therefore hypothesized that the MCI-unable group would show increased atherosclerotic risk factors relative to the other two groups.

We collected structural magnetic resonance imagery (MRI) data for all three groups. As reviewed above, both frontal and parietal areas have been involved in task switching and some studies have shown significant atrophy in these areas in MCI compared to controls. Therefore, we expected to find significant differences in the MCI-unable group relative to the MCI-able group in parietal and frontal areas.

Regarding genetic data, we compared the frequency of occurrence of the Apolipoprotein E (ApoE) 4 allele in the three groups. To our knowledge, no study has directly examined the effects of ApoE polymorphism on task switching; however, the presence of ApoE4 has been widely recognized as a significant risk factor for AD pathology (Corder, Saunders, Strittmatter, et al., 1995; Slooter, van Duijn, & Bots, 1998) and has been associated with working memory and covert attention deficits in non demented individuals (Parasuraman, Greenwood & Sunderland, 2002; Rosen, Bergeson, Putnam et al., 2002). Given this evidence, we expected to find higher frequency of ApoE 4 carriers in the MCI-unable group.

Finally, we present four-year follow-up data on the participants' diagnostic status to determine the possible predictive utility of this executive function deficit in this MCI group. Given previous reports of increased risk of AD conversion in MCI patients with deficits in multiple cognitive domains (Bozoki et al., 2001; Artero et al., 2006; Rasquin et al., 2005), we expected a larger proportion of conversions to AD in the MCI-unable group relative to the MCI-able participants.

To preview the results, we did not find evidence for increased vascular risk in the MCI-unable group, but we found a confluence of factors suggesting that MCI-unable patients possess less cognitive and brain “reserve” compared to the other two groups, and this may leave them vulnerable to severe cognitive decline.

Method

Participants

MCI group

MCI subjects were recruited from the Memory Clinic of the Sir Mortimer B. Davis–Jewish General Hospital (JGH), a tertiary care referral center of McGill University, Montreal. Their investigations included full medical, neuropsychological, and neuroradiological evaluations.

Twenty-seven individuals identified as having mild cognitive impairment (MCI) participated. They all received CDR scores of 0.5, indicating mild forgetfulness, minimal word finding difficulties, and a slight impairment in mental efficiency (Hughes et al., 1982). All patients met the original Petersen's (Petersen et al., 1999) criteria for mild cognitive impairment which included a reported decline (by either the individual or family) in memory function which was gradual and of at least 6 months duration, a documentation of impaired performance (i.e., ± 1.5 SD) on objective neuropsychological tests with appropriate norms for age and/or education, the absence of significant impairment in activities of daily living, and failure to meet the criteria for dementia, as determined by the assessing physician in the Memory Clinic.

Of these 27 MCI patients, eleven were not able to perform the task and were classified as the MCI-unable group whereas 16 were able to perform the task switching task and were classified as the MCI-able group for the purpose of this study. The MCI-unable patients were classified as such when they exceeded a 20% error rate on any one block. Six MCI-unable patients were not even able to complete the homogeneous blocks whereas 5 MCI-unable patients completed the homogeneous blocks but had extreme

difficulty on heterogeneous block. Although theoretically distinct, the two groups were combined for statistical analyses due to low sample size.

Control group

Nineteen healthy elderly adults were recruited from the Herzl Family Medicine Clinic of the JGH and screened at the JGH Memory Clinic to ensure they had no symptoms of dementia and their neuropsychological profile was normal (Clinical Dementia Rating, CDR = 0).

All participants gave informed consent for their participation. The study was approved by the Jewish General Hospital/McGill University and Concordia University Human Ethics committees.

Neuropsychological Evaluation

As part of their diagnostic clinical examination, the MCI participants underwent an extensive neuropsychological evaluation with the following tests:

Global cognition: the Mini-Mental State Exam (MMSE; Folstein et al., 1975), the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), Orientation and Mental Control from the Wechsler Memory Scale III (WMS–III; Wechsler, 1997), Digit Symbol Coding from the Wechsler Adult Intelligence Scale III (WAIS–III; Wechsler, 1997).

Episodic memory: Story A from the Logical Memory I and II (WMS–III; Wechsler, 1997) and the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958) to assess immediate and delayed verbal recall, Visual Reproduction I and II (WMS–III; Wechsler, 1997) to assess immediate and delayed visual recall.

Working memory: Letter Number Sequencing and Spatial Span from the WMS–III (Wechsler, 1997).

Executive functions: the Clock Drawing Test (Shulman et al. 1986) to assess goal directed behaviour; letter (letters F, A, and S) and semantic (animal) fluency (Strauss, Sherman & Spreen, 2006); the Trail Making Test (Lezak, 2004) to assess the ability to switch between tasks; and the Color Stroop Test (Victoria version; Lezak, 2004) to assess selective attention and response inhibition.

Visuo-constructional ability: Block Design (WAIS-III; Wechsler, 1997);

Language functions: Similarities (WAIS-III; Wechsler, 1997) to assess verbal abstract reasoning abilities, and the Boston Naming Test (Kaplan et al., 1983) to assess confrontation naming skills.

This same neuropsychological battery was also administered to the normal control participants.

Experimental Task Switching Paradigm

All stimuli in the experimental task were presented in 24 font size, Times New Roman white font, on a black background in the middle of a standard 15 inch computer screen. A cue (the word “Number” or “Letter”) instructed the participants on the upcoming task. The experimental stimuli consisted of bivalent letter/digit pairs (e.g., 5G or A2) and letter/digit-neutral pairs (e.g., %A). The compound stimuli were constructed from the following stimulus pools: letters: A, E, I, U, L, M, G, K; numbers: 2, 3, 4, 5, 6, 7, 8; and neutral symbols: %, #, &, \$.

The experimental procedure is depicted in Figure 3. Participants were asked to perform either a letter or number classification task on any given trial. The letter task entailed classifying a letter being as a vowel or consonant and responding with either the right or the left key. The digit task entailed classifying a digit as being either an even or

odd number and responding with either the right or left key. Each trial began with the presentation of a cue (i.e., letter or number) that instructed the participant as to what task to perform next. The cue remained on the screen for 1000 ms and was replaced by the presentation of the compound stimulus that remained on the screen until the participant responded or up to a maximum of 10 seconds. The following trial began following a 200 ms interval. Each participant was presented with eight blocks consisting of six practice trials and 90 experimental trials each. The first two blocks, called homogeneous blocks, consisted of trials cued by only one task, either “Letter” or “Number”, the order of which was counterbalanced across participants. In other words, no switching between tasks was required in these blocks. The following six blocks, called heterogeneous blocks, consisted of a semi-random mixture of letter (50%) and number (50%) task trials.

Participants held a standard mouse with both hands and responded by pressing either the left or right button with their thumbs. In case of response error, feedback was signaled by a 400 Hz 100 ms tone immediately following the response and the following trial began after an 800 ms delay. Participants were instructed to respond as quickly as possible while keeping errors to a minimum.

Image acquisition and processing

MRI scans at the Montreal Neurological Institute were acquired on a Philips Gyroscan ACS, 1.5 Tesla super-conducting magnet system. T1-weighted images were obtained using three-dimensional spoiled gradient-echo acquisition with sagittal volume excitation (TR518, TE510, flip angle 30°, 1 mm isotropic voxels, 140–180 sagittal slices). The scans were then processed using a standard set of image processing algorithms (Zijdenbos, Forghani, & Evans, 2002). Briefly, this first entailed correcting

for intensity inhomogeneity in the images using the N3 algorithm (Sled, Zijdenbos, & Evans, 1998) and then linearly registering the images to a standardized space (Collins, Neelin, Peters, & Evans, 1994). The Automatic Nonlinear Image Matching and Anatomical Labeling (ANIMAL) volumetric registration package and the Intensity Normalized Stereotaxic Environment for the Classification of Tissue (INSECT) procedure were used to quantify 16 cortical regions (see Table 8 for a list of cortical areas) by registering the T1-weighted images to a probabilistic atlas (Collins, Zijdenbos, Baare, & Evans, 1999). We chose these 16 areas according to two main principles. First, temporal lobe areas were included as the earliest regions affected in AD. Second, selected parietal and frontal areas were included because of their relevance in executive functions in general and task switching in particular.

Other study variables

Sociodemographic variables. Reported age was in years, at the time participants attempted the task switching paradigm. Education was assessed as the number of years of formal education.

Depression. Symptomatic depression was estimated with the Geriatric Depression questionnaire (GDS; Yesavage, Brink, Rose, et al. 1982) and was collected at the time of the neuropsychological evaluation.

Time since diagnosis. This variable represents the number of months elapsed between the date of the diagnosis of mild cognitive impairment and the task switching session. It is used in this study as an estimate of disease progression.

Genetic Data. Genotyping of apolipoprotein E was carried out using DNA extracted from peripheral leukocytes. DNA was amplified by polymerase chain reaction

(PCR), digested with HhaI, and separated by electrophoresis on an 8% polyacrylamide non-denatured gel. DNA fragments were viewed by ultraviolet illumination after the gel was treated with ethidium bromide for 30 minutes. Subjects were categorized as e4 carriers if they carried at least one copy of the e4 allele. One participant in the MCI-unable group had a 2/4 genotype and was not considered in the analyses.

Vascular risk factors. Information on atherosclerotic risk factors was collected from the patient's medical file and, in the case of participants in the control group, from a health questionnaire as part of the study intake. Each risk factor was coded as present or absent (1, 0) regardless of the severity. Six risk factors were included: 1) a smoking habit within the past 6 months, 2) prior history of a transient ischemic attack (TIA) or stroke, 3) prior history of atherosclerotic heart disease, 4) the presence of hypertension, 5) hypercholesterolemia, and 6) diabetes was also ascertained through the patient's medical records as well as the medication list. An overall atherosclerotic risk factor (ARF) was computed by adding the number of risks; thus, a higher number indicates a higher risk for atherosclerotic disease

Four-year follow-up

We obtained the diagnostic status of each participant approximately four years after the task switching session ($M=49$ months, $SD=4.9$). Two MCI-unable patients were lost to follow-up.

Data analyses

Because contrasts between the two MCI groups were considered planned comparisons, analyses were conducted even in the absence of a significant omnibus effect and statistical significance was set at the $\alpha = .05$ level. Socio-demographic and

health related variables were analyzed with the Chi-square (χ^2) statistic in the case of discrete variables and with a multivariate analysis of variance (MANOVA) in the case of ratio data. In the case of χ^2 analyses, $\alpha = .025$ level was used for post-hoc comparisons between the control group and the two MCI groups.

Neuropsychological data were analyzed using a multivariate analysis of covariance (MANCOVA) on the 25 measures from the 17 neuropsychological tests described above, with years of education and depression as covariates because these differed between the groups. Statistical significance was followed up by post-hoc comparisons using Tukey.

Neuroanatomical data were analyzed using a repeated-measures mixed ANCOVA with group as the between group factor, laterality and region as within group factors, and occipital lobe volume and education as covariates. The Greenhouse-Geisser (1959) correction for non-sphericity employed when appropriate. Following convention, unadjusted degrees of freedom are reported, along with the Greenhouse-Geisser adjusted p-value. Mean square error (MSE) values reported are those corresponding to the Greenhouse-Geisser correction. Main effect of variables are reported first but described only if they did not interact with other variables. In the case of significant interactions, post-hoc Bonferroni-corrected ANOVAs were conducted where appropriate. Statistical significance is assumed at the $\alpha = .05$ level unless otherwise specified.

Results

Socio-demographic and health related results

Table 6 summarizes the socio-demographic and health variables for the three groups. The overall MANOVA was significant ($F_{(8,82)} = 2.9, p = .005, \text{partial } \eta^2 = .233$). Follow-up analyses revealed that the three groups differed on the following variables: years of education ($F_{(2,43)} = 6.2, p = .004, \text{partial } \eta^2 = .224$) with the MCI-unable group showing less education ($M = 10.7, SE = .9$) than the control group ($M = 14.5, SE = .7; p = .004$) but no significant difference between controls and MCI-able or between the two MCI groups; depression scores ($F_{(2,43)} = 6.4, p = .004, \text{partial } \eta^2 = .230$) with MCI-unable patients reporting higher symptoms ($M = 9.4, SE = 1.4$) than MCI-able patients ($M = 4.8, SE = 1.2$) and than controls ($M = 2.9, SE = 1.1$). However, the three groups did not differ on age ($F_{(2,43)} = .13, p = .87$) and vascular risk ($F_{(2,43)} = .9, p = .39$). Chi-square analyses indicated that no group differences were found for other socio-demographic or health related variables including genetic data and therefore are not presented further (all $p > .12$).

Neuropsychological Results

Table 7 summarizes neuropsychological test performance for the three groups. A MANCOVA was performed with years of education, GDS scores, and MoCA scores as covariates. The first two covariates were chosen due to the differences reported above. The MoCA was included as a covariate because the three groups differed on this measure ($F_{(2,43)} = 16.0, MSE = 6.5, p < .001$) and, thus, we needed to rule out the possibility that any group difference may simply be due to global cognitive differences.

The overall MANCOVA was significant ($F_{(50,34)}= 2.4, p=.004, \text{partial } \eta^2 = .780$). Follow-up analyses revealed that the three groups differed on RAVLT Immediate Recall ($F_{(2,40)}= 6.5, p=.003, \text{partial } \eta^2 = .246$), RAVLT Delayed Recall ($F_{(2,40)}= 7.6, p=.002, \text{partial } \eta^2 = .277$), RAVLT Recognition memory ($F_{(2,40)}= 3.9, p=.027, \text{partial } \eta^2 = .165$), Trail Making B completion time ($F_{(2,40)}= 3.9, p=.028, \text{partial } \eta^2 = .164$), and Trail Making A/B completion time Ratio ($F_{(2,40)}= 6.9, p=.003, \text{partial } \eta^2 = .258$). The follow-up analyses described next revealed that, in general, MCI-able patients did not differ from the control group except on measures of verbal episodic memory whereas the MCI-unable patients showed lower scores on episodic memory measures and on the Trails B test compared to normal controls.

MCI-able vs. MCI-unable. The two MCI groups differed on the RAVLT Recognition score, with MCI-unable patients recalling fewer items ($M=8.9, SE=.9$) than MCI-able patients ($M=12.4, SE=.7; p=.03$). The two MCI groups also differed on the Trail Making Completion Time, with MCI-unable patients performing slower ($M=233.5, SE=21.4$) than MCI-able patients ($M=111.2, SE=16.9; p=.026$) and on the Trail Making Ratio, with MCI-unable patients being disproportionately slowed on Trails B relative to Trails A ($M=3.9, SE=.5$) compared to MCI-able patients ($M=1.3, SE=.4; p=.002$).

Control vs. MCI-unable. The MCI-unable group performed more poorly than the control group on the RAVLT, recalling fewer items on the Delayed Recall subtest ($M=2.1, SE=.9$ versus $M=8.5, SE=.6; p=.002$, respectively) and recognizing fewer items on Recognition subtest ($M=8.9, SE=.9$ versus $M=12.9, SE=.6; p=.05$). The two groups also differed on the Trail Making Ratio, with MCI-unable patients showing a larger ratio ($M=3.9, SE=.5$) than controls ($M=1.3, SE=.4; p=.012$).

Control vs. MCI-able. The MCI-able group performed more poorly than the control group only on the RAVLT, recalling fewer items on the immediate recall subtest ($M=5.1$, $SE=.7$ versus $M=9.3$, $SE=.6$, respectively; $p=.003$), and on the delayed recall subtest ($M=4.5$, $SE=.7$ versus $M=8.5$, $SE=.6$, respectively; $p=.008$).

Structural MRI Results

Brain volume data were analysed using a mixed ANOVA with group (control, MCI-able, MCI-unable) as the between subject factor and laterality (right and left hemisphere) and 16 cortical regions as within subject factors. Please see Table 8 for list of brain regions included in the analysis. There was a main effect of laterality ($F(1,43)=13.7$, $p<.001$, partial $\eta^2 = .243$) with the right hemisphere ($M=12156$ mm³, $SE=332$) larger than the left ($M=11976$ mm³, $SE=331$). However, the laterality factor did not interact with group ($p=.68$). Therefore, the two hemispheres were collapsed for all subsequent analyses.

There was a significant main effect of group ($F(2,43)=6.9$, $p=.002$, partial $\eta^2 = .244$) with MCI-unable patients ($M= 20858$ mm³, $SE= 1356$) having significantly lower volume than the control group ($M= 27193$ mm³, $SE= 1032$; $p=.002$) and the MCI-able group ($M= 25294$ mm³, $SE= 1125$; $p=.047$). The MCI-able and control group did not differ ($p=.66$). To rule out the possibility that the above group differences were due to reduced whole brain volume in the MCI-unable group, an ANCOVA was performed with group (control, MCI-able, MCI-unable) as the between subject factor and 16 cortical regions (Table 8) as within subject factors and occipital lobe volume as a covariate. We choose occipital lobe volume because we reasoned that it has been shown to be the least affected by AD pathology (Braak & Braak, 1991; Rowe, Ng, Ackermann et al., 2007)

and therefore constitutes a better control region than whole brain volume. Number of years of education was also added to the model as a co-variate to account for the significant difference between the MCI-unable group and the other two groups and because it correlated significantly with several brain regions under consideration (i.e., lateral and medial orbital cortex, middle and inferior frontal gyri, superior temporal gyrus, hippocampus and insula). We did not add depression scores and ARF to the model because these variables did not correlate with regional volumes in any consistent fashion.

This second analysis revealed a significant main effect of group ($F(2,41)=5.3$, $p=.009$, partial partial $\eta^2 = .204$) with the MCI-unable group having significantly lower volume than the control group ($p=.008$) but no other significant group difference (all $p>.21$). There was a significant interaction between the group and region factors ($F(30,615)=1.9$, $p=.031$, partial $\eta^2 = .088$). Bonferroni-corrected follow-up analyses revealed the following group differences.

MCI-able vs. MCI-unable. There was a trend toward the MCI-unable group having a smaller medial frontal gyrus ($M=23509 \text{ mm}^3$, $SD=5864$) compared to MCI-able patients ($M=29857 \text{ mm}^3$, $SD=6541$; $p=.08$). The two groups did not differ on any other region.

Control vs. MCI-unable. The MCI-unable group showed significantly lower volume in frontal lobes regions (see Table 8 for means and standard deviations), including the medial orbital gyrus ($p=.005$), the lateral orbital gyrus ($p=.004$), the middle frontal gyrus ($p=.004$), the medial frontal gyrus ($p=.03$), the cingulate gyrus ($p=.048$), and

the precentral gyrus ($p=.047$). Also, the two groups differed in two temporal lobe areas, namely the hippocampus ($p=.02$) and insula ($p=.03$).

Control vs. MCI-able. These two groups did not show any significant differences including on hippocampus volume ($p=.72$).

Status at four-year follow-up

Table 9 shows the diagnostic status of all participants at four-year follow-up. Normal controls were largely unaffected except for two deceased participants. Of the 16 MCI-able patients, five reverted to normal status (31.25%), eight remained stable and maintained the MCI diagnosis (50%), two transitioned to AD (12.5%) and one patient died (6.25%). In contrast, in the MCI-unable group, no patients showed improvement (0%), three remained stable (27%), three transitioned to AD (27%), and three were deceased (27%). Follow-up status on two patients in this group was unable to be determined (18%).

In an effort to increase power, the follow-up categories were collapsed into three levels: Improved, Stable, and Declined. As discussed later, an association between cognitive decline and increased mortality has been observed (Frisoni, Fratiglioni, Fastbom et al., 1999; Palmer, Wang, Bäckman et al., 2002; Tuokko, Frerichs, Graham, et al., 2003); therefore, the Declined category included those patients who transitioned to AD or were deceased. Table 10 shows the frequency counts for the two MCI groups and these three categories. These data were assessed using χ^2 tests and results show significant differences in diagnostic outcome between MCI-able and MCI-unable patients ($\chi^2=6.8$, $df=2$, $p=.03$). In order to further analyse these differences, two follow-up χ^2 tests were performed. In the first test, results were summarized in two categories: improved vs.

not improved. The two groups barely missed statistical significance with 31.25% of MCI-able patients returning to normal status but no MCI-unable patients doing so ($\chi^2=3.5$, $df=1$, $p=.06$). The second follow-up χ^2 test focused on the number of patients who had declined at four-year follow-up using the categories “declined” versus “not declined.” The two groups showed a significant difference ($\chi^2=5.7$, $df=1$, $p=.016$) with 18.8% of MCI-able patients having declined compared to 67% of MCI-unable patients.

Discussion

The goal of this study was to examine switching ability in MCI patients and its relationship to cognitive, health and outcome variables. To recall, a significant number of MCI patients that attempted the switching task, namely eleven out of twenty-seven, were not able to complete it. This paper characterizes this group of MCI patients and describes how they differ from the patients who were able to perform the task and controls, using neuropsychological and neuroradiological information as well as socio-demographic and health related variables. To review our hypotheses, we expected the MCI-unable group to show significant differences on most of the variables we looked at, including significant frontal and parietal lobe atrophy, increased atherosclerotic risk, longer time since receiving the MCI diagnosis, a higher frequency of ApoE 4 carriers, and a higher risk of AD conversion at follow-up. Further, we hypothesized that MCI-unable participants would show a deteriorating cognitive profile relative to the MCI-able group. By and large, our results tend to support the hypotheses. The MCI-unable group had poorer scores on neuropsychological tests measuring switching ability relative to the other two groups and showed increased risk of transition to AD or mortality. Also, they showed significant frontal and temporal lobe atrophy relative to the control group and

frontal lobe atrophy relative to the MCI-able group. However, they did not show increased vascular risk factors and did not differ from the MCI-able group in time since receiving diagnosis. We now discuss these findings in more detail.

Socio-demographic variables.

Although the three groups did not differ on gender or age, they showed significant differences in level of education such that the MCI-unable group had significantly fewer years of formal education than the controls. Because of a well-established link between cognitive impairment and lower level of education (Feil, Marmon, & Unutzer, 2003; Fischer, Jungwirth, Zehetmeyer, et al, 2007), most studies involving MCI patients attempt to match cases and controls in terms of education levels. Nevertheless, several studies have reported significantly less education in MCI relative to controls (Lopez et al., 2006; Hunderfund, Roberts, Slusser, et al., 2006; Loewenstein, Acevedo, Agron, & Duara, 2006), including one large-scale prospective community study (Chen et al, 2000). Of special relevance here, three of these studies (Hunderfund et al., 2006; Lopez et al., 2006; Loewenstein et al., 2006) compared MCI patients with isolated memory impairment, MCI with multiple domains impairments, and controls and found that MCIs with little impairment outside of episodic memory had similar education levels than controls whereas MCI patients with deficits in multiple domains tended to have lower levels of education. In particular, Lopez et al. (2006) found that MCI patients with lower levels of education had impairments in multiple cognitive domains based on a battery of age- and education-adjusted neuropsychological tests.

We interpret the fact that our MCI-unable group had significantly lower education plus significantly smaller brain volumes (discussed below) as reflecting the presence of

premorbid constitutional factors that left these patients more vulnerable to neuropathological changes presaging AD. This interpretation fits well with the brain/cognitive reserve hypothesis of cognitive decline that has been invoked to explain often dramatic differences in cognitive functioning in patients with similar brain lesions or brain atrophy. This reserve is believed to be the capacity of the brain to withstand ageing or pathology, after which deficits appear (Katzman, 1993; Stern, 2002; Valenzuela & Sachdev, 2006). Authors have made a distinction between passive models of reserve (i.e., brain reserve) that focus on brain size or number of synapses (Katzman, 1993; Valenzuela & Sachdev, 2006), and active models of reserve (i.e., cognitive reserve), in which the focus is on how efficient the brain is at performing operations and how well it can compensate for lesions in one area of the brain by recruiting other areas (Stern, 2002). Although theoretically distinct, the two models often lead to the same conclusion as is the case in our study where the MCI-unable group could be interpreted to have lower cognitive reserve as measured by educational attainment as well as lower brain reserve as measured by brain size (Staff, Murray, Deary, & Whalley, 2004; Stern, 2002).

It could be argued that the neuroanatomical and neuropsychological differences observed between the MCI-unable and control groups are simply an artefact of lower education in the MCI-unable group. Indeed, several studies have shown higher AD rates in individuals with lower education (Anttila, Helkala, Kivipelto, et al., 2002; Chiu, Lee, Hsiao, & Pai, 2004; Lindsay, J., Laurin, D., Verreault et al., 2002; Ngandu, von Strauss, Helkala et al., 2008; Ott, Breteler, van Harskamp, et al., 1995). On the other hand, the effect of education on cognitive ability in normal aging has been the subject of some debate. Whereas some have shown moderate effects of education on cognitive function,

(Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006; Van Hooren, Valentijn, Bosma, et al., 2007), others have found this relationship to be minimal (Christensen, Anstey, Parslow, et al., 2007; Rabbitt, Chetwynd, & McInnes, 2003; Van Gerven, Meijer, & Jolles, 2007). Therefore, we believe it is unlikely that the lower level of education observed in our MCI-unable group relative to the control group could, by itself, account for the severe task switching deficits exhibited by the MCI-unable group. This interpretation is bolstered by the fact that significant group differences remained even after statistically controlling for education, suggesting that the pronounced neuropsychological and neuroanatomical differences between the MCI-unable and control groups exceeded what would be expected from simple differences in education.

Health related variables.

We were able to rule out a number of possible health-related factors that might explain the cognitive differences between the groups. First, the MCI-unable group was not likely further along in a progression to AD relative to symptom onset since the two MCI groups did not differ on the time elapsed since their MCI diagnoses. Also, the three groups did not differ on vascular risk factors or Apo E4 frequency.

We also investigated atherosclerotic risk factors due to the mounting evidence for the contribution of vascular factors in precipitating AD symptomatology (Fein et al., 2000; Kivipelto et al., 2002; Launer et al., 2000; Mungas et al., 2001; Vermeer et al., 2003). However, our results did not reveal any group difference in atherosclerotic risk. We should emphasize that these results do not rule out the presence of vascular disease, but simply show that the three groups did not differ in clinically recognized vascular risk factors. It is possible that our reliance on clinical risk factors and not on objective MRI

measurement of lacunae and hyperintensities may have failed to detect any group differences. However, a recent study (DeCarli, Mungas, Harvey, et al., 2004) using both clinical and MRI measures of vascular disease in MCI patients showed that only moderate to severe levels of vascular disease contributed to AD conversion.

With respect to genetic risk factors, we expected to find a higher frequency of ApoE 4 carriers in the MCI-unable group, consistent with our hypothesis that these participants may be at increased risk of developing AD. Although the control and MCI-able groups had rates close to those in the general population, estimated to be 14% (Saunders, Strittmatter, Schmechel, et al., 1993) the MCI-unable group had almost three times as many ApoE 4 carriers than the other two groups (36%) but it failed to reach statistical levels of significance due to the small sample size.

The MCI-unable group reported more symptoms of depression than the other two groups, reporting GDS scores in the range consistent with mild depression. The comorbidity of depression and AD is frequent and their relationship is complex (Li, Meyer, & Thornby, 2001; Snowdon & Lane, 2001; Zubenko, Zubenko, McPherson et al., 2003). Further, there are reports that the presence of depression predates cognitive impairment and may hasten the transition from normal cognition to MCI (Barnes, Alexopoulos, Lopez et al., 2007; Gabryelewicz, Styczynska, Luczywek, et al., 2006) and from MCI to AD (Houde, Bergman, Whitehead, & Chertkow, 2008). Depression is known to affect episodic memory and executive function so it is possible that higher depression scores may have contributed in part to the MCI-unable group's impairments in episodic memory and task switching ability; however, it is unlikely to explain the severity of these deficits. Moreover, depression scores were included as a covariate in our analysis of the

neuropsychological results and, as discussed below, robust group differences remained even after depression was statistically controlled, suggesting that differences in self-reported symptoms of depression cannot fully explain the MCI-unable group's poor performance.

Neuropsychological profile.

The cognitive profile of the MCI-able group was similar to the control group except for their expected weakness in episodic memory scores. In contrast, the MCI-unable group showed cognitive deficits relative to the controls in memory impairment and test of executive function (i.e., Trial Making B) even after controlling for education, depression scores, and a global cognitive measure (MoCA). Thus, the MCI-unable patients were impaired on our experimental measure of task switching and on a neuropsychological measure of task switching. This is consistent with finding from Arbuthnott and Frank (2000) who showed that performance on a task switching paradigm similar to the one used in the current experiment correlated significantly with Trails B performance in a group of healthy adults. With respect to the impairment of the MCI-unable group on tests of memory and executive function, we interpret our results as evidence that these two cognitive domains may be particularly vulnerable in a subset of MCI patients who are at increased risk of developing AD. Whereas episodic memory tests distinguish MCI patients from normal controls, task switching measures appear to add a further refinement by distinguishing between subgroups of MCI patients, in which the group with impairment in multiple cognitive domains (i.e., our MCI-unable group), may be at increased risk of further decline. These results are consistent with reports that a combination of episodic memory and executive function tests are the best

neuropsychological predictors of MCI conversion to AD (Chen et al., 2000; Daly et al., 2000).

Structural MRI results

The brain volume data showed no significant differences between the MCI-able and control groups including medial temporal lobe areas and the hippocampus. The latter null effect was surprising given that the MCI-able group exhibited significant episodic memory deficits and that several studies have shown significant hippocampus grey matter loss in MCI patients relative to healthy controls (DeCarli, Frisoni, Clark et al., 2007; Jack, Petersen, Xu et al., 2000; Pennanen, Kivipelto, Tuomainen et al., 2004; Visser, Scheltens, Verhey et al., 1999). There maybe at least two reasons why we did not detect significant differences in hippocampus volume between the MCI-able and control groups. First, it has been reported before that not all MCI patients show hippocampal atrophy (Visser et al., 1999). Second, as will be discussed in the next section, several patients in this group reverted to normal status at four-year follow-up and may have skewed the MCI-able average closer to the control group's.

In contrast to the MCI-able group, the MCI-unable group showed a pervasive pattern of reduced brain volumes in frontal and temporal lobe regions relative to the control group. Specifically, when occipital lobe volume and education level were used as covariates, the MCI-unable group still showed significant lower volume in the medial and lateral orbital gyri, the middle and medial frontal gyri, the cingulate and precentral gyri, the hippocampus and the insula. Whereas hippocampal and insular atrophy are consistent with AD pathology (Braak & Braak, 1991; Rowe et al., 2007), our observation of significantly lower volumes in frontal regions is not consistent with what is typically

observed in AD or MCI. However, most studies do not distinguish between sub-categories of MCI or between different profiles of cognitive impairment as we have done (although see Bell-McGinty et al., 2005, for similar results).

One factor that could account for the smaller frontal lobes observed in the MCI-unable group is the presence of vascular disease but, as mentioned, the group did not differ in atherosclerotic risk factors. Another possibility is that MCI-unable participants have constitutionally (i.e., premorbid) smaller brains and, in particular, smaller frontal lobes than the other two groups. Again, this interpretation fits well with the “reserve” hypothesis advanced earlier. Whereas education is the most widely used proxy of “active reserve”, brain size is the most widely used proxy of “passive reserve” (Stern, 2002). For example, low levels of education and smaller brain size (indexed by head circumference) have been associated with increased risk of developing AD (Mortimer, Snowden, & Markersbery, 2003). Another study (Borenstein Graves, Mortimer, Bowen, et al., 2001) found that head circumference hastens the age of onset for AD but only in at-risk individuals (i.e., Apo E carriers) suggesting that, while smaller brain size and low educational attainment may not be etiological factors for AD, they can exacerbate its expression in people destined to become demented.

As mentioned above, MCI-unable patients showed particularly smaller frontal lobes compared to controls and the medial portions of the frontal lobes showed a statistical trend between the two MCI groups. This region, which includes the supplementary motor area (SMA), is frequently activated in task switching studies (see Wager, Jonides, & Reading, 2004 for a review). One study in particular (Rushworth, Hadland, Paus, & Sipila, 2002) highlighted the importance of the SMA in response

selection, which is a crucial component of task switching (Meiran, 2000; Schuch & Koch, 2003) and may be a critical factor contributing to the MCI-unable inability to perform this task.

Four-year follow-up.

One of the most interesting results of this study is the association between poor task switching ability and a higher risk of functional decline, defined as a transition to dementia or death, whereas adequate task switching performance was associated with a higher likelihood of a return to normal cognitive profile at four-year follow-up. It is possible that these patients who reverted to normal status may have been misdiagnosed as MCI; however, we do not believe this is likely since they had been repeatedly diagnosed as MCI at multiple evaluations ($M=2.8$, $SD=1.1$) prior to testing. Our rate of MCI-able patients (31.25%) who returned to normal is in the upper range of what has previously been reported. Busse, Hensel, Guhne et al. (2006) found a 20% of MCI patients returned to normal cognitive status after 6 years. Palmer, Fratiglioni, and Winblad (2003) reported a rate of improvement of between 15 and 44% and Ganguli et al. (2004) found that between 15 and 25% of MCI patients returned to normal after a 10 year follow-up. However, if we consider our MCI sample as a whole the rate of improvement in the current study (18%) is well within previously reported rates.

These results are also consistent with previous reports that MCI patients who have deficits in multiple domains are at increased risk of developing AD than MCI patients who have isolated memory deficits (Artero et al., 2006; Bozoki et al., 2001). Interestingly, a recent study found that impairment on a modified Stroop test that

included task switching requirements distinguished between MCI patients who remained stable and those that declined after a 2 year follow-up (Fine et al., 2008).

Our results indicate an increased mortality rate in the MCI-unable group, although we should be cautious in interpreting these results due to the low sample size.

Nevertheless, general cognitive impairment has been repeatedly linked to increased mortality (Frisoni et al., 1999; Palmer et al., 2002; Tuokko et al., 2003). A large scale study found that lower Trail Making B performance at baseline was associated with significant lower functional scores and higher mortality at 6 year follow-up (Johnson, Lui, & Yaffe, 2007). Another study comparing mortality rates between different groups of MCI patients and controls found that MCI multiple domain patients had significantly higher mortality rates than MCI amnesic only patients (Hunderfund et al., 2006).

Limitations

Several limitations of this study should be acknowledged. First, the results from this study can be applied to outpatient clinic settings in which patients present to the psychiatry or neurology department because of memory and cognitive difficulties, but may not be generalizable to other settings. Second, the way we chose to operationalize atherosclerotic risk factors may have lacked the power necessary to detect group differences. Finally, sample size was small especially for the MCI-unable group.

Conclusions

In conclusion, we observed that the MCI group that performed poorly on an experimental task switching paradigm had impairments in multiple cognitive domains and poorer prognosis for long-term follow-up, having controlled for a number of important variables. There was an interesting pattern of brain volume differences

between these patients and controls, both globally and in regions associated with task switching ability. We interpret our findings in view of the “cognitive reserve” hypothesis (Stern, 2002), namely that premorbid constitutional factors may have been present before the onset of mild cognitive impairment and may interact with incipient AD pathology to accelerate cognitive decline in these patients.

Cognitive reserve is usually discussed in the context of how much protection it confers an individual and the extent that it can delay the transition to AD. On this basis, clinicians often correctly emphasize even minor cognitive decline in individuals with high intellectual function and education as subtle evidence of a possible degenerative process. Following the same logic, a clinician might be tempted to minimise poor performance on cognitive tests in patients with low intellectual function and education. However, this may be an incorrect strategy. This study suggests that MCI individuals with low cognitive reserve are at increased risk of cognitive decline, and that executive function measures including task switching ability may be a sensitive marker of future transition to AD or mortality.

MANUSCRIPT 2

Event-related brain potentials reveal deficits during task switching
in patients with mild cognitive impairment

Marco Sinai¹, Natalie A. Phillips^{1,2}, and Howard Chertkow²

¹ Department of Psychology/Centre for Research in Human Development, Concordia
University, Montreal, Québec, Canada

² Lady Davis Institute for Medical Research/Jewish General Hospital, Montreal, Québec,
Canada

Corresponding Author:

Natalie A. Phillips, Ph.D.
Centre for Research in Human Development,
Department of Psychology, Concordia University,
7141 Sherbrooke Street West,
Montréal, Québec, Canada, H4B 1R6
Phone: 514-848-2424 ext. 2218, fax: 514-848-4537
E-mail: Natalie.Phillips@concordia.ca

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Authors' Note

Marco Sinai, Department of Psychology/Centre for Research in Human Development, Concordia University, Montreal, Canada; Natalie A. Phillips, Department of Psychology/Centre for Research in Human Development, Concordia University; Lady Davis Institute for Medical Research/Jewish General Hospital, Montreal, Canada; and Howard Chertkow, Lady Davis Institute for Medical Research/Jewish General Hospital, Montreal, Canada.

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Correspondence concerning this article should be addressed to Natalie A. Phillips, Ph.D., Centre for Research in Human Development, Department of Psychology, Concordia University, 7141 Sherbrooke Street West, Montréal, Québec, Canada, H4B 1R6, Phone: 514-848-2424 ext. 2218, fax: 514-848-4537, E-mail:

Natalie.Phillips@concordia.

Authors' Contributions

Marco Sinai: study design, subject recruitment, cognitive and ERP data collection, data reduction and statistical analysis, interpretation, and write-up.

Natalie Phillips: study design, subject recruitment, statistical analysis, and interpretation.

Howard Chertkow: subject recruitment, cognitive data collection.

Abstract

There is mounting evidence of executive function deficits in mild cognitive impairment (MCI), particularly involving set-shifting ability. We collected behavioural and event-related brain potential (ERP) measures for age- and education-matched groups of MCI patients and normal elderly controls (NECs) during a cued task switching paradigm. Although MCI patients were significantly slower than NECs, they did not show any difference on behavioural measures of switch or mixing costs. However, the two groups showed significant differences in their ERP waveforms. First, in the cue-locked interval, MCI patients but not NECs showed increased negativity to repeat versus switch trials. Further, NECs showed a flattening waveform in the later stages of the cue-locked interval whereas the MCI's waveforms showed sustained negativity. Second, in the target-locked interval, MCIs but not NECs showed reduced P300 to non-neutral foils. We interpret these results as evidence that MCI patients were not able to fully prepare for the upcoming target leading to increased foil interference. These results suggest subtle but significant deficits in task switching that are not yet manifested in the behavioural performance of MCI patients.

Event-related brain potentials reveal deficits during task switching in patients with mild cognitive impairment

Mild cognitive impairment (MCI) has been proposed to be a transitional state between healthy aging and dementia and is characterized by a decline in memory function without the full range of cognitive deficits and functional decline observed in Alzheimer's disease (AD; Petersen & Negash, 2008). The MCI diagnostic classification has shown clinical utility because individuals with MCI are at greater risk for conversion to AD than their age peers in the general population. Estimates of MCI progression to AD are in the 10–15% per year range compared with healthy elderly controls who progress at a rate of 1–2% per year (Petersen & Negash, 2008). Although the early definition of MCI focused on memory function, mounting evidence suggests the presence of non-memory deficits in MCI, with particular emphasis on attention and executive functions (Albert, Moss, Tanzi, & Jones, 2001; Belleville, Chertkow, & Gauthier, 2007; Chen, Ratcliff, Belle et al., 2000; Daly, Zaitchik, Copeland et al., 2000; Fabrigoule, Rouch, Taberly et al., 1998; Kaufmann, Ischebeck, Weiss et al., 2008; Kramer, Nelson, Johnson et al., 2006; Perry, Watson, & Hodges, 2000; Rapp & Reischies, 2005; Ready, Ott, Grace, & Cahn-Weiner, 2003; Traykov, Raoux, Latour et al., 2007; Wylie, Ridderinkhof, Eckerle, & Manning, 2007; Zamarian, Semenza, Domahs, Benke, & Delazer, 2007; Zhang, Han, Verhaegen, & Nilsson, 2007).

Executive function in AD and MCI

The term executive function refers to a variety of cognitive processes that integrate and organize other cognitive systems such as memory and attention to produce adaptive goal-oriented behaviour. Although a consensus on a precise definition of

executive function is still lacking, there is increasing agreement that it encompasses multiple domains such as planning, goal directed activity, organization, concept generalization, flexibility, multitasking, and self-monitoring (Royall, Lauterbach, Cummings et al., 2002; Stuss & Levine, 2002). These broad domains are, in turn, supported by more basic executive functions such as working memory and inhibition. Whereas working memory refers to the ability to store information and simultaneously manipulate it in real time, inhibition refers to the ability to suppress irrelevant information or unwanted actions.

Working memory deficits in AD are well documented (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Bayles, 2003; Belleville, Rouleau, Van der Linden, & Collette, 2003; Kensinger, Shearer, Locascio, Growdon, & Corkin, 2003; Waters & Caplan, 2002) and a recent review of inhibitory function in AD concludes the presence of severe impairment in both attentional inhibition as measured by negative priming tasks, and response inhibition as measured by the Stroop and Hayling tasks (Amieva, Phillips, Della Sala, & Henry, 2004). Although MCI patients do not show the breadth and severity of executive dysfunction seen in AD patients, reports of working memory and inhibitory abnormalities in MCI are growing. Several studies have found deficits in measures of working memory such the Letter Number Sequencing test (Griffith, Netson, Harrell et al., 2006), and the Brown-Peterson Task (Belleville et al., 2007). Missonier, Gold, Fazio-Costa et al. (2005) reported ERP abnormalities on the n-back task in some MCI patients despite the absence of behavioural deficits and Yetkin, Rosenberg, Weiner et al. (2006) reported increased fMRI activation in MCI patients during a visual working memory task, suggesting the presence of functional compensatory processes. However, evidence

regarding inhibitory deficits in MCI is mixed. While several studies have found impairment in response inhibition using the Stroop test (Lopez, Becker, Jagust et al., 2006; Kramer et al., 2006; Kaufmann et al., 2008; Traykov et al., 2007; Zamarian et al., 2007), on the flanker task (Wylie et al., 2007), and on the Hayling test (Johns, Phillips, Belleville et al., submitted), others have failed to find deficits on the Stroop test (Albert et al., 2001; Duong, Whitehead, Hanratty, & Chertkow, 2006; Zhang et al., 2007) or on the Hayling test (Belleville et al., 2007). To our knowledge only Zhang et al. (2007) have reported unimpaired MCI performance on negative priming, a measure of inhibition at the level of the stimulus set.

Attentional deficits in AD and MCI

The concept of attention refers to the ability to focus on a stimulus or set of stimuli, sustain this effort or shift it to another behaviorally appropriate set of stimuli. According to Posner and Petersen (1990), attention can be subdivided into four functions which require varying degree of executive control: sustained, selective, divided, and alternating attention. Sustained attention refers to the ability to focus on one task over a period of time, selective attention refers to the ability to filter out irrelevant information and focus on relevant stimuli, divided attention refers to the ability to carry out more than one task at a time, and alternating attention refers to the ability to shift rapidly between one task and another.

In an extensive review of the literature on attentional deficits in AD, Perry and Hodge (1999) highlighted the fact that the four main attentional functions are differentially affected in AD. Some debate still exists on how early divided attention is impaired, with some reporting involvement at the earliest stages of the disease (Baddeley

et al., 2001; Belleville et al., 2007), while others suggesting impairment only in the moderate stage of AD (Perry, Watson, and Hodge, 2000). However, there seems to be agreement that sustained attention tends to be preserved until the later stages of the disease, whereas selective attention and rapid shifting appear to be the earliest functions to be affected (Baddeley et al., 2001; Levinoff, Li, Murtha, and Chertkow, 2004; Perry et al., 2000). Several studies have shown MCI set-shifting impairments on the Trail Making B, a widely used clinical test of shifting abilities (Lopez et al., 2006; Zhang et al., 2007), and others have highlighted its ability to predict MCI conversion to AD (Albert et al., 2001; Chen et al., 2002; Daly et al., 2000; Kramer et al., 2006; Rapp & Reischies, 2005).

Task Switching

The ability to flexibly switch between tasks, locations or objects is emerging as one of the most ubiquitous cognitive functions, implicated not only in spatial and visual tasks but also in motor tasks (Rushworth, Hadland, Paus, & Sipila, 2002) and language (Gurd, Weiss, Amunts, & Fink, 2003; Jackson, Swainson, Mullin, et al., 2004). Further, if one considers the process of switching from one task to another, it involves a series of events such as disengaging from the old task, engaging the new task, recognizing the stimulus, and evaluating it, that may involve a combination of control processes that can be affected in AD and MCI. Identifying the affected components has obvious clinical benefit as they can be the target of therapy and can increase our understanding of these disorders.

Much of the data on task switching in MCI and AD come from traditional neuropsychological tests. These tests, such as the Trail Making B, are typically multifactorial, requiring a mix of executive and non-executive functions for adequate

performance and it is often impossible to determine which functions contribute to impaired performance. We chose a task switching paradigm from the experimental/cognitive literature for two reasons. First, this experimental paradigm is widely used and allows for the parcellation of attentional control such as the ability to multitask, goal-directed preparatory activity, stimulus-based, and response conflict (Allport, Styles, & Hsieh, 1994; Meiran, Chorev, & Sapir, 2000; Rogers & Monsell, 1995). Second, this experimental design allows for the recording of event-related brain potentials (ERP) as will be described in detail later on. The task switching paradigm comes in two major forms. One is an alternating run design, in which the task sequence is known a priori by the participant (e.g., AABBAABB...). The other is a cued task switching design where the task order is random and the participant is cued on every trial as to what task to perform next. This design allows researchers to split the inter stimulus interval (ISI) into a cue-target interval (CTI, also referred to in this paper as the cue-locked interval) and the target-response interval (TRI, also referred to here as the target-locked interval).

The broadest measure of switching ability is the performance cost involved in performing two tasks (i.e., mixed or heterogeneous blocks of trials) as opposed to performing only one task (i.e., pure or homogeneous blocks of trials). This comparison is referred to as the mixing cost and is thought to index the engagement of extra attention monitoring processes during mixed, as opposed to single task blocks (Meiran et al., 2000), and decreased availability of cognitive resources due to the requirement of maintaining two tasks in working memory (Kray & Lindenberger, 2000), as well as stimulus-response conflicts (Rubin & Meiran, 2005). Second, the most widely studied

aspect of the task switching paradigm is the contrast between trials where the participant must switch between performing a different task and trials where the participant is able to repeat a task. The reaction time difference, which typically results from slower switch trials and faster repeat trials, has been termed the switch cost (Rogers & Monsell, 1995). Although debate about the nature of the switch cost still remains, there is consensus that it reflects at least two distinct processes. The first is a goal-directed, endogenous set of processes, that reconfigure the task-set in anticipation of a new task. The second is a stimulus-driven, exogenous set of processes evoked by the target that complete the reconfiguration process (Meiran, 2000; Rogers & Monsell, 1995; Rubinstein, Meyer, & Evans, 2001; Rushworth, Passingham, & Nobre, 2002).

A critical aspect of the endogenous component, also referred to as the goal shifting (Rubinstein et al., 2001), or “attentional” component (Rushworth et al., 2002) is the disengagement of attention from the previous task. Although what exactly is affected at this stage of reconfiguration is still subject to debate, it is thought that the task rules associated with the just-performed task need to be deactivated² (Mayr & Kliegl, 2000). Indeed, failure to deactivate the previous task rules results in interference and decreased performance on the current task (Allport et al, 1994; Gilbert & Shallice, 2002). The extent to which the previous task-set can exert interference on the current task reflects a complex interplay between inhibitory processes, working memory capacity, and task difficulty. When working memory capacity is intact, a relatively easy or over learned just-performed task set may linger in working memory and interfere with subsequent task

² Task rules are general response rules associated with the task or with the cue in the case of a cued task-switching paradigm. For example, if the participant is required to judge whether a letter is a vowel or a consonant, the task rules could be: if a vowel is seen, press the left button, if a consonant is seen, press the right button.

performance and will need to be actively inhibited (see Sinai, Goffaux, & Phillips, 2007 for a more detailed discussion). On the other hand, when working memory is impaired, or when the previously performed task is difficult or novel, it will tend to decay more quickly and may not require active inhibition.

The second aspect of goal shifting is the activation of task rules required for the upcoming task and it is subject to the same interplay between task-set inhibition, WM and task difficulty as discussed above. For example, in situations where an individual is faced with difficult or novel tasks or where they may have compromised WM, task rules may need to be reactivated on every trial, including repeat trials, and this lack of “facilitation” on repeat trials may lead to reduced switch costs. Some authors have argued that most of what a subject can do to prepare for the upcoming target is to retrieve the task rules from long term memory (Mayr & Kliegl, 2000; Rubinstein et al., 2001). This may be a potent factor affecting performance in the present study because MCI patients may find it challenging to retrieve novel and arbitrary task rules even when they have been thoroughly rehearsed during a training session.

The second major component of the switch cost, the exogenous component, has also been referred as rule activation (Rubinstein et al., 2001), response set reconfiguration (Meiran, 2000) or the “intentional” component (Rushworth et al., 2002). These set of processes are thought to occur after the presentation of the target and act either at the level of the task-set (Rogers & Monsell, 1995) or at the level of stimulus-response (S-R) associations by possibly resolving conflicts that emerge when a stimulus is mapped to different response buttons (Allport, & Wylie 2000; Meiran, Gotler, & Perlman, 2001) by inhibiting the irrelevant S-R association (Schuch & Koch, 2003).

A final important manipulation concerns ambiguity or conflict in the target itself. In their landmark paper, Rogers and Monsell (1995) used compound stimuli composed of numbers and letters (e.g., A2, 3G) and asked participants to alternate between performing the number task (i.e., press left for even, press right for odd) and letter task (press left for letter, press right for consonant). One third of the targets also contained a neutral foil (i.e., an irrelevant character from a list of symbols not relevant to any of the two experimental tasks; e.g., “%E”). On non-neutral trials, target presentation will evoke both tasks resulting in “cross-talk” interference. Despite the fact that advanced preparation may be able to bias the system in favour of one task (e.g., the number task), both the number and letter tasks will be exogenously activated by the target and resources must be expended to suppress the irrelevant task. In a further step of the analysis, the two non-neutral trials can be distinguished on the basis of response selection processes. Whereas both conditions evoke both task sets and in both conditions the inappropriate task set needs to be inhibited, on congruent trials, both stimuli (e.g., “E” and “4”) map onto the same response key (e.g., right button), whereas on incongruous trials, the two stimuli map onto different response keys. Thus, on incongruous trials, there is added interference at the response selection level which produces similar demands as on Stroop and Flanker tasks; therefore, the difference between congruent and incongruent trials can be seen as index of response inhibition and stimulus-response (S-R) conflict resolution.

Task Switching and ERPs

One technique that has successfully been used in conjunction with more classical performance measures in the exploration of cognitive phenomena is the recording of event-related potentials (ERPs). The ERP is a measure derived from the human electro-

encephalogram (EEG) and is time locked to specific events. The usefulness of the ERP technique in the study of task switching processes is enhanced by the cued task switching paradigm. It can be argued that brain activity time-locked to the cue presentation reflects processes tied to endogenous preparation whereas brain activity time-locked to target presentation reflects exogenous processes related to target evaluation and S-R conflict resolution.

A growing number of studies have used ERPs to examine the different control processes involved in task switching with differing task switching designs (Karayanidis, Coltheart, & Michie, & Murphy 2003; Goffaux, Phillips, Sinai, & Pushkar, 2006, 2008; Lorist, Klein, Nieuwenhuis, DeJong, Mulder, & Meijman, 2000; Poulsen, Luu, Davey, & Tucker, 2005; Sinai, et al., 2007). Despite methodological differences, two consistent findings appear to cut across these studies. The first is the presence of a negative slow wave over posterior scalp regions in the later part of the cue-target interval. This is possibly a stimulus preceding negativity (SPN), which is believed to reflect attentional processes in anticipation of the upcoming target stimulus (Brunia & van Boxtel, 2001). This posterior negativity has been shown to be enhanced on homogeneous trials versus repeat trials which in turn are enhanced relative to switch trials and has been interpreted as facilitated processing during repeat trials relative to switch trials (Goffaux et al., 2006).

The second consistent electrophysiological finding observed among task switching studies is a P3b-like waveform following the presentation of the target (Goffaux et al., 2006, 2008; Karayanidis et al., 2003; Lorist et al., 2000; Poulsen et al., 2005, Sinai et al., 2007). The P3b component is a late (300 - 800ms), posteriorly distributed positive complex linked to stimulus evaluation and is believed to be an index

of attentional resources available for stimulus evaluation (Kok, 2001; Kramer & Spinks, 1991). Studies show enhanced target-locked P3b activity on homogeneous trials relative to repeat trials which in turn are enhanced relative to switch trials and this has been interpreted as increased resources available for target processing on repeat trials (Karayanidis et al., 2003; Lorist et al., 2000; Poulsen et al., 2005; Goffaux et al., 2008).

Current Study

To summarize thus far, there is mounting evidence that task switching ability may be one of the first functions outside of episodic memory to be affected in very early AD and MCI. However, because most of the evidence comes from traditional paper and pencil tests, it is unclear whether one or more component processes of task switching are affected in MCI.

To our knowledge, no ERP studies have yet investigated the difference between MCI patients and normal controls during task switching. In the context of this study, by examining ERP effects time-locked to the presentation of the cue and of the target, inferences can be made as to which control function is preferentially affected in MCI. For example, if significant group effects were found in the cue-target interval, it would suggest a deficit in preparatory activities such as inhibition of previous trial task rules and retrieval of task rules from long-term memory. On the other hand, if significant group differences were found in the target-locked interval, it would suggest difficulties at the level of stimulus evaluation, foil inhibition, and/or stimulus-response conflict resolution. If no ERP group differences were found despite behavioural reaction time group differences, we would be able to infer a problem at the level of motor preparation and execution. Finally, if ERP differences were found in the absence of behavioural effects,

this would suggest that subtle cognitive deficits that are not readily revealed by behavioural measures alone.

To this end, we tested a group of MCI patients and a group of age- and education-matched normal healthy controls. For both groups, electrophysiological responses were recorded during cued task switching performance in which participants had to switch their attention between the letter (i.e., vowel/consonant) and the number (i.e., odd/even) of a compound stimulus. We examined negative slow wave activity recorded during the cue-target interval and the subsequent positivity (P300) recorded during the target interval, as well as participants' behavioural performance. To preview the results, we found no behavioural performance differences between the two groups after adjusting for processing speed, including on the mixing cost. However, we found significant cue-locked ERP differences between the two groups as well as target-locked foil effects.

Method

Participants

Two groups of age- and education-matched MCI and control subjects (see Table 11 for group statistics) were recruited from the Memory Clinic of the Sir Mortimer B. Davis–Jewish General Hospital (JGH), a tertiary care referral center of McGill University, Montreal. Their investigations included full medical, neuropsychological, and neuroradiological evaluations. ERP testing was conducted in addition to these standard assessments. All subjects gave informed consent for their participation. The study was approved by the Jewish General Hospital/McGill University and Concordia University Human Ethics committees.

Control group

Twenty-one healthy elderly adults were recruited from the Herzl Family Medicine Clinic of the JGH and screened at the JGH Memory Clinic to ensure they had no symptoms of dementia. (Clinical Dementia Rating, CDR = 0). Participants typically underwent repeated neuropsychological testing for several years prior to this study. Two participants were excluded from analyses due to technical difficulties during ERP testing. In total, the control group consisted of nineteen participants.

MCI group

Twenty-seven individuals identified as having mild cognitive impairment (MCI) were recruited in the study. Of these patients, eleven were not able to perform the task and are discussed elsewhere (Sinai, Phillips, Chertkow, & Kabani, 2006). The remaining 16 subjects all received CDR scores of 0.5, indicating mild forgetfulness, minimal word finding difficulties, and a slight impairment in mental efficiency (Hughes et al., 1982). In all subjects, there was a reported decline (by either the individual or family) in memory

function which was gradual and of at least six months duration. This was documented by impaired performance (i.e., ± 1.5 SD) on objective neuropsychological tests with appropriate norms for age and/or education (see below). As indicated in Table 11, these subjects had documented mild memory dysfunction. None were considered to have significant impairment in activities of daily living and none met the criteria for dementia, as determined by the assessing physician in the Memory Clinic.

Neuropsychological Evaluation

As part of their diagnostic clinical examination, the MCI participants underwent an extensive neuropsychological evaluation which included the Mini-Mental State Exam (MMSE; Folstein, Folstein & McHugh, 1975), the Montreal Cognitive Assessment (MoCA; Nasreddine, Phillips, Bédirian, Charbonneau, Whitehead, Collin, Cummings, & Chertkow, 2005), several tests from the Wechsler Memory Scale III (WMS–III; Wechsler, 1997) including immediate and delayed verbal recall (Story A from the Logical Memory I and II subtests, respectively), immediate and delayed visual reproduction, Letter Number Sequencing, and Digit Span, several tests from the Wechsler Adult Intelligence Scale III (WMS–III; Wechsler, 1997), including Similarities, Block Design, and Digit Symbol Coding, and tests designed to assess language skills such as confrontation naming (Boston Naming Test; Kaplan, Goodglass, & Weintraub, 1982), orthographic (letters F and S) and semantic (category: animals) oral fluency in 60 s (Benton & Hamsher 1989), executive functions such as the ability to switch between tasks (Trail Making Test; Lezak, Howieson, & Loring, 2004), selective attention and response inhibition (Color Stroop Test; Lezak et al., 2004), and concept formation (Clock Drawing Test; Shulman, Shedletsky, & Silver, 1986). This same neuropsychological battery was also administered to the normal control participants.

For the MCI group the average time interval between the neuropsychological test battery and ERP testing was 6 months (SD = 3.9); for the normal group the interval was 8 months (SD = 5.5). To determine that there was no significant change in cognitive function during this period, we compared performance on the MMSE and the MoCA, which were sampled at both times. Results showed no significant differences (please see Table 12 for detail) indicating that, as a whole, the two groups showed stable cognitive function during the time between the cognitive evaluation and collection of the behavioural and ERP data.

Materials

Stimulus presentation, reaction times (RT) and error rate (ER) data collection were controlled by Presentation software (Neurobehavioral Systems). All stimuli were presented in 24 font size, Times New Roman white font, on a black background in the middle of a standard 15 inch screen. A written cue (“Number” or “Letter”) instructed the participants on the upcoming task. The experimental stimuli consisted of bivalent letter/digit pairs (e.g., 5G, A2) and letter/digit-neutral pairs (e.g., %A). The compound stimuli were constructed from the following letters: A, E, I, U, L, M, G, K, numbers: 2, 3, 4, 5, 6, 7, 8, and neutral symbols %, #, &, \$. Stimulus sequence was generated semi-randomly to avoid any stimulus repetition on subsequent trials and to meet other criteria described below.

Procedure

Participants were asked to perform either one of two tasks on any given trial: a letter or a number classification task. The letter task entailed identifying a letter as either a vowel or consonant which was mapped to the right or left key. The digit classification

task entailed identifying a digit as either an even or odd number which was mapped to the right or left key.

Each trial began with the presentation of a cue (i.e., “Letter” or “Number”) that instructed the participant as to which task to perform next. The cue remained on the screen for 1000 ms and was immediately followed by the presentation of the compound stimulus that remained on the screen until the participant responded or up to a maximum of 10 seconds. The following trial began 200 ms after the response (See Figure 3).

Each participant was presented with eight blocks consisting of six practice trials and 90 experimental trials each. The first two blocks, called homogeneous blocks, consisted of trials cued by only one task, either “Letter” or “Number”, whose order of presentation was counterbalanced across participants. In other words, no switching between tasks was required in these blocks. Six blocks followed, called heterogeneous blocks, consisting of a semi-random mixture of Letter (50%) and Number (50%) task trials. Each block of trials had the same number of responses (i.e., 50% left and 50% right button responses) and no more than three response repetitions in a row were allowed. As mentioned above, no feature of the compound stimulus was allowed to repeat in subsequent trials (e.g., E4 followed by 3E). Finally, stimulus-response mappings (e.g., press left for an even number) were counterbalanced across participants.

Participants held a standard mouse with both hands and responded by pressing either the left or right button with their thumbs. In case of response error, feedback was signaled by a 400 Hz 100 ms tone immediately following the response and the following trial began after an 800 ms delay. Participants were instructed to respond as quickly as possible while keeping errors to a minimum and to minimize muscle and eye movement.

The approximate duration of each block was three to four minutes and pauses between blocks were allowed to control for fatigue.

Electrophysiological Recording

The EEG was recorded from 74 Ag/AgCl electrodes mounted in an elastic cap (Easycap). A forehead location was used as ground. All sites were referenced to the left ear and re-referenced offline to linked ears. Electro-oculogram activity (EOG) was recorded from electrodes placed at the outer canthi of both eyes (horizontal EOG) and above and below the left eye (vertical EOG). Vertical and horizontal EOG artifacts were corrected off-line for all participants using the spatial filter procedure as implemented by the Neuroscan software (Edit 4.3, Neuroscan 2003, p. 246). Electrode impedances were kept below 5 k Ω and EEG data were amplified using Neuroscan Synamps in a DC-30 Hz bandwidth and sampled at 500Hz.

Behavioural Data Analysis

Behavioral data were obtained simultaneously with ERP data. Participants' RTs were measured as the time taken to respond to the target stimulus after it appeared on the screen. RTs were analyzed for correct trials only and the trials that followed an incorrect response were also excluded from analysis. RTs longer than three standard deviations from the mean and trials with RT less than 200 ms were excluded from analysis; these rejected outliers consisted of less than 2% of total trials.

ERP Data Analysis

ERPs were recorded time-locked to the cue and the target onsets and were analyzed separately. Consistent with the behavioural data, trials following an incorrect answer or trials tagged as statistical outliers on the basis of RT data were excluded from

analysis. Both cue-locked and target locked epochs spanned -100 to 1000 ms and employed a baseline 100 ms interval before cue or target presentation. Statistical analyses were performed on mean waveform amplitudes averaged across the following intervals: 0-200 ms, 200-400 ms, 400-600 ms, 600-800 ms, and 800-1000 ms. The six midline electrode sites (FPz, Fz, FCz, Cz, CPz, Pz) were chosen for the analyses since effects were most prominent there³.

Statistical Analysis

For behavioural data, mixing cost RT and error rate (ER) data were analysed with a mixed ANOVA with mix (repeat vs. homogeneous) as within subject factor and group (NEC vs. MCI) as between subject factor. Switch cost RT and ER data were each analysed with two mixed ANOVAs. The first consisted of switch (switch vs. repeat) and foil (Neutral vs. Congruous) as within subject factors and group as a between subject factor. The second ANOVA was identical to the first except that the foil factor contrasted congruous and incongruous trials.

ERP cue- and target-locked data were analysed separately. For each of these, three analyses were conducted; one involving the mixing cost contrast, and two on switch cost conditions which contrasted foil type. The mixing cost contrast was analyzed with a mixed ANOVA with mix (repeat vs. homogeneous), electrode (six levels) and time interval (five levels) as within subject factors, and group as between subject factor. For the switch cost contrasts, two mixed ANOVAs were used; the first employed switch (switch vs. repeat), foil (congruous vs. neutral), electrode, and time as within subject factors, and group as the between subject factor. The second ANOVA was identical to the

³ Preliminary analyses were conducted on lateral electrodes FP1, FP2, F3, F4, FC3, FC4, C3, C4, CP3, CP4, P3, and P4 were also selected to analyze laterality effects. No group by laterality effects were found ($p > .38$) and thus, are not reported further.

first with the exception that the foil factor contrasted the congruous and incongruous conditions.

The Greenhouse-Geisser (1959) non-sphericity correction was employed in the repeated measures ANOVAs when appropriate. Following convention, unadjusted degrees of freedom are reported, along with the Greenhouse-Geisser adjusted p -value. Mean square error (MSE) values reported are those corresponding to the Greenhouse-Geisser correction. Main effect of factors are reported first but described only if they did not interact with other factors. In the case of significant interactions, the highest order effects are reported only if they interact with the group factor and post-hoc Bonferroni-corrected ANOVAs were conducted where appropriate. Statistical significance is assumed at the $\alpha = .05$ level.

Results

Neuropsychological Results

Data were analyzed using a multivariate analysis of variance (MANOVAs). Table 11 summarizes group demographics and neuropsychological test performance for selected tests. As expected, MCI participants had significantly worse performance on episodic memory tests (Logical Memory Immediate and Delayed recalls). They had additional impairments on the MoCA, and on the number of Stroop errors.

Behavioural Results

Overall performance speed on heterogeneous blocks differed significantly between the two groups ($F(1,33) = 4.2$, $p = .04$, $MSE = 540766.3$, $\text{partial } \eta^2 = .113$) with the control group ($M=1055.9$ ms, $SE=68.9$) responding faster than the MCI group ($M=1265.0$ ms, $SE=75.1$). Also, the two groups differed significantly on homogeneous

block performance ($t(33)=2.1, p=.04$), with the control group ($M=751.6$ ms, $SE=22.6$) responding faster than the MCI group ($M=834.6$ ms, $SE=33.3$). To control for these differences in baseline performance, all subsequent analyses, including mixing and switching cost contrasts, were performed on data transformed as a proportion of the baseline performance (i.e., condition RT / homogeneous RT). However, we report raw reaction time (RT) data along with error rate (ER) data in Table 13 rather than transformed data to allow comparison with other studies.

Reaction Time

Mixing Cost. Group differences were analysed through a t-test and found not significant ($t(33)=1.0, p=.31$). There was a robust mixing cost main effect ($F(1,33) = 86.4, p < .001, MSE = 23228.8, \text{partial } \eta^2 = .724$) with homogeneous trials ($M=793.1$ ms, $SE=19.6$) significantly faster than heterogeneous blocks repeat trials ($M=1133.1$ ms, $SE=49.5$).

Switch Cost.

Neutral vs. Congruous Contrast

There was no significant main effect of group ($F(1,33) = .43, p = .51, \text{partial } \eta^2 = .013$) and the group factor did not interact with any other variable (all $ps > .25$). There was a switch factor main effect ($F(1,33) = 29.2, p < .001, MSE = .007, \text{partial } \eta^2 = .467$) with repeat trials faster ($M=1.357, SE=.039$) than switch trials ($M=1.436, SE=.047$). There was also a main effect of foil ($F(1,33) = 137.8, p < .001, MSE = .02, \text{partial } \eta^2 = .807$) with neutral trials ($M=1.242, SE=.037$) significantly faster than congruous ($M=1.55, SE=.05$) trials. There was a significant interaction between the foil and switch factors ($F(1,33) = 17.0, p < .001, MSE = .005, \text{partial } \eta^2 = .34$) with post-hoc analyses revealing

a significant switch vs. repeat effect on neutral ($F(1,33) = 34.8, p < .001, \text{partial } \eta^2 = .513$) but not on congruous trials ($F(1,33) = 3.3, p = .07, \text{partial } \eta^2 = .09$).

Congruous vs. Incongruous Contrast

There was no significant main effect of group ($F(1,33) = 1.03, p = .32, \text{partial } \eta^2 = .03$) and the group factor did not interact with any other variable (all $p > .12$). There was a switch factor main effect ($F(1,33) = 4.2, p = .05, \text{MSE} = .01, \text{partial } \eta^2 = .112$) with repeat trials faster ($M=1.54, SE=.046$) than switch trials ($M=1.58, SE=.052$). No other effect was significant.

Error Rate

Mixing Cost. No main effect of group was found ($F(1,33) = .2, p = .89$) and the group factor did not interact with any other variable. There was a mixing cost main effect ($F(1,33) = 5.8, p = .02, \text{MSE} = 1.39, \text{partial } \eta^2 = .148$) with fewer errors on homogeneous trials ($M=2.0, SE=.24$) than on heterogeneous blocks repeat trials ($M=2.7, SE=.24$).

Switch Cost.

Neutral vs. Congruous Contrast

There was no group main effect ($F(1,33) = 2.82, p = .10, \text{partial } \eta^2 = .079$) and the group factor did not interact with any other variable. There was a switch factor main effect ($F(1,33) = 11.77, p = .002, \text{MSE} = 3.4, \text{partial } \eta^2 = .263$) with fewer errors on repeat trials ($M=1.5, SE=.20$) than switch trials ($M=2.5, SE=.33$). There was also a main effect of foil ($F(1,33) = 9.6, p = .004, \text{MSE} = 3.7, \text{partial } \eta^2 = .226$) with neutral trials ($M=1.49, SE=.19$) significantly more accurate than congruous trials ($M=2.51, SE=.34$).

Congruous vs. Incongruous Contrast

There was no group main effect ($F(1,33) = .14, p = .71, \text{partial } \eta^2 = .004$) and the group factor did not interact with any other variable. There was a switch factor main effect ($F(1,33) = 16.98, p < .001, \text{MSE} = 8.7, \text{partial } \eta^2 = .340$) with fewer errors on repeat trials ($M=3.6, SE=.35$) than switch trials ($M=5.6, SE=.57$). There was also a main effect of foil ($F(1,33) = 46.4, p < .001, \text{MSE} = 13.3, \text{partial } \eta^2 = .584$) with congruous trials ($M=2.5, SE=.34$) significantly more accurate than incongruous trials ($M=6.7, SE=.63$). There was a significant interaction between the foil and switch factors ($F(1,33) = 10.0, p = .003, \text{MSE} = 4.04, \text{partial } \eta^2 = .234$) with post-hoc analyses revealing a larger switch vs. repeat effect on incongruous (switch cost = 3.1; $F(1,33) = 17.9, p < .001, \text{partial } \eta^2 = .353$) than on congruous trials (switch cost = 1.0; $F(1,33) = 5.3, p = .03, \text{partial } \eta^2 = .138$).

ERP Results

Cue-Locked

Mixing Cost

Figure 4 shows, for the selected sites, ERP grand average waveforms collapsed across subjects in control (left panel) and MCI (right panel) groups. Starting at approximately 300 ms for both groups, one can observe a generally negative sloping waveform from frontal to posterior sites (i.e., FCz, Cz, CPz, and Pz) that was more negative for repeat compared to homogeneous trials in both groups. Note that this waveform was positive going (more positive on repeat trials for both groups) at the prefrontal site (i.e., FPz).

There was no main effect of group ($F(1,33) = 1.1$, $MSE = 76.5$, $p = .30$) and the group variable did not significantly interact with any other factor (all $ps > .32$). There was a significant mixing by site by time interaction ($F(20,660) = 23.6$, $MSE = 2.9$, $p < .001$, $\text{partial } \eta^2 = .417$). Bonferroni corrected post-hoc analyses revealed that repeat waveforms more negative than homogeneous waveforms at Fz (800-1000 ms), FCz (600-1000 ms), Cz (600-1000 ms), CPz (600-1000 ms), Pz (800-1000 ms) and that homogeneous waveforms were more negative than repeat waveforms at FPz (600-1000 ms). Also, there was a significant effect from 200-400 ms for CPz and Pz sites with repeat trials more positive than homogeneous trials.

Switch Cost

Figure 5 shows, for the selected sites, ERP grand average waveforms averaged across subjects in control (left panel) and MCI (right panel) groups. As would be expected for cue-locked activity, preliminary analyses revealed no main effect of foil and the three conditions were visually undistinguishable; therefore ERP grand averages were collapsed over the foil conditions and the repeat vs. switch contrast irrespective of foil type is shown here. Starting at approximately 300 ms for both groups, a generally negative sloping waveform at central and posterior sites (i.e., FCz, Cz, CPz, and Pz) and a positive sloping wave at the prefrontal site (i.e., FPz) was observed.

ERP data were directly compared in MCI and control groups using a mixed ANOVA with the factors of switch condition (switch and repeat), foil condition (congruous, incongruous, and neutral), electrode site, and time. Although there was no main effect of group ($F(1,33) = 1.17$, $MSE = 122.3$, $p = .29$), the group factor significantly interacted with the switch factor ($F(1,33) = 5.4$, $MSE = 2.4$, $p = .03$, partial

$\eta^2 = .142$). Post-hoc analyses showed no significant switch cost for the control group ($F(1,33) = .27, p = .60$) but a significant switch cost for the MCI group ($F(1,33) = 13.3, p = .001, \text{partial } \eta^2 = .287$).

To further understand this effect, a follow-up ANOVA was conducted on the MCI group using the Switch, Site, and Time factors. There was a main effect of switch ($F(1,15)=9.1, \text{MSE}=3.46, p=.009$) and a switch by site by time interaction ($F(20,300)=2.7, \text{MSE}=.373, p=.038$). Bonferroni corrected post-hoc analyses on the latter revealed significant switch effects (i.e., repeat waveforms more negative than switch waveforms) from 400 to 1000 ms after cue presentation for all sites except the prefrontal site (i.e., Fz to Pz).

Upon visual inspection of the waveforms, a distinct morphological difference of the two participant groups' waveforms is clearly visible towards the end of the epoch. Whereas the control group showed a flattening of the negative sloping wave, waveforms for the MCI group showed a sustained negativity throughout the latter part of the Cue-Target interval. To quantify this effect, we calculated a more fine-grained average amplitude over this period in 100 ms intervals (t1: 700-800 ms, t2: 800-900 ms, t3: 900-1000ms) for repeat waveforms at Pz because the effects appears to be most prominent there. We then calculated the slope of the curve for each group by subtracting the average amplitudes in the 1st time interval (700-800 ms) from the average amplitude from the 3rd interval (900-1000 ms.). We then performed an independent t-test to compare the slope in both groups. Results showed a significant group difference ($t(33)= 2.52, p=.02$) with MCI patients showing a larger amplitude slope ($M=1.27 \mu\text{V}, SE= .40$) relative to normal controls ($M=.2 \mu\text{V}, SE=.19$).

A possible interpretation of the significant slope group difference is that, in contrast to the controls, MCI patients were not fully prepared to process the target by the end of the cue-target interval. To test this hypothesis, we correlated slope magnitude with repeat trials' RT for all participants and found the correlation to be significant ($r_{(35)} = .525$, $p = .001$; see Figure 6). That is, participants with greater negative slow wave slope performed more slowly.

Target-locked Data:

Mixing Cost

ERP waveforms (see Figure 7) were characterized by an early positive peak at approximately 250 ms after target presentation followed by a negative deflection peaking around 300 ms and a more sustained positive component peaking between 500 and 600 ms. ERP data were directly compared in MCI and control groups using a mixed ANOVA with the factors of mix condition (repeat and homogeneous), electrode site (6 midline electrodes) and time (t1: 0-200 ms, t2: 200-400 ms, t3: 400-600 ms, t4: 600-800 ms, t5: 800-1000 ms).

There was no main effect of group ($F(1,33) = 1.1$, $MSE = 80.5$, $p = .3$) and the group variable did not significantly interact with any other factor (all $ps > .15$). There was a significant mixing by site by time interaction ($F(20,660) = 7.8$, $MSE = 2.2$, $p < .001$). Bonferroni corrected post-hoc analyses revealed three effects. The first significant effect was at time 2 (200-400 ms) and showed increased negativity on homogeneous relative to repeat trials at FCz, Cz, CPz, and Pz, as well as increased positivity on homogeneous relative to repeat trials at FPz. The second effect showed increased positivity to homogeneous relative to repeat trials at time 3 (400-600 ms) at Fz and Pz. The third

effect was increased negativity on homogeneous trials at time 5 (800-1000 ms) at FCz, CPz, and Pz.

Switch Cost

Congruous vs. Neutral Contrast

Waveforms (see Figure 8) were characterized by an early positive peak at approximately 250 ms after target presentation followed by a negative deflection peaking around 300 ms and a more sustained positive component peaking between 500 and 600 ms. ERP data were directly compared in MCI and control groups using a mixed ANOVA with the factors of switch condition (switch and repeat), foil condition (congruous and neutral), electrode site, and time.

There was no significant main effect of group or switch (all $F_s < 1.7$, $p_s > .20$) and the group variable did not significantly interact with any other factor. However, there was a main effect of foil ($F(1,33) = 6.2$, $MSE = 1.3$, $p = .018$) with neutral trials ($M=2.0 \mu V$, $SE=.24$) significantly more positive than congruent trials ($M=1.9 \mu V$, $SE=.24$) and the foil factor also significantly interacted with the group factor ($F(1,33) = 5.2$, $MSE = 1.3$, $p = .03$). Bonferroni corrected post-hoc analyses revealed that, whereas the control group did not show a significant difference between congruous and neutral trials ($M=.007$, $SE=.05$, $p=.88$), neutral foil trials were significantly more positive than congruent trials ($M=.17$, $SE=.05$, $p=.002$) in the MCI group.

Although the group by foil by time interaction was not significant, we performed an analysis that targeted specifically the P300-like activity on the basis of a-priori hypotheses predicting group differences in the P300 component. A mixed ANOVA with group as the between group factor and switch (switch and repeat), foil (congruous and

neutral), electrode site (Cz, CPz, Pz) and time (t3: 400-600 ms, t4: 600-800 ms) as within group factors. The same results as for the wider ANOVA were found, namely a foil by group interaction ($F(1,33) = 3.9$, $MSE = 9.3$, $p = .05$), with the MCI group showing enhanced P300 activity to neutral vs. congruent trials ($p=.01$) but no significant difference in the control group ($p=.93$).

Congruous vs. Incongruous Contrast

Congruous vs. incongruous waveforms are not shown because they were virtually identical across group and conditions and followed the same general dynamic as for the previous contrast. A mixed ANOVA with the factors of switch condition (switch and repeat), foil condition (congruous and incongruous), electrode site (FPz, Fz, FCz, Cz, CPz, Pz) and time (t1: 0-200 ms, t2: 200-400 ms, t3: 400-600 ms, t4: 600-800 ms, t5: 800-1000 ms) was conducted and found no significant main effect of group, switch, or foil (all $F_s < 1.85$, all $p_s > .18$) nor any interaction with the group factor.

Discussion

The principal goal of this study was to examine task switching performance in patients with mild cognitive impairment on a widely used experimental task switching paradigm in order to shed light on which component process might be affected. Our findings show subtle but significant ERP abnormalities in this group of MCI patients in the absence of behavioural group differences.

Neuropsychological findings

As expected, the sixteen MCI patients considered in this study showed significant episodic memory deficits; in addition, they exhibited deficits on the MoCA, global cognitive measure designed to screen for mild cognitive impairment. The MoCA is better suited to dementia screening than the more widely used MMSE because it assesses episodic memory and executive function to a much larger extent than the MMSE. It is therefore not surprising that the two groups were significantly different on this measure. With respect to tests of executive function, the MCI participants committed significantly more errors on the Stroop test relative to controls. However, the two groups did not differ on any other measure, including the Trails B test. The lack of difference on this classical task switching test was unexpected. To our knowledge, all studies comparing MCI patients and controls on Trails B performance have shown significant differences (Albert et al., 2001; Chen et al., 2000; Lopez et al., 2006; Traikov et al., 2007). It is possible that our MCI subjects reported here may have been a select group with relatively intact task switching abilities on such a behavioural measure. Recall that an additional eleven patients were recruited for this study but could not perform the task. As presented elsewhere (Sinai et al., 2006) these patients showed significant deficits on the Trails B

test and, had they been included in the current MCI sample, MCI performance on the Trails B test may have been significantly worse than controls’.

Experimental task switching test: Behavioural measures

The analyses of the behavioural data on the experimental task switching test showed robust mixing cost, switch cost, and foil effects in both RT and error rate data. No differences between the MCIs and controls emerged on these measures, although the MCI group showed a significant overall decline in speed of processing. Again, the absence of group differences in mixing and switch costs was unexpected given previous reports that task switching is one of the earliest attentional functions to be affected in AD and given mounting evidence that MCI patients are impaired on neuropsychological tests of task switching (Chen et al., 2002; Daly et al., 2000; Zhang et al., 2007). It is possible that the present lack of group differences on mixing or switch costs is due to the fact that the parameters of the task we used were not difficult enough to discriminate between the MCI patients and the controls. However, we find this explanation unlikely given that 11 of the recruited patients were not able to do the task at all. Thus, the task we employed did distinguish between two groups of MCI, those who were unable to perform the task at all and those who could and who then performed similarly to the normal controls. The failure to see behavioural differences between the MCIs and the controls is consistent with Belleville, Bherer, Lepage, Chertkow, and Gauthier (2008) who found increased mixing cost in MCI patients only when asked to switch spatial locations but not when asked to switch between tasks similar to the present study, and with Zamarian et al. (2007) who found evidence of response inhibition deficits but not of mixing cost deficits in a group of MCI patients when switching between arithmetic tasks.

Contrary to our hypothesis, the MCI and control groups did not differ on trials with congruous versus incongruous response mappings. This is surprising given several reports of MCI impairment on tests where inhibitory mechanisms are required to resolve response conflict such as on Stroop-like conditions (Kaufmann et al., 2008; Kramer et al., 2006; Perry et al., 2000; Traykov et al., 2007; Zamarian et al., 2007) and on flanker tasks (Wiley et al, 2008) and given our own finding of increased Stroop errors in MCIs. Instead, we found both groups were equally penalized on incongruous trials on which response conflict is the highest, compared to congruous trials, on both reaction time and error rate. It is possible that the simple comparison of reaction time or error rate between the two groups may not be a sensitive enough tool to detect subtle deficits. This explanation is supported by the results of a recent study (Wiley et al, 2008) that showed no group difference on standard reaction time and error rate measures on a flanker task, but significant group differences when intra-subject RT distribution was analyzed. Still, this does not explain the lack of difference between the groups on foil effects in our set-switching task, despite the fact that the groups differed in terms of Stroop errors. One important difference between this task switching design and the Stroop task is that the experimental task used two tasks that are equipotent whereas in the Stroop task, by definition, one task must be prepotent over the other. Therefore, the Stroop task may require additional inhibitory control compared to this task switching design. Our results suggest that MCI patients in this study have little difficulty resolving response conflict between two equally potent tasks, but that they start to show impairment when inhibitory control needs to be exerted on a dominant task.

Experimental task switching test: Cue-locked ERP effects

Despite the lack of differences between the groups on behavioural measures, there were significant group differences documented in cue- and target-locked ERP data. These were evident in the switch contrasts rather than the mixing cost contrasts. First, there was a significant group difference in the switch cost (i.e., the switch vs. repeat waveforms). Specifically, while there was no difference between these waveforms for the control group, a switch effect was observed for the MCI group in the form of an enhanced negativity to repeat waveforms relative to switch waveforms at centro-parietal sites from 400 ms to 1000 ms after cue presentation. This posterior negativity has previously been interpreted as an index of attentional resources allocated in preparation for target processing (Goffaux et al., 2006). Work from our lab suggests that this effect is due to the activation of task rules required for optimal processing of the upcoming target (Goffaux et al., 2008), rather than task-set inhibition (Sinai et al., 2007). Accordingly, enhanced negativity during repeat trials suggests that the activation of task rules is facilitated due to the fact that task rules from the previous trial remain semi-active in working memory. In the context of this study, the enhanced negativity of repeat trials suggests that the MCI patients benefited from a task repetition and that working memory capacity was adequate to maintain the just-performed task rules.

The lack of differences in the late negativity associated with switch and repeat trials in the control group should not be interpreted as a lack of facilitation on repeat trials, but is rather likely due to the fact that the time between the cue and the target (1000 ms) was long enough to allow ample time for retrieval of task set rules and optimal allocation of resources even on switch trials. This explanation is supported by the

flattening of the waveform during the late period of the cue-target interval observed in the normal controls but not in the MCIs, suggesting that optimal preparation may have been reached before the end of the cue-target period for normal controls but not for MCI patients. Following from this, if the waveform slope in the late period of the cue-locked epoch reflects the extent to which a task-set is fully instantiated, then it should be correlated with reaction time on the upcoming trial. The correlation analysis supported this hypothesis. That is, as Figure 6 illustrates, participants who showed a steep slope in the late period of the cue-locked interval were slower in responding to the target and these participants tended to be in the MCI group. On the other hand, the controls tended to show a flat or even negative slope and responded more quickly, suggesting that they were optimally prepared for the upcoming target. Thus, the significant correlation between slope and response time on repeat trials suggests that the extent to which a participant is able to fully prepare for the upcoming task accounts for at least part of the group difference in overall reaction time difference.

Experimental task switching test: Target-locked ERP effects

The second ERP group effect observed in this study was a target-locked P300 difference between congruous and neutral trials in the MCI group but not in the control group. The P300 component is a late (300 - 800ms), posteriorly distributed positive-going deflection that decreases proportionally as fewer attentional resources are available for stimulus processing (Kok, 2001; Kramer & Spinks, 1991). Thus, a smaller post-target positivity on congruous trials likely indicates that they are more demanding of resources than neutral trials due to a larger interference load. This effect was not observed in the control group. It is possible that the controls were able to bias their attention toward the

relevant task set to the maximum extent possible during the cue-target interval and were therefore less susceptible to interference provided by the congruent foil. On the other hand, MCI participants appear to be more susceptible to the interference provided by the non-neutral foil and showed the expected neutral vs. non-neutral foil enhancement. This interpretation is consistent with the group difference observed in the cue-locked interval. We interpreted the lack of difference in the late negativity between switch and repeat trials and the flattening of the slope in the control group as evidence of optimal task-set reconfiguration. Since biasing attention toward the now relevant task set may be an important part of what can be prepared ahead of target presentation, optimal task set reconfiguration leads to reduced interference from a non-neutral foil. In contrast, the MCI group showed less-than-optimal task set reconfiguration as evidenced by a robust difference in the negativity associated with switch and repeat trials cost and a steep slope toward the end of the cue-locked epoch, leaving the participant exposed to potential interference from a non-neutral foil.

Limitations

Before we conclude, some limitations of the study should be discussed. The experimental manipulations in this study were relatively limited. We compared MCI and control participants on measures of mixing cost, switch costs, and foil effects using a fixed (and relatively long) cue-target interval. Other task switching designs may have yielded different results. For example, the alternating runs design places more demands on working memory capacity because the participant has to keep track of the task sequence which may enhance group differences. Moreover, we employed a relatively

easy task in order to maximize the likelihood that the MCI patients could perform it accurately. Thus, the results may not generalize beyond the parameters we used here.

Summary and Conclusions

To summarize, this study found subtle but significant electrophysiological differences in the absence of behavioural differences in a group of relatively high functioning MCI patients compared to normal older controls, the form of continued preparatory activity at the end of the cue-target interval and cost of processing targets when a competing foil is present. We interpret these group differences as incipient deficits in the MCI patients in terms of task preparation and stimulus evaluation. These are more striking when one considers that more than a third of MCI patients recruited for this study were not able to perform the task (Sinai et al., 2006).

In the group of MCI patients able to perform the task, the present results show the potential utility of ERPs in understanding the nature of cognitive deficits related to mild cognitive impairment. Although no behavioural deficits were seen, the ERP measures revealed subtle functional changes that could be the harbinger of future performance deficits. These results are consistent with other published studies reporting ERP abnormalities in MCI patients (Missonier et al., 2005; Olichney, Taylor, Gatherwright et al., 2008; Phillips, Chertkow, LeBlanc, Pim, & Murtha, 2004). Taken together, the results support the presence of deficits in task switching in MCI some of which might be obscured by using behavioural measures alone.

GENERAL DISCUSSION

The principal goal of this dissertation was to examine the extent to which each component process of task switching may be impaired in MCI. The processes that have been shown to be critical for successful task-switching include endogenous processes such as retrieval and maintenance of task rules from long term memory into working memory, and exogenous processes such as resolution of stimulus-response (S-R) interference.

In the first manuscript, we found a high degree of heterogeneity in MCI patients' task switching ability. Whereas sixteen patients were able to perform the task (MCI-able), 11 could not (MCI-unable). Neuropsychological, neuroanatomical, genetic, demographic, health-related data from these two MCI sub-groups and normal controls were compared in an effort to characterize MCI patients with poor task switching ability. Results showed that, although the three groups did not differ on age, gender, APO E4 frequency, and atherosclerotic risk factors, the MCI-unable group had significantly lower scores on episodic memory and the Trails B test, and had smaller temporal and frontal lobes relative to the control group. In contrast, the MCI able group did not differ from the control group except on episodic memory tests. Interestingly, when comparing the fate of the two MCI groups at four year follow-up, a larger proportion of MCI-unable patients transitioned to dementia or died compared to the MCI-able group.

In the second manuscript, behavioural and ERP responses were recorded for MCI patients and age and education matched normal elderly controls. Although MCI patients were significantly slower than controls, they did not show any difference on behavioural measures of switch or mixing costs. However, the two groups showed some statistically

significant differences in their ERP waveforms. First, in the cue-locked interval, MCI patients but not controls showed increased negativity to repeat versus switch trials. Further, controls showed a flattening waveform in the later stages of the cue-locked interval whereas the MCI's waveforms showed sustained negativity. Second, in the target-locked interval, MCIs but not controls showed reduced P300 to non-neutral foils. These results, suggest subtle abnormalities in task switching that are not yet manifested in the behavioural performance of MCI patients.

The following discussion is divided in two parts. The first part seeks to integrate the results from the two studies submitted for publication and non-published results from the MCI-unable group, in an effort to shed light on the various task-switching processes that may be affected in MCI. The discussion will focus on task switching studies but is also informed by relevant studies of episodic memory function and rule representation. In the second part, implications of these results will be discussed in the context of current theories of mild cognitive impairment and will attempt to provide an explanation for the apparent ability of task-switching to single out MCI patients at higher risk of AD conversion.

Rule Retrieval from Long Term Memory

The way that most task switching experiments are designed, participants are first allowed to learn arbitrary stimulus response association through extensive practice prior to the experimental session. This process relies on intact episodic memory function which is presumably compromised in MCI patients. It is therefore important to examine how MCI's difficulties in episodic memory may affect task switching abilities. Optimal performance on standard episodic memory tests such as word list recall requires at least

two intact mechanisms. The first is encoding and consolidation which allows the information to be attended to and established in long term memory (LTM) and the second is the retrieval of information from LTM when needed. The importance of medial temporal regions in the consolidation of newly acquired memory traces has been established for decades (Squire, 1987) and, given that several studies have shown medial temporal lobe atrophy in MCI, it is not surprising to expect memory consolidation difficulties in MCI. On the other hand, there is mounting evidence that the retrieval of memory traces from LTM involves a distributed network of parietal, temporal and prefrontal areas. Whereas the actual LTM memory trace is stored in posterior parietal cortex and middle temporal gyrus, the ventral portions of the lateral prefrontal cortex (VLPFC) appears to be instrumental in memory retrieval (Bunge, Burrows, & Wagner, 2004; Konishi, Wheeler, Donaldson, & Buckner, 2000) as well as retrieving arbitrary task rules from LTM (Brass & von Cramon, 2004; Bunge, Kahn, Wallis, Miller, & Wagner, 2003; Donohue, Wendelken, Crone, & Bunge, 2005). In light of this dissociation between brain areas involved in memory encoding and memory retrieval from LTM, we would expect MCI patients to have difficulty encoding the stimulus-response associations due to medial temporal lobe atrophy but have relatively intact retrieval functions relative to age matched controls since the inferior frontal gyrus (i.e., the area that roughly corresponds to the VLPFC) has not been shown to be affected in MCI (Chetelat, Landeau, Eustache et al., 2005; Whitwell, Przybelski, Weigand et al., 2007).

The Free and Cued Selective Recall Reminding Test (FCSRT) has been designed to distinguish between memory encoding and retrieval processes in a word list paradigm. In this test, participants are asked to recall a list of words first without and then with a

cue. There are reports that this and similar tests (the California Verbal Learning Test), or contrast between performance on free recall and recognition tests can differentiate between encoding and retrieval failures. A so called “retrieval” profile, characterized by poor free recall but normal performance following a cue, is believed to suggest frontal lobe dysfunction. In contrast, a profile of poor free and cued recall is indicative of a problem with encoding, and suggests medial temporal lobe dysfunction. As expected, several studies with AD patients (Grober, Buschke, Crystal, Bang, & Dresner, 1988; Tounsi, Deweer, Ergis, et al., 1999) and MCI patients who will convert to AD (Sarazin, Berr, De Rotrou, et al., 2007) show impaired recall without a cue and minimal benefit of cueing, suggesting that the memory trace was never encoded in LTM and consistent with MTL atrophy. However others have found mixed results suggesting that both MCI and AD patients have heterogeneous profiles with respect to retrieval or encoding deficits (Lowndes, Saling, Ames, et al., 2008; Pike, Rowe, Moss, & Savage, 2008). In one study (Sarazin, et al., 2007) MCI converters and non-converters differed significantly in FCSRT total recall with converters showing an “encoding” profile and non-converters showing a “retrieval” profile. This suggests that non-converters’ did encode the words but had difficulty retrieving them from LTM whereas converters showed an encoding failure (i.e., the memory trace cannot be accessed even with a cue).

As in most task switching studies, the current study employed a design in which participants were asked to learn arbitrary stimulus-response associations (e.g., if number is even press left key, if number is odd press right key) which would then be rapidly retrieved from LTM during the experimental conditions. In study 2 we presented ERP results that show statistically significant group differences between MCI-able and

controls in the cue target interval. Whereas both groups showed a sustained negativity from about 400 ms, the control group showed a plateau from about 700 ms whereas the MCI group exhibited a sustained negativity until target presentation in both repeat and switch trials. We interpreted these results as difficulty retrieving task rules from LTM on the part of MCI participants and hypothesized that this delay in retrieving the task rules may account for at least part of the MCI's RT increase observed in mixed task conditions. Even though they appear to have some retrieval difficulty, these results show that the task rules were properly encoded in LTM. It must be noted however that we did not measure the trials participants needed to learn the S-R association during the extensive training period and it is possible that the MCI participants may have required significantly more trials to learn the arbitrary associations. Nevertheless, the neuropsychological battery administered to all participants contained a measure of word list free recall and recognition (from the RAVLT) and the MCI-able group indeed showed a "retrieval" profile with impaired free recall and normal recognition performance. Therefore our results are more in line with reports of "retrieval" profiles in many MCI patients (Pike et al., 2008). This may explain why, although MCI-able participants showed reduced hippocampal volume relative to controls, it did not reach statistical significance, suggesting that the atrophic process may not have reached the tipping point after which encoding difficulties become so great that arbitrary S-R rules can no longer be registered in LTM. In contrast to the MCI-able group, MCI unable participants' neuropsychological performance on the RAVLT showed an "encoding" profile with poor free recall and recognition. In fact, the RAVLT recognition score was the only memory measure that differentiated between the two MCI groups. This suggests that contrary to the MCI-able

group, the MCI-unable participants had encoding difficulties indicative of compromised medial temporal lobe function and our neuroanatomical data support this interpretation with a significant atrophy in hippocampal volume of the MCI-unable group relative to controls.

The data submitted in the second study only included ERP data for the MCI-able and control groups. However, although not reported for reasons explained below, we also collected ERP data on a subset of MCI-unable participants that will be discussed next. The heterogeneity in task switching ability of the MCI group allowed us to distinguish between the MCI-able and MCI-unable groups. However, the eleven MCI-unable patients can be further classified on the basis of their performance on this task. In fact, about half this group (six patients), were not even able to perform the homogeneous blocks whereas the five remaining participants were able to complete the homogeneous blocks during training but were unable to perform on mixed task conditions. The six MCI patients that could not perform the homogeneous task had difficulty encoding the S-R associations, demonstrating a clear “encoding” difficulty. In contrast, the remaining five MCI patients were able to learn the task rules, as evidenced by their ability to retrieve them in single task conditions, but were unable to perform the task during mixed task conditions. In an effort to collect ERP data on these patients, the original design was modified for these five participants to enable performance and data collection. The original paradigm presented the cue on the screen for 1000 ms which was immediately replaced by the target. The modified design also presented the cue for 1000 ms but allowed the cue to remain on the screen with the target until the response (see Figure 9). Under these conditions, the five MCI patients were able to complete the heterogeneous conditions.

These results were not published for two reasons. First the sample size was judged too small and second the data collected from these five patients could not be statistically compared to the other two groups because of differing methodologies. Nevertheless, the cue-locked waveform from these five patients could be considered qualitatively in light of the results from the other two groups to infer the extent to which these patients experienced retrieval difficulties. In the following discussion of these results, I will refer to these five MCI patients as the MCI with cue (MCI-wc) group and to the six MCI patients that could not perform the homogeneous task as the MCI-unable group. This should not be confused with the notation used in the first manuscript, in which I referred to the eleven MCI patients who could not perform the task as the MCI-unable group.

Figure 10 shows the cue-locked homogeneous, repeat, and switch waveforms at the centroparietal midline site (CPz) for all three groups (control, MCI-able, MCI-wc). What can be readily observed is that the MCI-wc group shows a similar cue-locked negativity as the MCI-able group on switch and repeat trials, suggesting that the two MCI groups did not differ qualitatively regarding their ability to retrieve task rules from LTM. Instead, the fact that these patients could only perform the task when the cue remained on the screen for the duration of the trial suggests difficulty maintaining the retrieved task rules in working memory.

Working Memory

There are several converging lines of evidence suggesting that the lateral prefrontal cortex (LatPFC) is essential to the ability to maintain a set of goals (i.e., intention to act) “on line” even in the absence of external cues. First, a subset of LatPFC neurons show sustained activation when monkeys are required to keep information in

mind over a few seconds before using it to make a response (Fuster, 1997; Goldman-Rakic, 1987). Further, it has been shown that monkey's LatPFC neurons are selectively involved in both the maintenance of task rules as well as response planning during a few seconds delay (Funahashi & Takeda, 2002; Fuster, 2000). Converging evidence from fMRI studies confirms that the human LatPFC is involved in the maintenance of information regardless of the modality of the information received to guide action (Wallis, Anderson, & Miller, 2001). However, there is debate as to which part of the LatPFC is involved in task maintenance and other areas have also been implicated in the maintenance of information in working memory.

Bunge et al. (2003) required subjects to maintain a specific motor plan over a delay period until a target was presented and found activation in the dorsal premotor cortex as well as in pre-SMA. Calvina-Pratesi, Valyear, Culham et al. (2006) also showed that pre-SMA and left inferior parietal lobule were more active when subjects maintained two S-R mappings (e.g., press A if target is a house, press B if target is a face) instead of one (press A if target is any stimulus). These results suggest that pre-SMA and parietal cortex can maintain representations of possible responses online.

There is solid evidence that verbal working memory requires posterior left VLPFC when participants engage in subvocal rehearsal (Smith & Jonides, 1999; Wagner, Bunge, & Badre, 2004) perhaps due to this region's proximity to Broca's area. Interestingly, verbal rehearsal has been implicated as an important factor in task preparation during task switching (Harvey, Galletly, Field, & Proeve, 2009). Another PFC area that has often been implicated in task maintenance is the DLPFC although as will be discussed later, this area seems to be more involved in response selection when

task rules must be maintained in working memory (Goldman-Rakic, 1987; Rowe & Passingham, 2001).

To return to the results from the current study, the five MCI-wc patients were able to retrieve task rules in single task blocks but were unable to do so in mixed blocks unless the cue remained on the screen. Therefore these patients experience a working memory deficit rather than retrieval difficulty. This hypothesis is supported by ERP data shown in Figure 11 which depicts the target-locked waveforms for the three groups at CPz for homogeneous, repeat and switch waveforms. What is notable here is the absence of the P300 component (positive deflection between 300 and 800 ms) in the MCI-wc patients compared to its robust showing in the other two groups. The P300 has been proposed as an index of working memory resources available for stimulus evaluation (Kok, 2001; Kramer and Spinks, 1991) and its absence in the MCI-wc group suggests limited resources available for stimulus processing ahead of the target. Although this deficit may at first seem to be due to impaired verbal rehearsal, this may not be these participants' main difficulty for several reasons. First, despite providing the cue for the duration of the trial, these participants still showed profound behavioural deficits (i.e., increased reaction time and error rates). Second, although the MCI-wc group showed lower scores on a neuropsychological measure of verbal working memory, the number-letter sequencing task, these were not statistically significant. Finally, these three groups did not differ in inferior frontal gyrus volume which, according to our segmentation method is the region of the frontal cortex that best corresponds to VLPFC (Please see Table 15). Although lack of group difference in regional brain volume may conceal functional changes that predate structural atrophy, the pattern of structural changes observed in the MCI-wc

group points to other frontal cortex regions that have been involved in task-switching and working memory alike.

The MCI-wc group showed lower volumes in the lateral orbitofrontal cortex and middle frontal gyrus. Although the orbitofrontal cortex has not, to our knowledge, been involved in task switching, the middle frontal gyrus, which corresponds to the DLPFC, has been shown to be activated in task switching studies. As will be discussed shortly, this area has also been implicated in studies where participants have to maintain task rules in working memory in order to select between more than one response rule or when one set of response has to be inhibited.

Finally, the MCI-unable group showed lower volumes in almost all analysed regions (except the superior frontal, parahippocampal, and supramarginal gyri), including areas known to be important in task switching such as the middle and medial frontal gyri, precentral gyrus, cingulate gyrus, and the superior parietal gyrus relative to the control group, as well as in the medial frontal gyrus relative to the MCI-able group. The medial frontal gyrus which includes the SMA, has reliably been activated in task switching studies. As discussed previously, this area has been implicated in studies where participants have to maintain two sets of task rules in working memory.

Stimulus-Response interference

As presented in the introduction, the principal determinant of switch costs is the extent to which a stimulus is able to determine the appropriate task. In situations where the same stimulus can evoke two or more sets of response rules as in the current study, resources must be spent to resolve this ambiguity and this property of bivalent stimuli is thought to be an important source of both switch and mixing costs (Rubin & Meiran,

2005). Several studies have shown increased activation in dorsal primary motor areas, the medial frontal gyrus with particular focus on the SMA, as well as the posterior parietal lobe, when subjects prepare between two responses (i.e., bivalent condition) rather than one (i.e., univalent condition; Brass, Ruge, Meiran et al., 2003; Calvina-Pratesi et al., 2006) and when participants are asked to switch between response rules (Rushworth et al., 2002) suggesting that these areas are crucial in maintaining S–R mappings online while subjects prepare to respond.

Another PFC area that has often been implicated in response processes is the DLPFC. MacDonald, Cohen, Stenger, and Carter (2000) asked participants to switch between the dominant and nondominant Stroop tasks. Greater DLPFC activation was observed during nondominant relative to dominant trials. Hester, Murphy, Foxe et al. (2004) used a go/no-go paradigm in which subjects were warned that they would sometimes have to withhold their response and found greater DLPFC activation in no-go trials. In both cases, these studies implicate the DLPFC in task switching situations in which participants are required to inhibit prepotent responses. Interestingly, there is mounting evidence that low level inhibitory mechanisms, known as backward inhibition, may be recruited automatically in task switching situations (Mayr & Keele, 2000) and that inhibitory control acts mainly at the response selection stage (Schuch & Koch, 2003; Sinai, Goffaux, & Phillips, 2007). Also, since this form of inhibition acts at a low control level, it is likely to be exerted locally in posterior parietal lobe (Sinai et al., 2007) whereas the right VLPFC appears to be involved in overcoming this inhibition perhaps reflecting increased effort retrieving the inhibited task rules stored in posterior parietal lobe (Dreher & Berman, 2002).

The DLPFC has also been implicated in response selection when task rules must be maintained in working memory (Goldman-Rakic, 1987; Passingham & Rowe, 2002). DLPFC activation is observed in brain imaging studies in which demands on response selection have been manipulated (Hazeltine, Poldrack, & Gabrieli, 2000; Rowe, Stephan, Friston, Frackowiak, & Passingham, 2004; Schumacher, Elston, & D'Esposito, 2003). This area may therefore be preferentially activated in mixed block situations in which two sets of task rules have to be selected from, relative to single task blocks in which response selection is less demanding.

In sum, there appears to be a distributed network of brain areas that are involved in resolving the conflict created by overlapping s-r associations inherent in most task switching designs. According to our segmentation method, this network includes frontal areas such as the precentral gyrus (equivalent to dorsal motor cortex), the medial frontal gyrus (that includes the SMA and pre-SMA), and the middle frontal gyrus (equivalent to the DLPFC), as well as posterior parietal areas. Interestingly, all the aforementioned regions involved in s-r representation and response selection show reduced brain volumes in the MCI-unable group relative to controls. It is therefore not surprising that this group exhibited such poor switching ability.

Although the MCI-wc participants did not show the same pattern of smaller cortical volumes as the MCI-unable group in areas thought to be important for task-switching, they nonetheless showed smaller middle frontal gyrus volume compared to the control group. pervasive lower brain volumes, not impaired to the same extent as the MCI-unable group, the MCI-wc participants showed nevertheless Table 14 shows reaction time (RT) results for the 5 MCI-wc as well as the MCI-able and control groups.

Although as discussed previously direct comparisons between the 5 MCI-wc patients and the other two groups should be made with caution due to design differences, a simple glance at the results shows that despite the cognitive support they received, their RT were dramatically increased relative to their counterparts. Importantly, the MCI-wc group showed a significantly larger mixing cost ($p < .001$) but no increased switch cost or foil effects (all $ps > .19$). This argues in favor of a general difficulty holding more than one task rule in working memory and is consistent with DLPFC dysfunction.

To sum up, our effort to integrate neuropsychological, neuroradiological and electrophysiological data from the three groups suggests a high degree of heterogeneity in the extent to which task switching processes are affected in MCI. The MCI-able group's difficulties appear to be limited to mild retrieval deficits. In contrast, the MCI-wc group showed difficulties in working memory and had more difficulty resolving S-R interference, as well as experiencing the same retrieval difficulties experienced by the MCI-able group. Patients in the MCI-unable group could not perform the task even with cognitive support, probably due to episodic memory difficulties so severe that they could not encode the task rules well enough to perform the task. Given these group differences in cognitive symptoms, it is tempting to see an intensification of deficits as patients move closer to dementia. Although plausible, this interpretation should be made with caution because the number of patients is too small, especially in the MCI-wc and MCI-unable subgroups, to reach firm conclusions. Nevertheless, these results do suggest that MCI-able participants represent the mildest formulation of mild cognitive impairment, which in many cases includes individuals who will revert back to normal status whereas the

MCI-wc and MCI-unable groups consists of patients closer to the dementia side of the cognitive aging spectrum.

Overlap between brain regions involved in Task switching and MCI atrophy

The intra parietal sulcus (IPS), which divides the superior from the inferior parietal lobe, is a region that has been consistently implicated in task-switching studies (Wager, Jonides, & Reading, 2004). Although this region is not usually reported as a site of significant atrophy in MCI patients, a region adjacent to it, the temporo-parietal juncture has been shown to be one of the earliest non temporal areas to be affected in AD (Hoffman, Welsh-Bohmer, Hanson, et al., 2000) and studies have shown atrophy in this area in MCI (Chetelat et al., 2005). It has been proposed that AD can be regarded as a disconnection syndrome that targets neurons with long axons that provide cortico-cortical connections causing deficits in cognitive functions, such as task switching, that rely on distributed networks connecting anterior and posterior regions (Delbeuck, Van der Linden, & Collette, 2003; Perry & Hodges, 1999). It is therefore possible that MCI-unable patients' difficulties may have been due, at least in part, to either reduced superior parietal lobe volume as well as posterior parietal functional abnormalities not yet detected by structural imaging methods. However, whether or not posterior parietal lobe contributed to the MCI-unable's cognitive deficits, our data strongly point to the role of frontal areas in task switching and a pattern of brain atrophy observed in the MCI-unable patients that is not typical of MCI.

The earliest region showing AD pathological changes such as neurofibrillary tangles and deposition of amyloid plaque, and therefore the site of most likely brain atrophy in MCI patients, consist of medial temporal lobe structures. From there,

pathological changes spread to the infero-lateral temporal, inferior parietal, posterior cingulate and medial frontal regions. The dorsolateral prefrontal cortex appears to be affected at a later stage and the primary motor and sensory cortices are typically spared until the latest stages of the disease (Coleman & Flood, 1987). This general pattern of disease evolution derived from post-mortem histopathological analysis is replicated by Structural Magnetic Resonance (MRI) studies showing the medial temporal lobe to be the earliest loci of cerebral atrophy (Adak, Illouz, Gorman, et al., 2004; Bottino, Castro, Gomes, et al., 2002; Convit, de Asis, de Leon, et al., 2000; DeCarli et al., 2007; deToledo-Morrell et al., 2004; Dickerson, Goncharova, Sullivan, et al., 2001; Geroldi, Rossi, Calvagna, et al., 2006; Killiany, Hyman, Gomez-Isla, et al., 2002; Korf et al., 2004; Pennanen et al., 2004; Wolf et al., 2004). Further, two recent longitudinal studies tracking the extent of brain atrophy in MCI patients beyond the medial temporal lobe using whole-brain structural MRI techniques, detected atrophy in the medial and inferior temporal lobes, as well as in the posterior cingulate and precuneus approximately one year prior to diagnosis (Chetelat et al., 2005; Whitwell, et al., 2007) whereas other whole brain studies of MCI patients showed no significant atrophy outside of temporal lobe areas (Wang, Golob, Bert et al., 2009).

This MCI pattern of regional brain atrophy clearly differs from the pattern observed in the MCI-unable patients who showed heavy frontal lobe burden. This raises the possibility that the MCI-unable group may be an atypical group of MCI patients or may perhaps include individuals whose cognitive impairment may be due to aetiologies other than AD. In the first study, we argued in detail about the possibility that these patients' significantly smaller frontal lobes may have predated their MCI diagnosis. We

based this argument on the fact that these patients had significantly lower levels of education compared to the control group and interpreted these findings as evidence for reduced cognitive and brain reserve in the MCI-unable patients, leaving them more vulnerable to AD pathology. Also, although we cannot rule out the presence of other disorders that could have exacerbated their cognitive symptoms, we did not find evidence of increased cardiovascular risk in this group. Rather, these patients possessed certain characteristics consistent with AD such as an increased frequency of Apo E4 carriers (although it did not reach statistical significance perhaps due to very low sample size) and increased mortality and AD transition at four year follow-up. In sum, it appears that the MCI-unable participants were “legitimate” MCI patients and not just individuals whose cognitive impairment could be explained by lower education or reduced brain size. The fact that this task switching paradigm was able to identify MCI patients with poor task-switching ability has important ramifications as to the nature of MCI.

The nature of MCI

There is a lack of consensus in the literature as to the nature of MCI. Some authors have conceptualized MCI as simply the prodromal phase of AD (Morris, Storandt, Miller, et al., 2001). However, this position either minimizes or disregards the documented heterogeneity of MCI. With respect to diagnostic outcome, four groups have been described in the literature. The first is those that have incipient dementia and will transition to AD within 3 to 5 years. The second is a group of patients who remain stable over long periods of time, the third is a group of patients who will revert to normal status and finally there is a group that will fluctuate between MCI and the normal range. Clearly, not all amnesic MCIs – up to 40% in some large scale studies – represent

prodromal AD. Some have argued that this heterogeneity casts doubts on the validity of MCI as a diagnostic category (Dubois, 2000). I would argue on the contrary that this heterogeneity actually validates the usefulness of the MCI concept. Put simply, if there was a one to one correspondence between amnesic MCI and AD, there would be no need for such an intermediate classification. As it stands, the MCI classification fulfills its intended purpose, which is to detect individuals at increased risk of developing AD. Once identified as a high risk population, these individuals can be followed more closely for signs of cognitive and functional deterioration, contributing to early detection of AD.

The observation that some MCI patients remain stable or even revert to normal status, and some MCI patients are destined to progress to AD has led to the emergence of the concept of “stable” (SMCI) versus “progressive” MCI (PMCI) and several studies have sought to explore the cognitive (Bozoki et al., 2001), neuroanatomical (Wang et al., 2009), neurofunctional (Stefani, Sancesario, Pierantozzi et al., 2009), and electrophysiological (Giannakopoulos, Missonnier, Kovari, Gold, & Michon, 2009) markers that distinguish these two MCI categories. Results from the current study support the concept of stable versus progressive MCI and adds detail to the specific cognitive functions that may be affected in both stable and progressive MCI. Aside from the obvious episodic memory impairment that warranted the MCI diagnosis, the MCI-able participants showed an overall performance deficit in the form of significant longer reaction time on the experimental task that, coupled with analysis of ERP cue-locked waveforms, we interpreted as a difficulty retrieving task rules from long term memory. Whereas a significant minority of individuals in this group reverted to normal status at follow-up, the vast majority of the remaining participants retained a stable MCI diagnosis

four years later. These MCI individuals possess characteristics that distinguish them from both controls and AD patients. As such, they may represent the quintessential MCI profile, a true intermediate state between normal cognitive aging and dementia. In contrast, the poor task switching ability and weak cognitive profiles of the MCI-wc and MCI-unable group were clearly qualitatively different from the control group and included a high proportion of patients who converted to AD as well as higher morbidity rates. One factor that may mediate executive function's ability to predict conversion to AD or mortality is their influence on the patient's functional status.

Executive functions and functional status

When the diagnostic features of both MCI and AD are compared, the major difference between the two consists in their ability to function in daily life and this is even more so when we consider MCI patients with deficits in multiple cognitive domains. This suggests that a patient's functional status may hold the key to understand MCI transition to AD. Functional status is usually conceptualized as the ability to perform self-care, self-maintenance and physical activities (Wilson & Cleary, 1995). The Instrumental Activities of Daily Living Scale (IADL; Lawton & Brody, 1969) is a widely used measure of functional status in the elderly and consists in the assessment of eight major skills that are thought to be important for independent living. These skills are: ability to use the phone, shopping, food preparation, housekeeping, laundry, transportation, medication, and ability to handle finances. As the MCI patient's skills to perform these activities decline, the chances of AD diagnosis increases. It is possible that the reported sensitivity of executive functions in general and task switching abilities in particular in predicting MCI transition to AD may be due to the association between functional status

and executive functions. It is not difficult to see how intact executive functions are required for successful performance on the aforementioned skills. For example, task switching ability is particularly important in light housework, meal preparation, grocery shopping, and managing money. It is therefore not surprising that several studies have found an association between executive functions and IADL. Carlson, Fried, Xue, et al. (1999) found that Trails B accounted for a significant proportion of the variance in IADL performance in a sample of community-dwelling older adults and that a factor score derived from four tests of executive function was more strongly associated with IADLs than with episodic memory performance. Likewise, Cahn-Weiner, Malloy, Boyle, et al. (2000) found that executive measures were better predictors of functional status than memory, language, visuospatial, or psychomotor function. Also, Johnson, Lui, and Yaffe (2007) found that Trails B performance predicts functional decline as measured by IADL six years later. Finally, a recent study of MCI patients (Kim, Lee, Cheong et al., 2009) found that MCI patients that have executive as well as episodic memory function impairments had significantly lower scores on telephone, transportation, finances and household chores sections of the IADL relative to controls whereas MCI patients who only had memory problems did not. These results strongly suggest that executive functions may be a sensitive marker of MCI transition to AD because of their significant influence on a patient's functional status. Therefore, whereas deficits in episodic memory deviates an individual's trajectory away from normal cognitive aging, executive function decline may precipitate conversion to AD. Viewed from another angle, intact or quasi-intact executive functions could be seen as a sort of cognitive reserve at the disposal of an individual with MCI. Healthy executive functions in MCI may exert beneficial effects

through compensatory mechanisms deployed to mitigate episodic memory decline as well as by prolonging their functional independence. This hypothesis fits well with the results from this study. Although we did not collect functional data, our results clearly show that impaired task switching ability was associated with reduced frontal lobe volumes, lower education, and negative prognosis, whereas adequate switching ability was associated with stable and improved outcomes at follow-up.

Final Thoughts and Conclusion

This is the first study that explores MCI abilities in a task-switching paradigm. Results confirm that MCI is a heterogeneous category. The most significant finding of this project is that task-switching ability can be a powerful tool in characterizing this heterogeneous population. We found that most MCI patients exhibit some form of task-switching deficits, but to vastly different degrees. On the one hand there are individuals closer to the normal aging side of the cognitive spectrum; these individuals may present with memory deficits relative to their normal age peers but can compensate these with quasi-intact executive functions. These individuals have a high probability of remaining dementia free as long as their executive functions remain adequate. On the other side of the spectrum, there are individuals who perform poorly on executive tasks as well as having significant episodic memory deficits. These individuals appear to have a high probability of developing AD or dying within four years.

Several limitations of this study should be noted and by addressing them avenues for future research will be proposed. The first two limitations regard the manner in which we designed the experiment. Conscious of the time constraints involved in testing patient populations, we limited our design to a single cue-target interval (CTI). Future studies

that vary the CTI would test our finding that MCI patients have early difficulties in retrieving task rules from LTM. Given more time to prepare, the group differences between MCI-able and controls which include overall RT, and flattening of the cue locked waveforms should be attenuated.

The second limitation of our design relates to the inability of some patients to perform the task. On the one hand, this unexpected result highlighted the dramatic heterogeneity of the original MCI group. But on the other hand, it limited our ability to study task switching ability in a significant minority of patients. We attempted to rectify this situation by modifying the design so to provide cognitive support to the MCI-unable patients. However, this effort was limited and ad-hoc. Future studies could further investigate the processes involved in the MCI-unable failure to perform the task. For example, we argued that some MCI-unable patients had working memory problems because when we allowed the cue to be present on the screen for the duration of the trial, they were able to perform the task (i.e., MCI-wc participants). However, other informative manipulations could be attempted such as allowing S-R associations on the screen for the duration of the trial so to decrease task rule retrieval demands.

One of the most interesting hypotheses raised by this study is the possibility that MCI transition to AD may be mediated by the deleterious effects of executive function decline on the functional status of the patient. Unfortunately no data on the functional status of participants was collected in this study. Future research should explore this association further as well as the association between task-switching and skills necessary for independent living.

Finally, our results show that the MCI-unable group had significantly lower education levels than the controls. There is a need for more investigation regarding the possible association between task-switching ability and level of education in MCI and to find out whether severe task switching deficits are limited to patients with relatively low education or whether it also applies to higher educated MCI patients.

In conclusion, a final thought on the clinical implications of these findings. It has been proposed that standardized tests should reflect not only the age of the patient but also her level of education. Although I agree in principle with this sensible approach, I would caution against the over reliance on education adjusted scores, especially when it relates to the assessment of executive functions in low educated individuals. A clinician assessing an MCI patient may interpret low scores on executive function tests as normal given the patient's low average intelligence and low levels of education. However, the results of this study suggest that impaired task switching ability and executive functions in general should be treated as an additional risk factor of MCI transition to AD regardless of the patient's level of education.

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Table 1

Summary of studies examining Dual Task ability in MCI

Study	MCI Characteristics			Test	Deficit
	Age (SD)	Educ. (SD)	MMSE (SD)		
Belleville et al., 2007	64.8 (10.8)	14.3 (4.7)	28.4 (2.0)	Brown Petersen Task	(+)
Johns et al., 2009	72.4 (8.6)	13.1 (3.1)	28.1 (1.4)	Brown Petersen Task	(+)
Lopez et al., 2006	79.9 (3.4)	n/a	n/a	Baddeley Dual Task	(+)
Nordlund et al., 2005	64 (8.2)	n/a	28.5 (1.5)	Baddeley Dual Task	(-)
Perry et al., 2000	68.2 (7.6)	n/a	26.1 (1.6)	Baddeley Dual Task	(-)
Silveri et al., 2008	74.7 (3.8)	9.8 (4.7)	26.0 (1.4)	TEA Dual Task	(-)

Educ: Years of education; MMSE: Mini mental State Examination; TEA: Test of Everyday Attention

Table 2

Summary of studies examining Working Memory Updating in MCI

Study	MCI Characteristics			Test	Deficit
	Age (SD)	Educ. (SD)	MMSE (SD)		
Bisiacchi et al., 2008	76.3 (7.4)	8.8 (3.8)	25.7 (1.6)	BDS	(-)
Kramer et al., 2006	75.0 (6.1)	16.5 (3.2)	28.5 (1.5)	BDS	(-)
Grundman et al., 2004	72.9 (7.3)	14.7 (3.1)	27.3 (1.9)	BDS	(-)
Lopez et al., 2006	79.9 (3.4)	n/a	n/a	BDS	(+)
Belleville et al., 2007	64.8 (10.8)	14.3 (4.7)	28.4 (2.0)	Alpha Span	(-)
Borkowska et al., 2007	61.9 (5.6)	11.7 (5.6)	25.3 (0.9)	N-back	(+)
Griffith et al., 2006	68.5 (8.6)	13.4 (2.0)	28.4 (1.6)	LNS	(+)
Johns et al., 2009	72.4 (8.6)	13.1 (3.1)	28.1 (1.4)	LNS	(+)

Educ: Years of education; MMSE: Mini mental State Examination; BDS: Backward Digit Span; LNS: Letter Number Sequencing.

Table 3.

Summary of studies examining Response Inhibition in MCI

Study	MCI Characteristics			Test	Deficit
	Age (SD)	Educ. (SD)	MMSE (SD)		
Belleville et al., 2007	64.8 (10.8)	14.3 (4.7)	28.4 (2.0)	Hayling	(-)
Bisiacchi et al., 2008	76.3 (7.4)	8.8 (3.8)	25.7 (1.6)	Hayling	(-)
Johns et al., 2009	72.4 (8.6)	13.1 (3.1)	28.1 (1.4)	Hayling	(+)
Belleville et al., 2007	64.8 (10.8)	14.3 (4.7)	28.4 (2.0)	Victoria Stroop	(-)
Duong et al., 2006	74.7 (6.5)	11.0 (3.7)	27.2 (2.2)	Victoria Stroop	(-)
Nordlund et al., 2005	64 (8.2)	n/a	28.5 (1.5)	Victoria Stroop	(-)
Johns et al., 2009	72.4 (8.6)	13.1 (3.1)	28.1 (1.4)	Victoria Stroop ER	(+)
Kramer et al., 2006	75.0 (6.1)	16.5 (3.2)	28.5 (1.5)	Color Stroop RT	(+)
Lopez et al., 2006	79.9 (3.4)	n/a	n/a	Color Stroop RT	(+)
Perry et al., 2000	68.2 (7.6)	n/a	26.1 (1.6)	Color Stroop RT	(+)
Traykov et al., 2007	73.2 (8.0)	12.1 (3.1)	28.95 (1.1)	Color Stroop RT	(+)
Nordlund et al., 2005	64 (8.2)	n/a	28.5 (1.5)	Picture Stroop ER	(+)
Duong et al., 2006	74.7 (6.5)	11.0 (3.7)	27.2 (2.2)	Picture Stroop ER	(+)
Kaufmann et al., 2008	69.8 (5.3)	n/a	24.8 (1.2)	Numerical Stroop	(+)
Zamarian et al., 2007	68.0 (6.9)	10.2 (3.0)	27.0 (1.4)	Math Stroop	(+)

Educ: Years of education; MMSE: Mini mental State Examination; RT: Reaction Time; ER: Error Rate.

Table 4

Summary of studies examining Task switching ability in MCI

Study	MCI Characteristics			Test	Deficit
	Age (SD)	Educ. (SD)	MMSE (SD)		
Baudic, 2006	81.4 (6.8)	8.4 (3.1)	25.6 (1.0)	MCST	Category (+), PE (+)
Nagahama et al., 2003	72.8 (5.4)	10.9 (2.7)	26.4 (2.0)	MCST	Category (+), PE (+)
Traykov et al., 2007	73.2 (8.0)	12.1 (3.1)	28.95 (1.1)	MCST	Correct (-), PE (+)
Nordlund et al., 2005	64 (8.2)	n/a	28.5 (1.5)	MCST	Correct (-)
Silveri et al., 2008	74.7 (3.8)	9.8 (4.7)	26.0 (1.4)	WCST	Category (+), PE (-)
Perry et al., 2000	68.2 (7.6)	n/a	26.1 (1.6)	MCST	Category (-)
Borkowska et al., 2007	61.9 (5.6)	11.7 (5.6)	25.3 (0.9)	WCST	Category (+), PE (+)
Baudic, 2006	81.4 (6.8)	8.4 (3.1)	25.6 (1.0)	Trails B	(+)
Silveri et al., 2008	74.7 (3.8)	9.8 (4.7)	26.0 (1.4)	Trails B	(+)
Nordlund et al., 2005	64 (8.2)	n/a	28.5 (1.5)	Trails B	(+)
Traykov et al., 2007	73.2 (8.0)	12.1 (3.1)	28.95 (1.1)	Trails B	(-)
Lopez et al., 2006	79.9 (3.4)	n/a	n/a	Trails B	(-)
Kramer et al., 2006	75.0 (6.1)	16.5 (3.2)	28.5 (1.5)	Modified Trails	(+)
Perry et al., 2000	68.2 (7.6)	n/a	26.1 (1.6)	Visual Elevator	ER (-), RT (+)
Silveri et al., 2008	74.7 (3.8)	9.8 (4.7)	26.0 (1.4)	Visual Elevator	ER (-), RT (+)
Belleville et al., 2008	66.3 (10.9)	13.9 (5.0)	28.1 (2.1)	Task Switching	(-)
Belleville et al., 2008	66.3 (10.9)	13.9 (5.0)	28.1 (2.1)	Spatial Shifting	(+)

Educ: Years of education; MMSE: Mini mental State Examination; MCST: Modified Card Sorting Test; WCST: Wisconsin Card Sorting Test; PE: Perseverative Errors; Correct: Correct answers; RT: Reaction Time; ER: Error Rate.

Table 5.

Mean (and SE) of groups performance on MMSE and MoCA at both data collections times.

	NP testing	Task-Switching Session	t-value	p
Control group				
MMSE	28.6 (.4)	28.6 (.4)	0	1.00
MoCA	25.5 (.3)	26.2 (.6)	1.4	.19
MCI able group				
MMSE	28.3 (.4)	28.5 (.4)	.4	.69
MoCA	23.2 (.9)	24.5 (1.1)	1.2	.25
MCI unable group				
MMSE	27.2 (.5)	25.6 (.7)	1.6	.14
MoCA	21.7 (.7)	20.9 (1.1)	1.1	.29

NP testing: Neuropsychological testing; MMSE : Mini Mental State Examination; MoCA : Montreal Cognitive Assessment.

Table 6

Sociodemographic and health related characteristics of the Control, MCI-able, and MCI-unable groups (Manuscript 1)

	Controls	MCI able	MCI unable
N	19	16	11
<i>Continuous Variables, Mean (SE)</i>			
Demographics			
Age	75.7 (1.5)	75.5 (1.7)	76.7 (1.9)
Education (years)	14.5 (.7) [#]	12.2 (.7)	10.7 (.9) [#]
Atherosclerotic Risk Factor (ARF /6)	1.2 (.3)	1.9 (.3)	1.5 (.4)
Depression (GDS)	2.9 (1.1) [#]	4.8 (1.2) [*]	9.4 (1.4) ^{#*}
Time Since Diagnosis	na	42.9 (6.2)	33.5 (8.4)
<i>Discrete Variables, Frequency (Percentages)</i>			
Demographics			
Sex, Female	12 (63)	10 (62)	6 (55)
Cardiovascular risk			
Transient Ischemic Attack (TIA)	2 (11)	1 (6)	1 (9)
Heart Disease	6 (32)	7 (44)	2 (18)
Hypertension	9 (47)	11 (69)	8 (73)
Hypercholesterolemia	3 (16)	7 (44)	5 (45)
Smoking	2 (11)	1 (6)	0 (0)
Diabetes	1 (5)	3 (19)	1 (9)
Apolipoprotein e4 carrier	3 (16)	2 (12)	4 (36)

GDS: Geriatric Depression Scale; Continuous variables were analyzed with multivariate analysis. Discrete variables were analyzed with Chi-Square.

+: Significant difference between Controls and MCI able

#: Significant difference between Controls and MCI unable

*: Significant difference between MCI able and MCI unable

Table 7

Mean (and SE) scores and group differences on neuropsychological tests among controls, MCI able, and MCI unable (Manuscript 1)

	Controls	MCI able	MCI unable
N	19	16	11
<u>Global Functioning</u>			
MOCA (/30) ^l	26.5 (.6) [#]	24.3 (.6) [*]	21.0 (.8) ^{**}
MMSE (/30)	28.6 (.4)	28.4 (.4)	25.6 (.6)
Orientation (/11)	10.8 (.1)	10.8 (.1)	10.5 (.2)
Mental Control (/40)	25.5 (1.2)	21.7 (1.4)	20.0 (2.0)
Digit Symbol Coding (/133)	51.2 (1.9)	48.7 (2.1)	36.8 (2.9)
<u>Episodic Memory</u>			
Logical Memory (Immediate)	14.0 (.7)	10.6 (.8)	8.8 (1.3)
Logical Memory (Delayed)	12.5 (.9)	8.6 (1.0)	6.5 (1.6)
RAVLT (Immediate)	9.3 (.6) ⁺	5.1 (.7) ⁺	4.0 (.8)
RAVLT (Delayed)	8.5 (.6) ^{+#}	4.5 (.7) ⁺	2.1 (.9) [#]
RAVLT (Recognition)	12.9 (.6) [#]	12.4 (.7) [*]	8.9 (.9) ^{**}
Visual Reproduction (Immediate)	77.0 (3.3)	64.4 (3.7)	51.6 (4.7)
Visual Reproduction (Delayed)	50.5 (4.3)	37.3 (4.8)	24.9 (6.0)
<u>Working Memory</u>			
Spatial Span	13.4 (.6)	12.1 (.7)	11.5 (.9)
Letter Number Sequencing	8.7 (.6)	8.6 (.6)	6.0 (.8)
<u>Executive Functions</u>			
Clock	8.7 (.3)	8.8 (.3)	8.6 (.4)
Trail Making A	46.1 (2.6)	48.1 (2.9)	50.0 (3.6)
Trail Making B	94.3 (15.2)	111.2 (16.9) [*]	233.5 (21.4) [*]
Trail Making Ratio (B-A)/A	1.1 (.3) [#]	1.3 (.4) [*]	3.9 (.5) ^{**}
Fluency (Letter, FAS)	46.1 (3.1)	41.1 (3.5)	30.1 (4.4)
Fluency (Category, Animals)	17.0 (1.1)	15.8 (1.2)	13.4 (1.5)
Victoria Stroop Color (RT)	29.7 (2.5)	37.6 (2.4)	38.0 (3.7)

Table 7 (continued)

Mean (and SE) scores and group differences on neuropsychological tests among controls, MCI able, and MCI unable (Manuscript 1)

Executive Functions

Victoria Stroop Color (Errors)	.3 (.4)	1.3 (.4)	2.6 (.5)
<u>Visuo-spatial</u> : Block Design	31.4 (1.9)	32.7 (2.2)	22.3 (2.7)

Language Functions

Boston	54.1 (1.5)	50.8 (1.7)	45.4 (2.1)
Similarities	23.3 (1.0)	21.4 (1.1)	20.0 (1.4)

MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment;

RAVLT: Ray Verbal Learning Test.

Multivariate analysis on all neuropsychological tests had education, GDS score, and MoCA as covariates. Data presented are unadjusted. Post-hoc tests were performed on adjusted means.

‡: Used as covariate

+: Significant difference between Controls and MCI able

#: Significant difference between Controls and MCI unable

*: Significant difference between MCI able and MCI unable

Table 8

Selected Regions Volume (mm³) with their Standard Deviation (SD) for Control, MCI-able, and MCI-unable Groups. (Manuscript 1)

Region	Control	MCI able	MCI unable
Medial Orbital Gyrus	4788 [#] (817)	4176 (974)	3433 [#] (740)
Lateral Orbital Gyrus	27037 [#] (3283)	24113 (5191)	20029 [#] (4685)
Superior Frontal Gyrus	23780 (4836)	23256 (5042)	18352 (4911)
Middle Frontal Gyrus	52907 [#] (7601)	46179 (12179)	37271 [#] (9469)
Inferior Frontal Gyrus	27980 (5110)	25518 (6793)	20504 (6282)
Medial Frontal Gyrus	31022 [#] (4982)	29857 [*] (6541)	23509 ^{#*} (5864)
Cingulate Gyrus	33056 [#] (3625)	30675 (6415)	26382 [#] (5291)
Precentral Gyrus	33707 [#] (5738)	31255 (7279)	25049 [#] (6247)
Superior Temporal Gyrus	39385 (6362)	36903 (8006)	29534 (6087)
Middle Temporal Gyrus	61940 (9456)	58024 (10702)	49687 (11950)
Inferior Temporal Gyrus	16507 (2232)	14987 (2635)	13545 (2210)
Hippocampus	9790 [#] (1296)	9222 (1628)	7599 [#] (1159)
Parahippocampal Gyrus	12629 (1398)	12311 (2226)	11109 (1766)
Insula	18617 [#] (2439)	17136 (2895)	14328 [#] (3223)
Superior Parietal Gyrus	26613 (6048)	24659 (6811)	19230 (5239)
Supramarginal Gyrus	11065 (1818)	10756 (2896)	8953 (2168)
Occipital Lobe	31463 (5889)	30982 (8842)	26063 (7875)

The ANCOVA used occipital lobe volume and years of education as covariates, although the data presented are unadjusted. Post-hoc tests were performed on adjusted means.

#: Significant difference between Controls and MCI unable

*: Trend toward significance between MCI able and MCI unable

Table 9

Status of participants at four-year follow up for the Control, MCI-able, and MCI-unable. (Manuscript 1)

Diagnosis at follow-up:	Diagnosis at time of testing		
	Controls	MCI-able	MCI-unable
Normal	17	5	0
MCI	0	8	3
AD	0	2	3
Deceased	2	1	3
Lost to follow-up	0	0	2

Table 10

Status of participants at four-year follow up for the two MCI groups
classified according to their change in status. (Manuscript 1)

	MCI able	MCI unable
Improved	5	0
Stable	8	3
Declined	3	6

Table 11

Mean (and SE) of participant's demographics and neuropsychological performance.
(Manuscript 2)

	Controls	MCI	F(1,33)	p
Number of participants	19	16		
Sex	12 F, 7 M	10 F, 6 M		
Age	75.7 (1.5)	75.5 (1.7)	1.3	.93
Education (years)	14.8 (.7)	12.9 (.8)	1.7	.09
MMSE (/30)	28.6 (.4)	28.5 (.4)	.1	.81
MoCA (/30)	26.5 (.5)	24.3 (.6)	6.6	.02
Logical Memory (Immediate Recall)	13.9 (.6)	10.6 (.7)	10.0	< .01
Logical Memory (Delayed Recall)	12.5 (.9)	8.6 (.9)	8.4	< .01
Spatial Span	13.4 (.6)	12.1 (.7)	1.7	.20
Letter Number Sequencing	8.7 (.6)	8.6 (.6)	.1	.94
Trail Making A	46.1 (2.6)	48.1 (2.9)	.25	.62
Trail Making B	94.3 (7.8)	111.2 (8.7)	2.0	.29
Fluency (Letter)	46.1 (3.3)	41.1 (3.7)	.95	.34
Fluency (Category, Animals)	17.0 (1.1)	15.7 (1.2)	.56	.46
Boston	54.1 (1.5)	50.7 (1.9)	1.6	.21
Stroop Errors on Interference Block	.32 (.28)	1.3 (.30)	5.1	.03
Stroop Interference (Color RT/Dots RT)	2.0 (.2)	2.2 (.2)	.46	.50

MMSE : Mini Mental State Examination ; MoCA : Montreal Cognitive Assessment.

MMSE & MoCA results collected at time of ERP and behavioural testing. All other data were collected during the neuropsychological evaluation.

The slight difference between MoCA results reported in this table and those reported in Table 2 are due to some missing observations during the neuropsychological evaluation that resulted in some participants being omitted from the t-test.

Table 12

Mean (and SE) of groups performance on MMSE and MoCA at both data collections times.

	NP testing	Behavioural and ERP data	t-value	p
<u>Control group</u>				
MMSE	28.6 (.4)	28.6 (.4)	0	1.00
MoCA	25.5 (.3)	26.2 (.6)	1.4	.19
<u>MCI group</u>				
MMSE	28.3 (.4)	28.5 (.4)	.4	.69
MoCA	23.2 (.9)	24.5 (1.1)	1.2	.25

NP testing: Neuropsychological testing; ERP: Event Related Potentials;
MMSE : Mini Mental State Examination; MoCA : Montreal Cognitive
Assessment.

Table 13

Mean Raw Reaction Times (RT in ms) and Error Rates (ER) with their Standard Error (SE) for Switch and Repeat trials by Foil Type for both Groups. (Manuscript 2)

Controls		Homogeneous	Repeat	Switch	Mixing Cost	Switch Cost
Overall	RT (SE)	751.6 (26.6)	1028.6 (66.9)	1082.9 (71.9)	277.0	54.3
	ER (SE)	2.28 (.32)	2.52 (.32)	4.74 (.55)	.24	2.22
Neutral	RT (SE)		872.5 (48.9)	957.2 (65.1)		84.7
	ER (SE)		1.09 (.21)	2.5 (.42)		1.41
Congruous	RT (SE)		1113.9 (79.9)	1132.2 (78.9)		18.3
	ER (SE)		2.29 (.40)	3.62 (.65)		1.33
Incongruous	RT (SE)		1100.4 (76.7)	1159.4 (76.9)		59.0
	ER (SE)		4.18 (.80)	8.1 (1.1)		3.92
Congruous vs. Neutral	RT		241.4	175.0		
	ER		1.2	1.12		
Congruous vs. Incongruous	RT		-13.5	27.2		
	ER		3.09	4.48		
MCI		Homogeneous	Repeat	Switch	Mixing Cost	Switch Cost
Overall	RT (SE)	834.6 (28.9)	1237.6 (72.9)	1290.2 (77.2)	402.9	52.6
	ER (SE)	1.8 (.36)	2.87 (.36)	4.24 (.62)	1.07	1.37
Neutral	RT (SE)		1000.5 (52.8)	1123.9 (69.9)		123.4
	ER (SE)		.68 (.23)	1.57 (.47)		.89
Congruous	RT (SE)		1341.6 (85.9)	1365.1 (84.7)		23.5
	ER (SE)		1.61 (.45)	2.63 (.73)		1.02
Incongruous	RT (SE)		1377.3 (82.4)	1381.7 (82.6)		4.4
	ER (SE)		6.32 (.89)	8.51 (1.23)		2.19
Congruous vs. Neutral	RT		341.1	241.2		
	ER		.93	1.06		
Congruous vs. Incongruous	RT		35.7	16.6		
	ER		4.71	5.88		

Table 14

Mean Raw Reaction Times (RT in ms) with their Standard Error (SE) for Switch and Repeat trials and Foil conditions for control, MCI-able and MCI-wc Groups.

Condition	Controls	MCI-able	MCI-wc
Homogeneous Trials	751.6 (26.6)	834.6 (33.5)	1046.1 (59.9)
Repeat Trials	1028.6 (66.9)	1237.6 (72.9)	2020.6 (128.4)
Switch Trials	1082.9 (71.9)	1290.2 (77.2)	2114.8 (140.9)
Mixing Cost †	277.0 (53.2) [#]	402.9 (57.9) [*]	974.4 (103.6) ^{#*}
Switch Cost	54.3 (21.1)	52.6 (23.1)	94.8 (41.3)
Neutral	914.9 (54.6)	1062.2 (59.5)	1807.2 (106.4)
Congruous	1123.0 (78.3)	1353.3 (85.3)	2199.0 (152.6)
Incongruous	1129.9 (76.5)	1379.5 (83.4)	2196.0 (149.2)
Congruous vs. Neutral	208.2 (35.2)	291.1 (38.4)	391.8 (68.6)
Congruous vs. Incongruous	6.8 (20.3)	26.1 (22.1)	-2.9 (39.6)

Due to non-homogeneity of variance, the Brown-Forsythe Robust Test of Equality of Means was used for the omnibus analysis and the Games-Howell test was used for post-hoc multiple comparisons.

† : Significant omnibus test $\alpha < .05$

#: Significant difference between Controls and MCI-wc

*: Significant difference between MCI able and MCI-wc

Table 15

Selected Regions Volume (mm³) with their Standard Deviation (SD) for Control, MCI-able, MCI-wc, and MCI-unable Groups.

Region	Control	MCI able	MCI-wc	MCI unable
Medial Orbital Gyrus	4788 [#] (817)	4176 (974)	3394 (791)	3467 [#] (770)
Lateral Orbital Gyrus	27037 ^{#**^} (3283)	24113* (5191)	19956 [^] (5110)	20089 [#] (4796)
Superior Frontal Gyrus	23780 (4836)	23256 (5042)	19087 (5393)	17739 (4897)
Middle Frontal Gyrus	52907 ^{#**^} (7601)	46179* (12179)	37054 [^] (8978)	37452 [#] (10712)
Inferior Frontal Gyrus	27980 [#] (5110)	25518 (6793)	20980 (7413)	20109 [#] (5879)
Medial Frontal Gyrus	31022 [#] (4982)	29857 [†] (6541)	23653 (5140)	23390 ^{#†} (6899)
Cingulate Gyrus	33056 [#] (3625)	30675 (6415)	26886 (5193)	25962 [#] (5827)
Precentral Gyrus	33707 [#] (5738)	31255 (7279)	25710 (5899)	24499 [#] (7028)
Superior Temporal Gyrus	39385 [#] (6362)	36903 (8006)	29622 (6232)	29461 [#] (6558)
Middle Temporal Gyrus	61940 [#] (9456)	58024 (10702)	52067 (13511)	47704 [#] (11367)
Inferior Temporal Gyrus	16507 [#] (2232)	14987 (2635)	13897 (2845)	13252 [#] (1753)
Hippocampus	9790 [#] (1296)	9222 [†] (1628)	7860 (1164)	7382 ^{#†} (1218)
Parahippocampal Gyrus	12629 (1398)	12311 (2226)	11189 (1532)	11042 (2085)
Insula	18617 [#] (2439)	17136 (2895)	14227 (3423)	14412 [#] (3373)
Superior Parietal Gyrus	26613 [#] (6048)	24659 (6811)	20011 (5045)	18580 [#] (5782)
Supramarginal Gyrus	11065 (1818)	10756 (2896)	8925 (2066)	8976 (2447)
Occipital Lobe	31463 (5889)	30982 (8842)	24450 (7476)	27408 (8633)

The ANCOVA used occipital lobe volume as a covariate, although the data presented are unadjusted. Post-hoc tests were performed on adjusted means.

#: Significant difference between Controls and MCI unable

^: Significant difference between Controls and MCI-wc

*: Significant difference between Controls and MCI able

†: Significant difference between MCI able and MCI unable

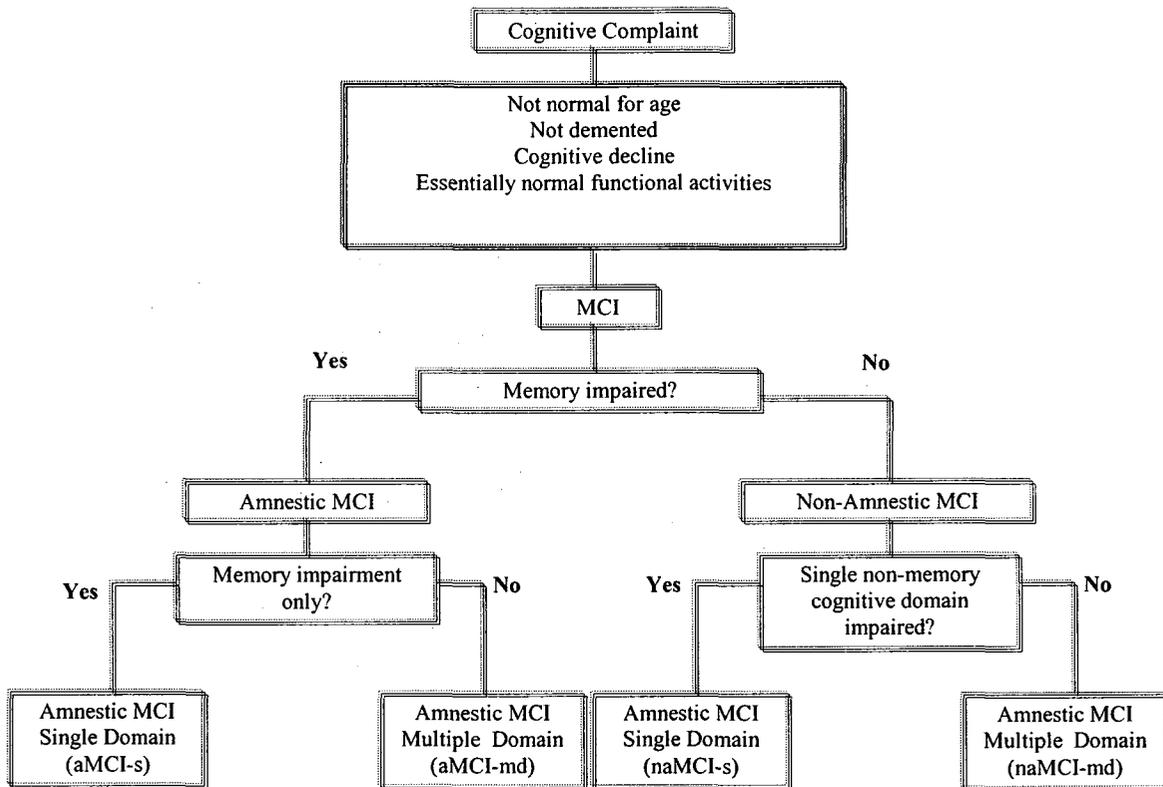


Figure 1. MCI classification process (adapted from Winblad et al., 2004).

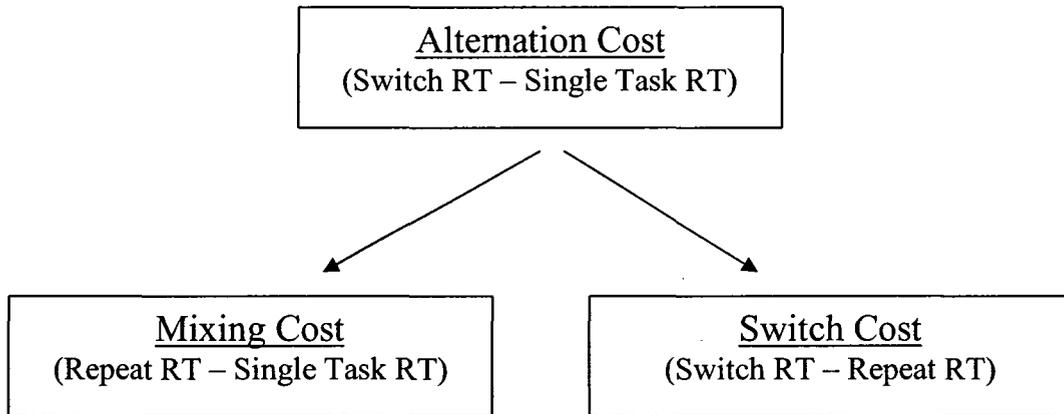


Figure 2. Components of alternation cost. From Meiran, Chorev, and Sapir (2000).

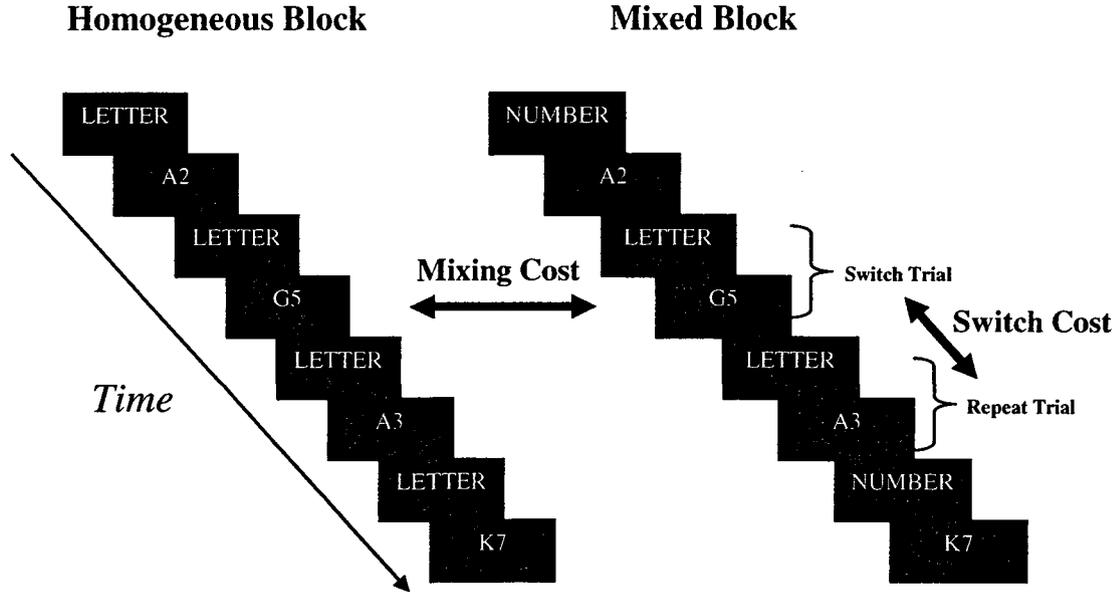


Figure 3. Time course of stimulus presentation for homogeneous (left side) and mixed (right side) blocks. Each trial started with the presentation of a cue followed by a blank screen, followed by the presentation of a target that remained on the screen until the participant responded.

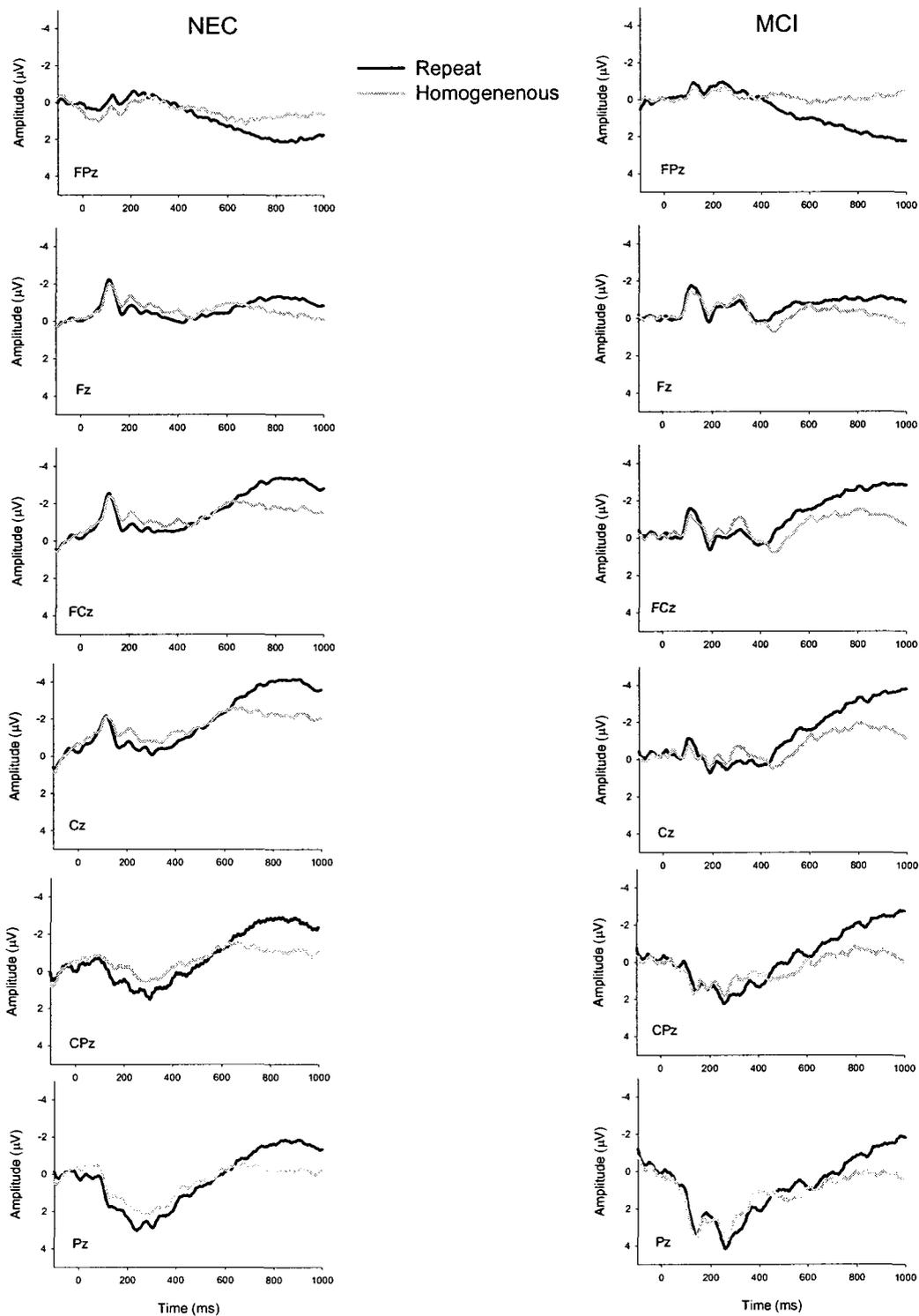


Figure 4. Cue-locked ERP grand average waveforms. Left panel: Normal controls. Right panel: MCI patients. Heterogeneous repeat trials are represented in black, homogeneous trials are represented in grey.

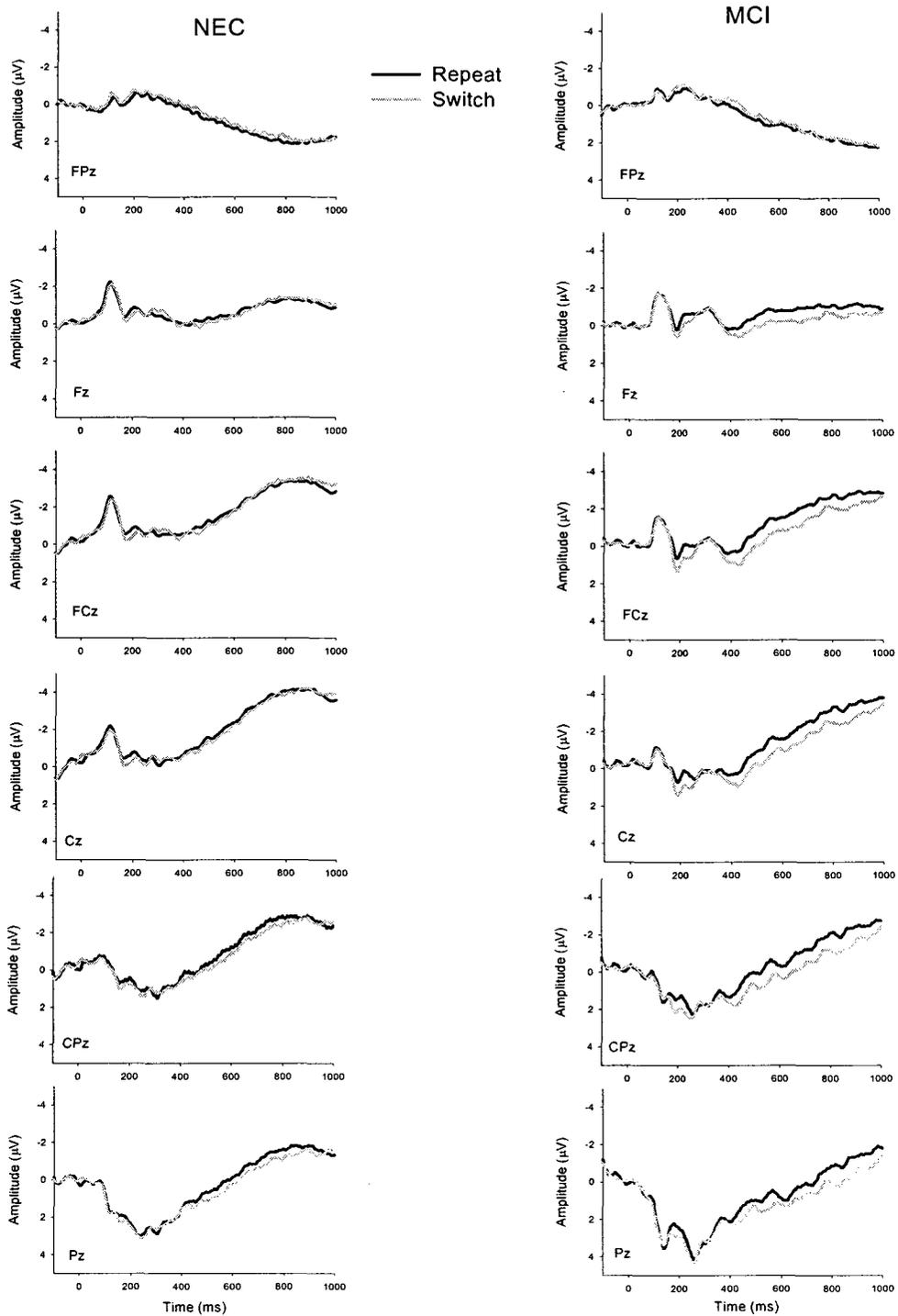


Figure 5. Cue-locked ERP grand average waveforms. Left panel: Normal controls. Right panel: MCI patients. Repeat trials are represented in black, switch trials are represented in grey.

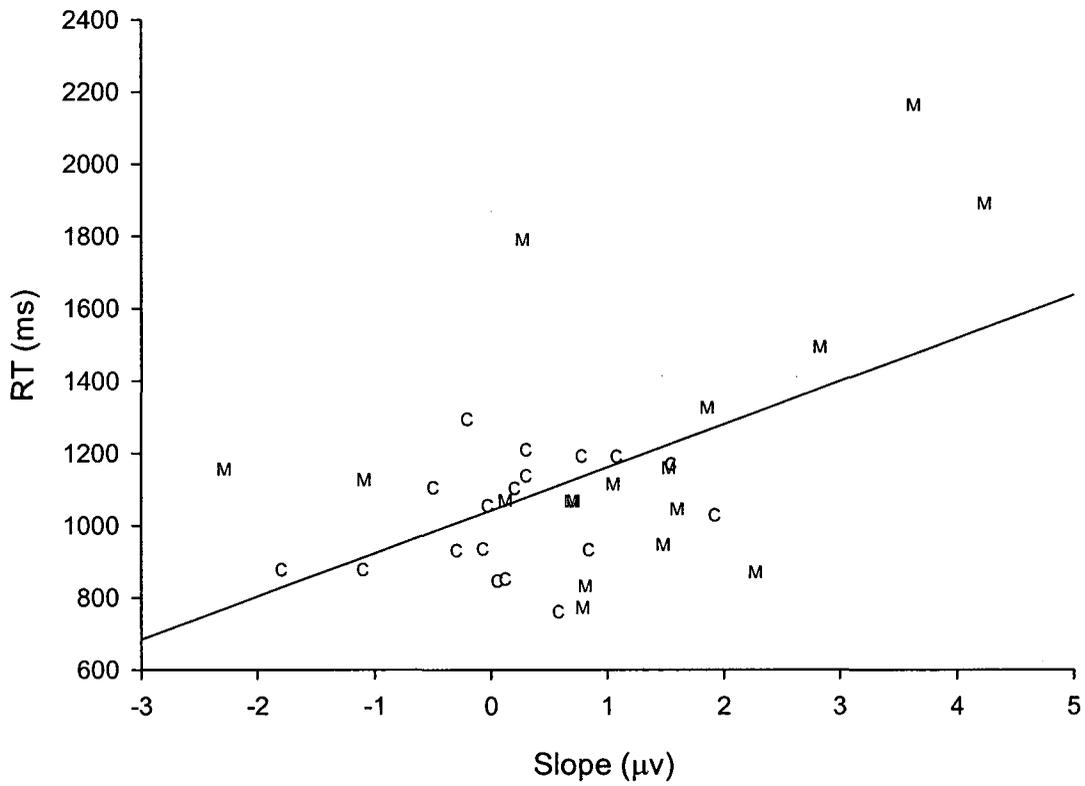


Figure 6. Correlation between repeat trials waveform slope amplitude in the 700-1000 ms period after cue presentation and reaction time for repeat trials across MCI patients (M) and normal controls (C).

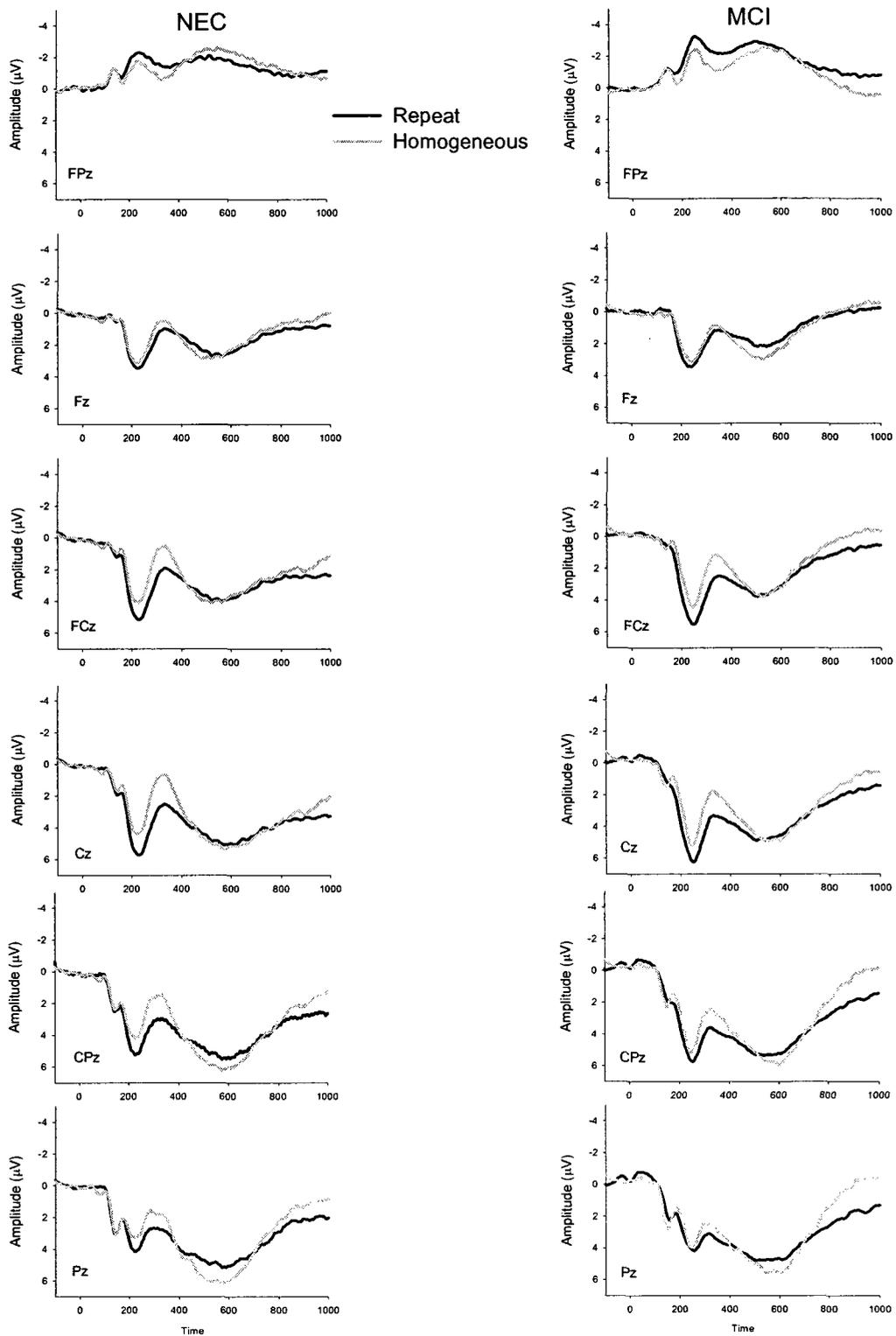


Figure 7. Target-locked ERP grand average waveforms. Left panel: Normal controls. Right panel: MCI patients. Heterogeneous repeat trials are represented in black, homogeneous trials are represented in grey.

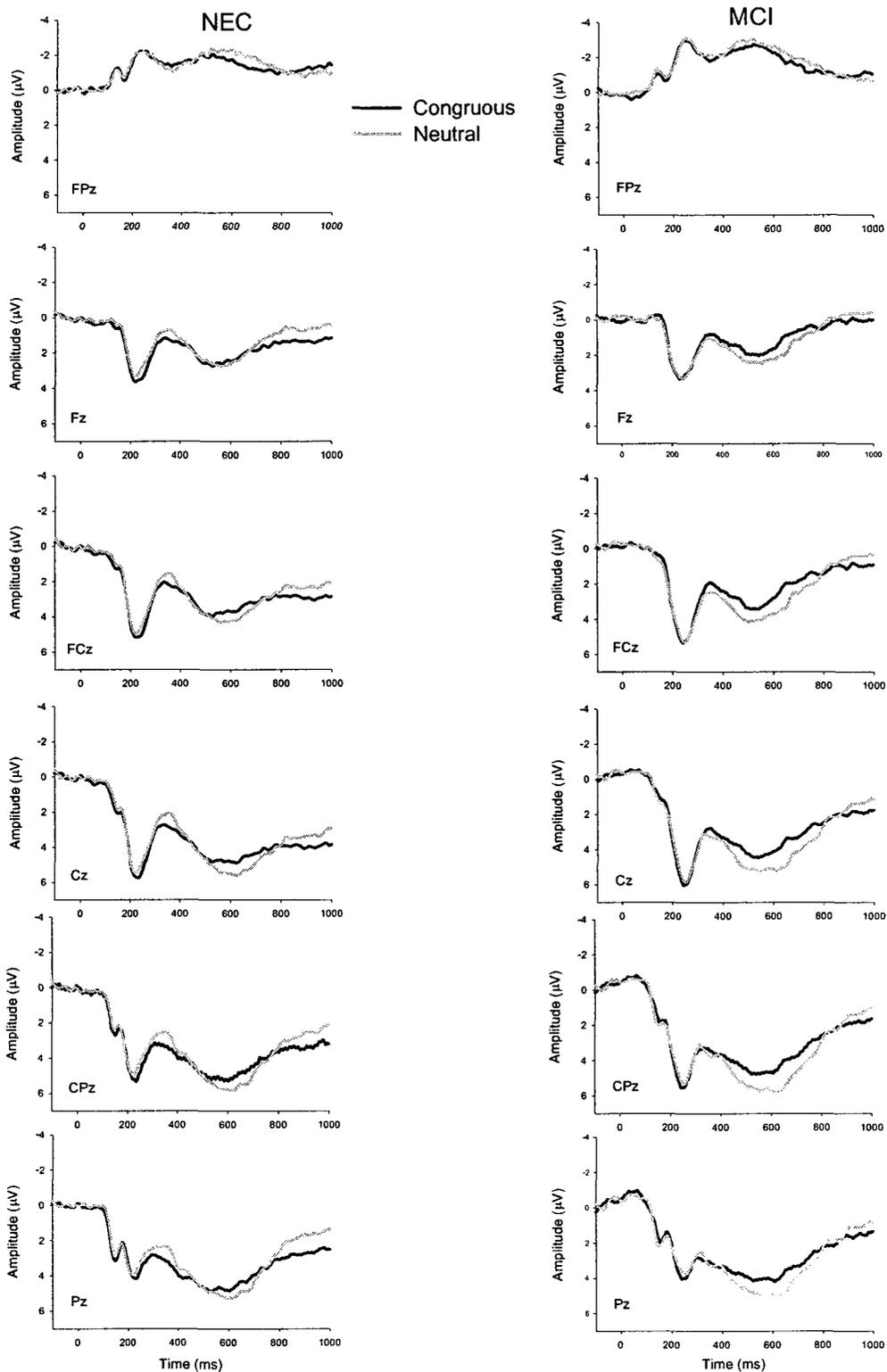


Figure 8. Target-locked ERP grand average waveforms. Left panel: Normal controls. Right panel: MCI patients. Congruous trials are represented in black, neutral trials are represented in grey.

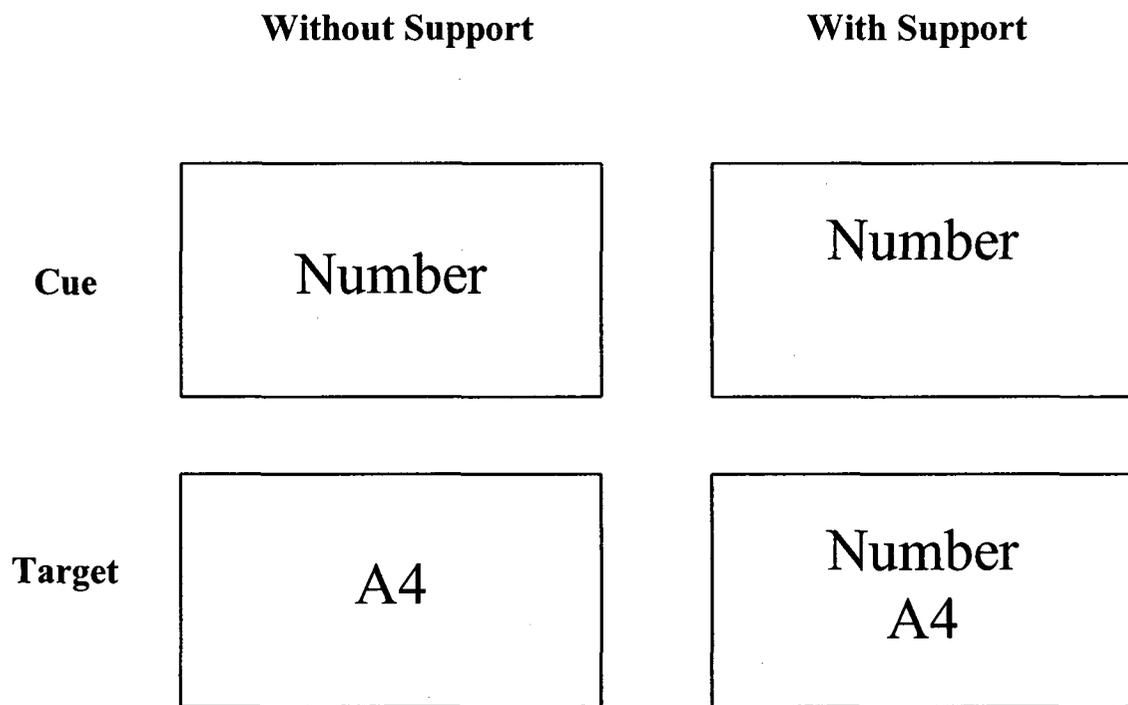


Figure 9. Illustration of cue and target presentation with and without cognitive support. Left panel: normal controls and MCI-able participants were able to perform the task when the cue disappeared just prior to target presentation. Right panel: some MCI-unable participants (referred in the general discussion as MCI with cue or MCI-wc participants) were able to perform the task when the cue remained on the screen along with the target until response.

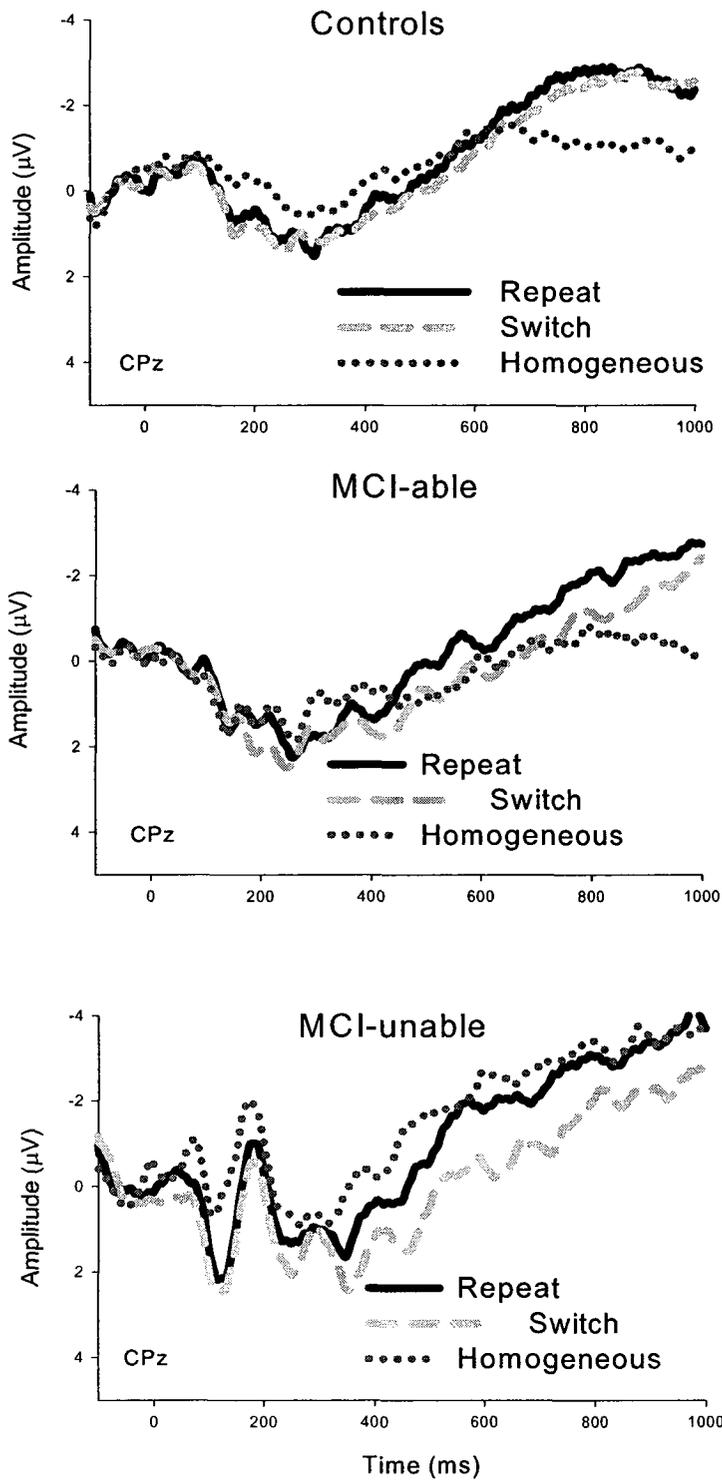


Figure 10. Cue-locked ERP grand average waveforms at CPz. Top panel: Normal controls. Middle panel: MCI-able patients. Bottom Panel: MCI-wc patients. Repeat trials are represented in black, switch trials are represented in grey dashed line, and homogeneous trials are represented in black dotted line.

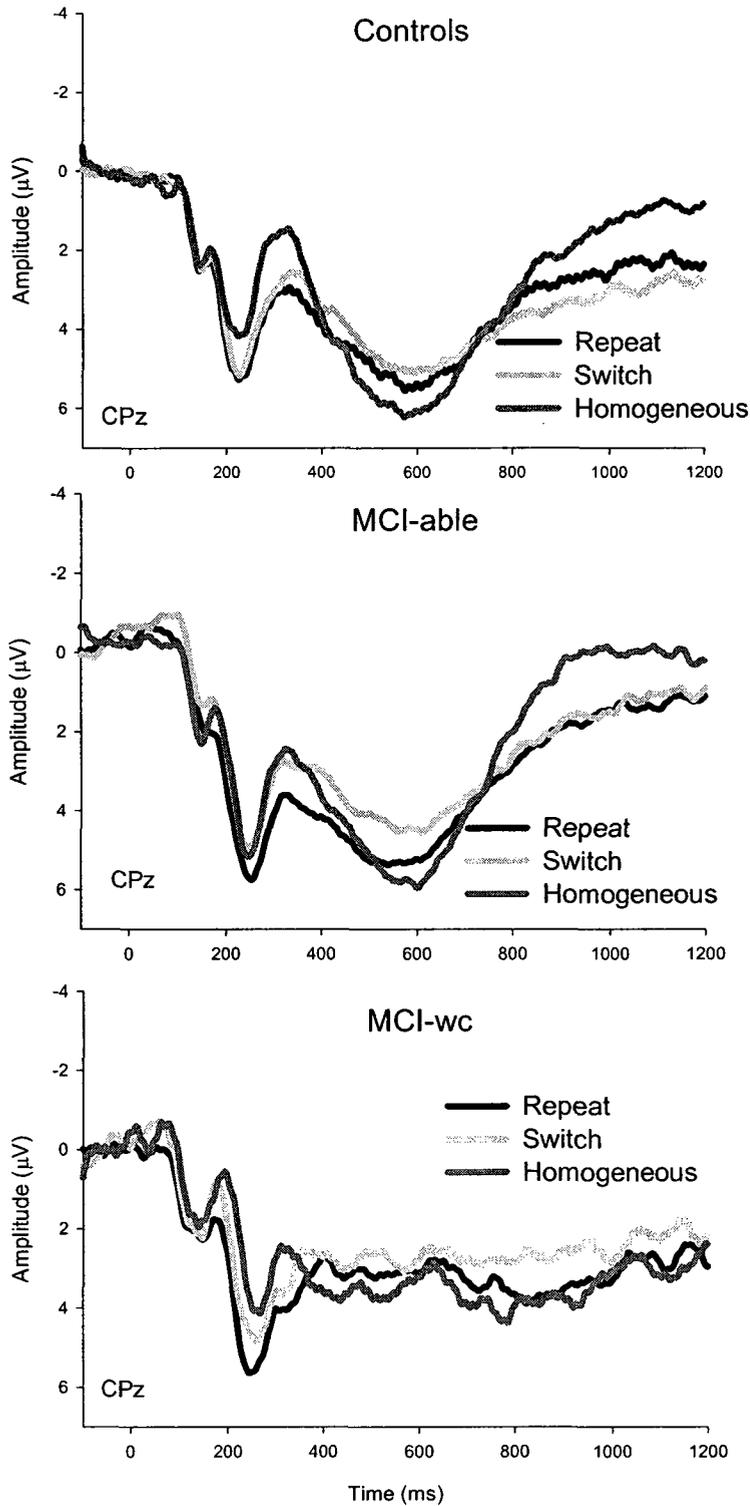


Figure 11. Target-locked ERP grand average waveforms at CPz. Top panel: Normal controls. Middle panel: MCI-able patients. Bottom Panel: MCI-wc patients. Repeat trials are represented in black, switch trials are represented in grey dashed line, and homogeneous trials are represented in black dotted line.